Evaluation of haematological response to granulocyte colony-stimulating factor therapy in a patient with Chediak Higashi syndrome: A case report

Hassan Alhashem, Fellowship in paediatric allergy and immunology[1], Noura Alibrahim, Bachelor in Doctor of Medicine[1], Banan Alotaibi, Bachelor in Doctor of Medicine[1], Fatemah A. Hashem, Fellowship in haematology[1], Awal Alhusain, PhD in Medicine[2]

[1]Maternity and children Hospital, Dammam, Saudi Arabia, [2]Dammam Regional Laboratory and Blood Bank, Dammam, Saudi Arabia

SUMMARY

Chediak-Higashi syndrome (CHS) is a congenital immunodeficiency disorder characterised by recurrent bacterial infections, oculocutaneous albinism and abnormal intracellular protein transport. One of the manifestations of the disease is severe neutropaenia. This case report presents the haematological effects of granulocyte colony-stimulating factor (G-CSF) therapy on a 16-month-old girl who was recently diagnosed with CHS. The patient exhibits classic features of CHS, including silver hair, albinism and recurrent infections. Initially, the patient was treated with antibiotics, but due to severe neutropaenia, G-CSF therapy was initiated. This resulted in an increase in absolute neutrophil count (ANC) with no adverse effects observed. This case highlights the effectiveness of G-CSF therapy and its rapid response in treating CHS-associated neutropaenia.

INTRODUCTION

Chediak-Higashi syndrome (CHS) is an autosomal recessive disorder, characterised by a range of symptoms, including partial oculocutaneous albinism, silver hair, severe immunodeficiency and the presence of abnormal large cytoplasmic granules in specific cells. The underlying cause of CHS is a mutation in the CHS1 gene, which is located on chromosome 1 and encodes the lysosomal trafficking regulator protein. This mutation disrupts protein synthesis and results in dysfunctional lysosomes.[2]

The immunological manifestations of CHS involve either a normal or reduced number of natural killer cells with impaired function, neutropaenia (low neutrophil count), and compromised neutrophil function.[3]

Around 85% of individuals with CHS progress to a fatal accelerated phase characterised by pancytopaenia (low blood cell counts), hemophagocytic lymph histiocytosis (HLH), and significant infiltration of organs by lymphocytes. These complications lead to multi-organ dysfunction and ultimately result in death.[4]

The management of CHS depends on the specific presentation of the individual and whether they have entered the accelerated phase (HLH). The severity of symptoms at the time of diagnosis also influences the appropriate management approach. In this study, we present a case involving a 16-month-old baby girl with severe neutropaenia and her response to granulocyte colony-stimulating factor (G-CSF) therapy. G-CSF is a therapeutic agent that stimulates the production and function of neutrophils.

By examining this case, we aim to contribute to the understanding of CHS management and highlight the potential benefits of G-CSF therapy in individuals with severe neutropaenia. This study underscores the importance of personalised treatment approaches in CHS and emphasises the need for further research to enhance our knowledge and improve the prognosis for individuals affected by this rare genetic disorder.

Consent form was obtained from the father of this patient and this study was ethically approved by IRB number (H-05-D-114).

CASE PRESENTATION

A 16-month-old Saudi girl was admitted to the paediatric medical ward with a 2 days history of fever accompanied by oral ulcers persisting for 1 week. The patient had a previous medical admission due to recurrent infections since the age of 6 months, which prompted an investigation into possible immunodeficiency. The lymphocyte subset (flow cytometry) showed normal results (Table I).

During the physical examination, the patient's silver hair caught the attention of the medical team (Photo 1). Notably, her hair had been darker at birth and gradually lightened, as she grew older. Additionally, abnormal pigmentation on her back “Café au lait” had been present since birth. The patient had positive consanguinity of the parents, and a family history of silver hair noted in her grandfather, who also had a low platelet count. Furthermore, two of her siblings exhibited the same hair colour.

