Pediatr Infect Vaccine. 2024 Apr;31(1):122-129
https://doi.org/10.14776/piv.2024.31.e14
pISSN 2384-1079·eISSN 2384-1087

PIV PEDIATRIC INFECTION & VACCINE

Case Report

Check for updates

Variants of *LYST* and Novel *STK4* Gene Mutation in a Child With Accelerated Chediak Higashi Syndrome

Asrar Abu Bakar,[1] **Haema Shunmugarajoo**,[2] **Jeyaseelan P. Nachiappan**,[2] **Intan Hakimah Ismail**[3]

[1]International Islamic University Malaysia, Kuala Lumpur, Malaysia
[2]Ministry of Health Malaysia, Putrajaya, Malaysia
[3]Universiti Putra Malaysia, Seri Kembangan, Malaysia

OPEN ACCESS

Received: Jan 15, 2024
Revised: Feb 29, 2024
Accepted: Mar 2, 2024
Published online: Mar 22, 2024

Correspondence to
Asrar Abu Bakar
Department of Paediatrics, Kulliyah of Medicine, International Islamic University Malaysia, P.O. Box 10, Kuala Lumpur 50728, Malaysia.
Email: asrarabubakar@iium.edu.my

© 2024 The Korean Society of Pediatric Infectious Diseases
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs
Asrar Abu Bakar
https://orcid.org/0009-0008-6138-1077
Haema Shunmugarajoo
https://orcid.org/0009-0007-5378-491X
Jeyaseelan P. Nachiappan
https://orcid.org/0000-0002-6836-2927
Intan Hakimah Ismail
https://orcid.org/0000-0003-4614-0140

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Chediak-Higashi syndrome (CHS) is a rare haematological and immunodeficiency disorder that occurs in childhood leading to recurrent infections, bleeding tendencies and progressive neurological dysfunction. Partial oculocutaneous albinism occurs in almost all cases. The exact prevalence is unknown, and the disease is caused by over 70 identified mutations in the lysosomal trafficking regulator gene. The presence of a bright polychromatic appearance from hair shaft and abnormally large intracytoplasmic granules, especially within neutrophils and platelets in the bone marrow is highly suggestive. Treatment is largely supportive, and the only curative treatment is through an allogeneic hematopoietic stem cell transplant. Without transplant, most patients will enter an accelerated phase of hemophagocytic lymphohistiocytosis (HLH) which carries a high mortality rate. We present a young male with CHS who we had followed through and eventually developed a fulminant accelerated phase. We believe this is only the second reported case of CHS in Malaysia.

Keywords: Chediak-Higashi syndrome; LYST protein; Hemophagocytic lymphohistiocytosis

INTRODUCTION

Chediak-Higashi syndrome (CHS) is a complex immune autosomal recessive disorder that is caused by a mutation to the lysosomal trafficking regulator (*LYST*) gene.[1] This leads to impaired lysis of phagocytized pathogens leading to recurrent pyogenic infections, abnormal bleeding tendencies and hypopigmented skin and eyes. In milder form of the disease, patients progress to multitude of neurological sequelaes. Almost 80% of patients however do not survive beyond childhood as they enter the accelerated phase characterised by lymphoproliferative infiltration of the bone marrow and reticuloendothelial system.[2] The finding of a large granules within peripheral blood cells is thought to be pathognomonic for CHS. Treatment is largely supportive with aggressive antibiotic treatment and prophylaxis, interferon gamma, steroids and granulocyte colony stimulating factor (G-CSF). However, recent development of stem cell transplant have paved way for a potential curative treatment which have found to be successful in a number of reported cases.

Generated by ximilinkpress

PIV PEDIATRIC INFECTION & VACCINE

Author Contributions

Conceptualization: Abu Bakar A, Shunmugarajoo H; Investigation: Ismail IH; Resources: Shunmugarajoo H, Nachiappan JP, Ismail IH; Supervision: Nachiappan JP; Writing - original draft: Abu Bakar A; Writing - review & editing: Abu Bakar A, Shunmugarajoo H, Nachiappan JP, Ismail IH.

CASE

We present a 4-month-old male infant who presented with recurrent febrile episodes associated with greenish loose stools and bilateral finger redness. There was minimal pus discharge from his left middle finger. He appeared pale and lethargic but breastfeeding well with good urine output. There was no history of swollen lymph nodes, conjunctivitis or rash. On further history, the infant was born term at 39 weeks via emergency C-section due to fetal distress with a birthweight of 3.45 kg. His antenatal and postnatal history was uneventful. He is thriving along the 25th centiles for both weight and height, up to date with immunisations including Bacillus Calmette-Guérin and achieving appropriate developmental milestones. He is the only child from non-consanguineous parents. Clinical examination revealed pallor, hepatosplenomegaly and brisk lower limb reflexes. On closer inspection, the child had fair skin with hypopigmented areas over his eyebrows and silvery grey hair appearance. A formal eye examination revealed bilateral ocular albinism type 2.