The physical examination revealed light skin complexion, oral ulcers, thrush and Cafe au lait spots on her back were observed. Detailed ophthalmological examination was normal. Initial investigations (Table I) revealed severe

This article was accepted: 02 June 2024
Corresponding Author: Alhusain Awal
Email: lali_kari@yahoo.com; aalmohmedhusain@moh.gov.sa

Table I: Lab investigations

Investigation	Value before treatment	Value after treatment	Reference range
WBC	10.6 10^9/L	39.3 10^9/L	4.5 11.0 10^9/L
ANC	0.0	20.1 10^3/uL	0.6-5.1 10^3/uL
Haemoglobin	11.7 g/dl	11.7 g/dl	10.0 -14.0 g/dl
MCV	77.7 fL	77.5 fl	75.0 – 115 fL
MCH	24.7pg	24 pg	26.0 – 34.0 pg
Platelet	387 10^3/uL	647 10^3/uL	150 – 550 10^3/uL
CBC count before and after G-CSF			
Lymphocyte subset			
CD3	2787 (53%)	-	(1900 5900) (49 76%)
CD 4	2038 (39%)	-	(1400 4300) (31 56%)
CD 8	542 (10%)	-	(500 1700) (12 24%)
CD 19	1669 (32%)	-	(610 2600)(14 37%)
Natural killers cells	738 (14%)	-	(160950) (03 15%)

MCV: Mean corpuscular volume, MCH: Mean corpuscular haemoglobin, ANC: Absolute neutrophil count, WBC; White blood count

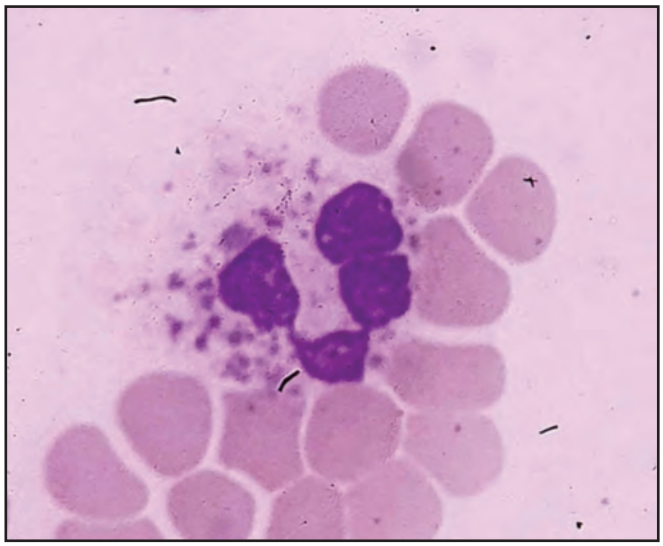


Fig. 1: Neutropaenia and giant granulocyte.

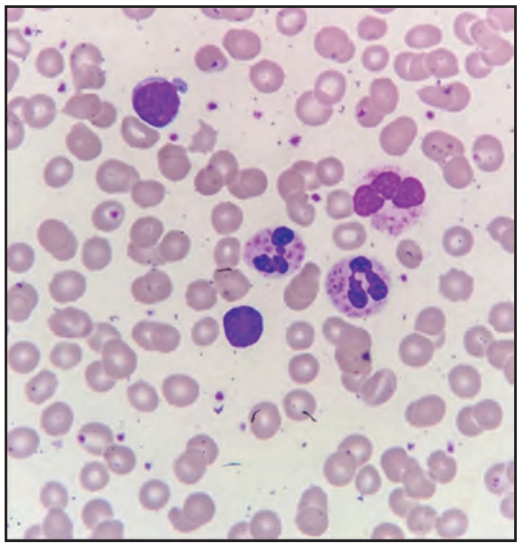


Fig. 2: Normalisation of neutrophil count after G-CSF.



Photo 1: Fair skin and thin hair.

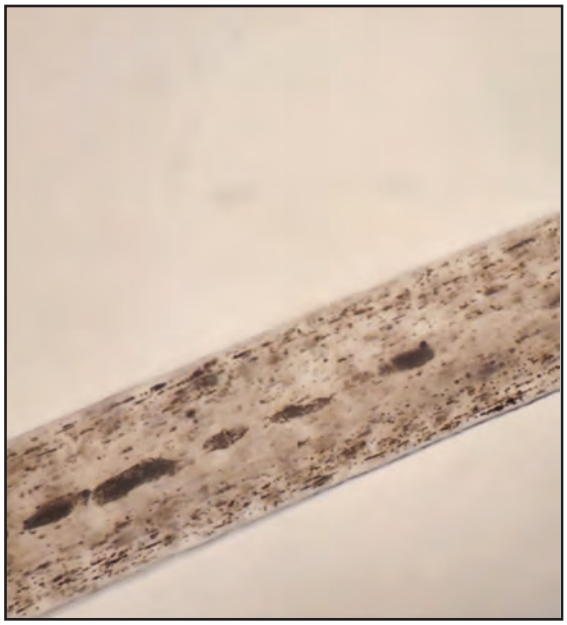


Photo 2: Thinning of hair shaft.

neutropaenia, with an absolute neutrophil count of zero. Upon closer examination of the peripheral blood film, rare neutrophils with giant granules were identified (Figure 1). Considering the severe neutropaenia and the presence of abnormal giant granules in neutrophils. The preliminary assessment indicated a suspicion of CHS as the potential diagnosis.

The hair shaft of the patient was examined under a light microscope, revealing an abnormal pattern of melanin clump distribution in the cortex of an irregular pattern and regular melanin granules larger than those seen in normal hair (Photo 2). Additionally, abdominal ultrasound was done, and it was normal. Subsequent ferritin testing showed a value of 112.59 µg/l (13 150), which further support that the patient was not exhibiting any signs of HLH.

The patient was prescribed piperacillin/tazobactam, next day of admission and continued for 7 days resulting in the resolution of fever within a few days. The absolute neutrophil count was still markedly low. After 5 days from admission, the treating physician decided to start the patient with granulocyte-colony stimulating factor (G-CSF) at a dose of 5 µ/kg/day for 3 days. There was dramatic increase in ANC from $0.2 \times 10^3/\mu L$ to $20.1 \times 10^3/\mu L$ (Table I) measured on the following day of G-CSF (Figure 2). Throughout the course of treatment, patient remained stable, a febrile and did not experience any side effects from the medication. Consequently, the patient was discharged with a follow-up plan in the outpatient department and was referred to a tertiary hospital for the purpose of undergoing genetic testing and further evaluation.

The results of the genetic test confirmed the diagnosis of CHS, revealing the presence of the pathogenic c.8869c>T p.(Arg2957*) variant in the "LYST" gene. Notably, this variant was detected in probable homozygosity. These findings provide valuable insights into the genetic basis of the patient's condition. Further analysis and interpretation of the results will be necessary to fully understand the implications of this specific variant in relation to the patient's clinical presentation.

DISCUSSION

CHS is a rare lysosomal disease characterised by abnormal fusion of primary lysosomes and the resulting enlargement of lysosomes in all tissues.[5] To date, approximately 500 cases of CHS have been reported.[1] The average age of onset is 5.85 years, with most patients succumbing to the disease before the age of 10 years. In those who do survive beyond childhood, neurological problems persist and may worsen over time.[4]

CHS is characterised by partial oculocutaneous manifestations, recurrent infections and presence of abnormal giant granules in neutrophils, lymphocytes and platelets, which are pathognomonic for the disease.3 Primary concern in this syndrome is the recurrent infections and the development of an accelerated phase of HLH.[1] In this reported case, the patient exhibited typical features of CHS, including light skin, silver hair and severe neutropaenia. The diagnosis of CHS is based on clinical manifestations, laboratory findings and confirmed through genetic testing.[5] In the laboratory investigation, the patient had a neutrophil count of zero and a history of recurrent infections, prompting suspicion of CHS. A hair shaft sample was examined under a microscope, revealing clumps of melanin, which are highly characteristic of the syndrome compared to normal hair.[1]

The management of CHS aims to prevent lethal complications such as HLH and recurrent infections.[1] In this case, G-CSF therapy established following the European guidelines for treatment of neutropaenia.[6] There was dramatic improvement of neutrophil count observed from the next day of starting the G-CSF therapy. G-CSF is a growth factor that promotes the maturation of neutrophil precursor cells, which are then released into the peripheral blood.[1] Throughout the course of treatment, the patient maintained a stable clinical condition. However, it is important to note that the use of G-CSF therapy can potentially lead to inflammatory responses.[1] Using G-CSF in stable patients with CHS requires careful consideration of its safety.