Laboratory investigations revealed haemoglobin of 8.6 g/dL (normal 10.6–13.2 g/dL), total leukocyte count 5.2×10^3/μL (normal 4.3–11.4×10^3/μL), absolute neutrophil count of 0.2×10^3/μL (normal 2.0–7.2×10^3/μL) and platelet count of 30×10^3/μL (normal 199–367×10^3/μL). An urgent full blood film showed presence of inclusion bodies within neutrophils with large single azurophilic granules seen in lymphocytes along with occasional giant platelets (**Fig. 1**). Hair shaft examination revealed evenly distributed melanin granules of regular diameter (**Fig. 2**) with bright polychromatic appearance under polarized light microscopy (**Fig. 3**). Bone marrow aspirates reported large lymphocytes with inclusion bodies and cytoplasmic azurophilic granules consistent with peripheral blood smear findings. A diagnosis of CHS and Chediak-Higashi-like syndrome was suspected.

Subsequently, he spent few days in hospital in view of his pancytopenia and was commenced on broad spectrum antibiotics and intravenous immunoglobulins. His blood cultures however revealed no growth. His chest X-ray and echocardiogram was unremarkable. An inborn error of immunity screen showed normal immunoglobulin G 8.81 g/L (normal 2.2–11.3 g/L), IgM 0.64 g/L (normal 0.07–0.65 g/L) and IgA 0.28 g/L (normal 0.08–0.9 g/L) and normal levels of

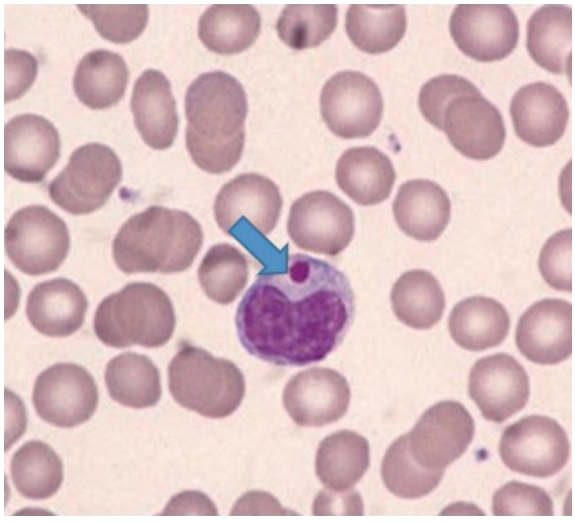

Fig. 1. A single giant azurophilic granule seen (blue arrow) in lymphoblast often pathognomonic for CHS.
Abbreviation: CHS, Chediak-Higashi syndrome.

https://doi.org/10.14776/piv.2024.31.e14

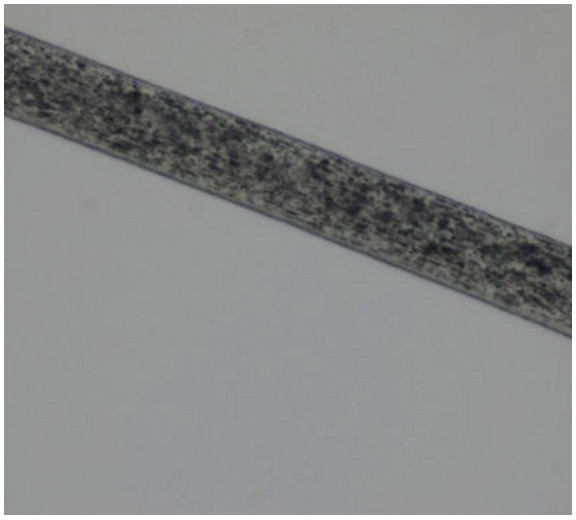

Fig. 2. Hair shaft examination under normal light microscopy in CHS shows regularly distributed melanin granules with diameters larger than normal hairs.
Abbreviation: CHS, Chediak-Higashi syndrome.

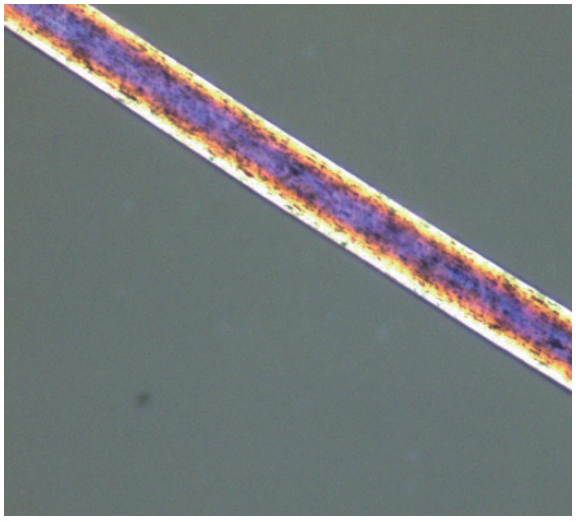

Fig. 3. Under polarized light microscopy, hair shafts in CHS appears bright with central polychromatic refringence appearance.
Abbreviation: CHS, Chediak-Higashi syndrome.

T cells, 3,757×10^6/L (normal 1,700–3,600×10^6/L), B cells 585×10^6/L (normal 500–1,500×10^6/L and NK cells 412×10^6/L (normal 300–700×10^6/L. He was commenced on oral trimethoprim-sulfamethoxazole and itraconazole prophylaxis in view of persistent neutropenia. He was subsequently discharged with close follow up planned.

Next-generation sequencing test sent to Invitae Laboratories in San Francisco confirms heterozygous mutations in the *LYST* gene involving 2 pathogenic variants, namely NM_000081.3, c.1406T>A (p.Leu469*) and NM_000081.3, c.2832del (p.Ser945Leufs*29) leading to the diagnosis of CHS. Both sequences create a premature translational stop signal leading to an absent or disrupted protein involving the *LYST* and their loss-of-function role has been reported previously in individuals with CHS. Sequencing also revealed a variant of uncertain significance NM_006282.3 STK4, Exon 7, c.823C>G (p.Leu275Val). Mutations in

https://doi.org/10.14776/piv.2024.31.e14

STK4 gene has been implicated in combined immunodeficiency and neutropenias. In silico modelling of this particular variant have not reached a conclusion of clinical significance at the present time. Further data is required, and it remains to be seen whether this variant played any role in the evolution of our patient's disease progress. Unfortunately, parental genetic testing was not performed as parents refused in view of costs. Suitability for hematopoietic stem cell transplant was explored however as he was the only child no suitable donor was found.

He presented again at 6 months of age with persistent fever, septic shock, worsening hepatosplenomegaly and pancytopenia. He had coagulopathy with an international normalized ratio of 4.15, prothrombin time 62.7, and activated partial thromboplastin time of 73.1. He responded to fluid resuscitation and correction of his coagulopathy. His blood culture grew extended-spectrum beta-lactamase *Klebsiella pneumoniae* thus he was treated with 10 days of intravenous meropenem. During this admission, it was noted that his ferritin levels were >100,000 μg/L, fibrinogen of 0.46 g/L (normal range 2.1–3.9 g/L) and triglycerides of 2.77 mmol/L. Bone marrow aspiration revealed a haemodiluted marrow along with presence of leucocyte inclusion bodies and cytoplasmic eosinophilic granules with no evidence of blast cells or hemophagocytosis. However, he fulfilled the modified 2009 hemophagocytic lymphohistiocytosis (HLH) criteria and was commenced on the HLH-2004 treatment protocol of oral dexamethasone, intravenous (IV) etoposide (VP-16) and oral cyclosporine A.

After a brief clinical improvement, he represented few weeks later with status epilepticus, high grade fever, severe neutropenia and electrolyte imbalance. He was subsequently intubated and admitted to paediatric intensive care unit. His computed tomography (CT) brain showed left frontotemporal subdural effusion which was treated with left burr hole drainage and external ventricular drain catheter insertion. Despite controlling his seizures and broad spectrum antibiotics, he had persistent fever with worsening pancytopenia, deteriorating liver functions and disseminated intravascular coagulopathy. A diagnosis of accelerated HLH secondary to CHS was made and the child was subsequently started on salvage therapy with IV thymoglobulin and IV methylprednisolone. Unfortunately, the child succumbed few days later.

We can confirm that written consent has been obtained from the caregiver for the production of this manuscript.