Of particular note, Mesfer et al.1 have used the same protocol for treating another patient with CHS. However, in that patient the effect of G-CSF takes more time to normalise the neutrophil count. This variation in time of response and the need to adjust the treatment highlight the fact that different people have different sensitivity to the treatment. This supports the idea of customised treatment according to the patient condition and response to treatment.

Other treatment options for CHS include chemotherapy, high-dose methylprednisolone, and IL-2 administration. Yet, allogenic hematopoietic stem cell transplantation (HSCT) is considered the most successful option in patients experiencing an accelerated phase of the disease.[5]

The researchers studied the genetic basis of CHS to better understand the disease mechanisms and be able to explore treatment options for this condition. CHS is caused by mutation in the LYST gene. LYST gene mutation result in abnormal lysosomal trafficking and impaired function of neutrophils and other immune cells.

The use of G-CSF in CHS aims to stimulate the production of neutrophils in the bone marrow and improve immune function, which subsequently reduce the recurrent infection. According to the literature, G-CSF does not address the underlying genetic defect or correct the abnormalities in neutrophil function in patients with CHS.

Moreover, it is important to acknowledge the limitations of this report, as it is based on a single case. Further evaluation of G-CSF therapy and its potential side effects would be more effective in larger studies involving a greater number of patients or in case series with similar clinical manifestations and the use of G-CSF in patients with severe neutropaenia. Additionally, follow-up of the patient is crucial, as they have been referred to a tertiary centre for further workup and possible bone marrow transplant. Research into the molecular genetics of CHS and the mechanisms of G-CSF therapy in this condition is mandatory.

CONCLUSION

This case report highlights the effectiveness and prompt response of granulocyte colony-stimulating factor (G-CSF) therapy in a patient with Chediak-Higashi syndrome (CHS). The administration of G-CSF not only improved the patient's immune function but also effectively controlled the infection. Importantly, the patient remained stable throughout the course of G-CSF therapy without experiencing any adverse effects.

Further studies should focus on investigating the efficacy of G-CSF therapy in a larger sample size of CHS patients who are not in the accelerated phase. This will provide more robust evidence of the potential benefits of G-CSF therapy in this patient population. We believe that such research endeavours will contribute to the development of more targeted and effective treatment modalities for patients with CHS.

REFERENCES

1. Almesfer A, Alradhi S, Alamr F, AlSaiary M. Management of severe neutropaenia in a child with Chediak-Higashi syndrome using granulocyte-colony stimulating factor (G-CSF): a case report. Cureus 2023; 15(11): e49010.
2. Gil-Krzewska A, Wood SM, Murakami Y, Nguyen V, Chiang SCC, Cullinane A, et al. Chediak-Higashi syndrome: Lysosomal trafficking regulator domains regulate exocytosis of lytic granules but not cytokine secretion by natural killer cells. J Allergy Clin Immunol 2015; 137(4): P1165-77.
3. Carneiro I, Rodrigues A, Pinho L, De Jesus Nunes-Santos C, De Barros Dorna M, Castro APBM, et al. Chediak–Higashi syndrome: lessons from a single-centre case series. Allergologia Et Immunopathologia 2019; 47(6): 598-603.
4. Mâaloul I, Talmoudi J, Chabchoub I, Ayadi L, Kamoun T, Boudawara T, et al. Chediak–Higashi syndrome presenting in accelerated phase: a case report and literature review. Hematol/Oncol Stem Cell Therapy 2016; 9(2): 71-5.
5. Elfaituri SS, Matoug I. Chédiak-Higashi syndrome: case report and review of the literature. Clin Case Rep Int 2020; 4: 1204.
6. Fioredda F, Julia S, Hannah T, Spanoudakis M Farruggia P, Almeida A, et al. The European guidelines on diagnosis and management of neutropaenia in adults and children: a consensus between the European hematology association and the EuNet-INNOCHRON COST action. HemaSphere 2023; 7(4): e872.|