DISCUSSION

CHS is a rare yet well described autosomal recessive disorder often diagnosed during infancy. The condition increases the person's susceptibility to infections and life-threatening haematological complications such as recurrent bleeding and lymphoma like syndromes. Defective granulation of neutrophils and abnormal natural killer (NK) cells remains the hallmark of this childhood disease, which was first described by Chediak, a Cuban haematologist and later reported by Higashi, a Japanese paediatrician giving rise to the syndromic name.[1)]

There are fewer than 500 cases reported worldwide since the first case was reported nearly 20 years ago with only 1 reported case in Malaysia to date.[2)] The typical age of presentation is usually around 5–6 years old but cases diagnosed in adulthood have also been reported.[3)]

https://doi.org/10.14776/piv.2024.31.e14

An earlier presentation at a young age is often associated with poor prognosis and early childhood death. There is no known gender, racial or ethnical predisposition. CHS can present as a spectrum of phenotypes with some children having classical symptoms and some have more atypical presentations.

The genetic defect that results in CHS was recorded in 1996 and mapped to human chromosome 1q42–44 involving the *LYST* gene.[3] This gene effects protein synthesis that maintains storage & secretory granules within lysosomal of leukocytes and fibroblast, dense bodies of platelets, azurophilic granules of neutrophils and melanosomes of melanocytes.[4] Defect in this gene leads to inability of lysosomes to be transported and carry normal function within cells including neutrophils and NK cells rendering it ineffective in killing pathogens, due to impaired chemotaxis and inability to transport melanin effectively into skin cells. Affected individuals almost always carry more than one gene mutation of the identified gene.[4]

Helmi et al suggested in their review that affected children exhibit either classic or mild forms of the disease.[5] Classic CHS presents with oculocutaneous albinism, recurrent bacterial infections and easy bruising. Patients often have light coloured eyes in contrast to their parents. They may also experience photophobia and nystagmus. Infections are largely pyogenic ranging from minor skin infections, pneumonia and deep-seated abscesses with predilection to *Staphylococcus aureus* and β-hemolytic *Streptococcus* organisms. Hepatosplenomegaly is a common finding even in those with normal marrow function to begin with. Around 80–85% of patients in the classical form goes into an accelerated phase manifested by HLH.[6] HLH is often triggered by infections hence identifying and treating infections early is essential. Nonetheless, despite initial response to treatment it is common for HLH to relapse more aggressively. Milder forms do not usually cause early childhood symptoms but would often present with worsening neurological function as they get older. These may consist of peripheral neuropathy, loss of balance, progressive intellectual decline, seizures and rarely Parkinson-like motor disorders and dementia in later stages of life if they survive into adulthood. It is worth noting that clinical manifestations of CHS often overlaps with similar oculocutaneous albinism disorders such as Griselli syndrome, Hermansky-Pudlak syndrome and Vici syndrome. Comparison between their clinical features, investigations and treatment are summarised in **Table 1**.

Diagnosis of CHS can be done by finding characteristic giant cytoplasmic granules in all the granule-containing cells of the body, particularly in white blood cells of the blood and the bone marrow. Under normal light microscopy, hair shafts from CHS patients shows evenly distributed, regular melanin granules, larger than those seen in normal hairs. Under polarized light microscopy, shafts exhibits a bright and polychromatic refringence appearance.[7] In limited resource settings, this useful simple test can be performed and is often pathognomonic for CHS. Definitive diagnosis is based upon identifying mutations in the *LYST* gene which have been recently renamed the *CHS1* gene. The gene is rather large and about 147 mutations have been identified so far and novel mutations have continued to be found.[8]

The discovery of a novel mutation involving the *STK4* gene necessitates a closer examination. *STK4* deficiency has been documented to result in intermittent neutropenias and a compromised T-cell response, leading to B-cell lymphoproliferation and hypergammaglobulinemia.[9] Nehme et al.[10] further described two families with an *STK4* truncation mutation, exhibiting a clinical phenotype characterized by progressive loss of

https://doi.org/10.14776/piv.2024.31.e14

Table 1. Genetic disorders with hypopigmentation and oculoalbinism

	CHS	Griselli syndrome	Hermansky-Pudlak syndrome	Vici syndrome
Mode of inheritance	AR	AR	AR	AR
Incidence	<1 in 1,000,000	<1 in 1,000,000	1 in 500,000	Unknown
Affected gene	*LYST*	*MYO5A*, *RAB27A*, *MLPH*	*HPS1*, *AP3B1*, *HPS3*, *HPS4*, *HPS5*, *HPS6*, *DTNBP1*, *BLOC1S3*, *PLDN*, and *AP3D1*	*EPG5*
Clinical features				
Hypopigmentation	+	+	+	+
Ocular manifestation	+	+	+	+
Immunodeficiency	+	+	+/−	+
Coagulopathy	+	+/−	++	−
Neurological dysfunction	++	+	−	++
Pulmonary fibrosis	−	−	+	−
Cardiomyopathy	−	−	−	+
HLH	++	+	−	−
Investigations				
Neutropenia	++	+	+/−	+/−
Absent NK cytotoxicity	+	+	−	+/−
Giant inclusion bodies in granulocytes	+	−	−	−
Absent delta granules in platelets	−	−	+	−
Hair shaft under polarized light	Polychromatic	Uniformly white	−	−
Treatment of choice	HSCT	HSCT	Supportive Lung transplant if PF	Supportive
Prognosis	Poor if no HSCT	Poor if no HSCT	Good if no lung involvement and bleeding controlled. 10-year survival if PF present	Poor but improves if cardiac and immunological manifestations managed proactively

Abbreviations: CHS, Chediak-Higashi syndrome; AR, autosomal recessive; HLH, hemophagocytic lymphohistiocytosis; NK, natural killer; HSCT, hematopoietic stem cell transplant.

naïve T cells, recurrent skin and respiratory infections, and autoimmunity. Additional reports have linked *STK4* mutations to mild cardiac anomalies and a predisposition to lymphoma.[11] Despite this, the significance of *STK4* in relation to other inborn errors of immunity, such as CHS, remains unclear. The accelerated phase of CHS occurs in 85% of cases, yet the factors contributing to or protecting against this phase are not well understood. Nevertheless, we cannot discount the possibility of *STK4* deficiency or another inborn error of immunity playing a role in accelerating complications associated with CHS.

There is no specific treatment of CHS and treatment largely is supportive. This includes aggressive antimicrobial treatment during episodes of bacterial or fungal infections. Antivirals may also be used to treat certain viral infections. Prophylactic antibiotics and G-CSF to correct neutropenia are often used as prophylaxis against further infections. The role of Ascorbic acid in improving immunity in CHS patients have been reported however there are lacking clinical trials to support its use.[12] Live vaccines are generally contraindicated in children with CHS[13] due to concerns regarding immunodeficiency. Blood and platelet transfusions are frequently needed to correct haematological complications. Prior to elective surgical or dental procedures, desmopressin is recommended as prophylaxis for excessive bleeding.[13] In view of oculocutaneous albinism, patients should be educated on skin and eye protection against excessive sunlight. Once patients enter the accelerated phase, treatment should focus on achieving remission with chemotherapy and treating any potential triggers such as infection or malignancy. High dose methylprednisolone, IV immunoglobulin and chemotherapy such as etoposide have been used and help induce transient remission in CHS patients with HLH.[14]

The only curative treatment is allogenic hematopoietic stem cell transplant (HSCT). HSCT reconstitutes normal haematopoietic and immunologic function and correct the NK cell

https://doi.org/10.14776/piv.2024.31.e14

deficiency in patients with CHS.[5] Transplant appears to be most successful if a human leucocyte antigen identical donor is used. The outcome of HSCT also depends on the timing of the procedure with higher cure rates when performed before the accelerated phase and if prior infections can be cleared effectively. Successful HSCT done early in the disease have shown to improve neutrophil and NK cell function and halt progression to accelerate phase or HLH. Nonetheless, even patients who have developed HLH seem to benefit from HSCT and that haploidentical donors also resulted in remission of active disease.[15]

Without treatment, the prognosis of CHS is very poor. Most CHS patients will die before the age of 10 years due to accelerated phase and recurrent overwhelming infections. For patients who receive HSCT, the mean 5-year survival was found to be 62% in a small study of 32 CHS patients.[16] Unfortunately, HSCT does not prevent the development of neurological deficits in later life leading to difficulties in mobilising, ataxia, poor cognition and peripheral neuropathy.[17] It is thought that the degenerative changes in axons and myelin sheaths during the disease progression is non reversible due to neuronal cells with no regenerative capacity.[18] Finally, genetic counselling should be offered to parents of affected children with discussions regarding the risk to future offspring and necessity for early diagnosis and interventions including HSCT.

Despite its rarity, CHS is a well-recognised genetic disorder with distinct clinical and haematological features. This is only the second reported CHS case in Malaysia to date however few cases might be unaccounted for. In resource limited healthcare settings, findings on peripheral blood smear and hair shaft examination would be sufficient in diagnosing a child with CHS. Few variants of *LYST* gene mutation have been implicated but role of other concurrent inborn error of immunity mutation remains uncertain. Treatment of CHS should focus on prevention and timely treatment of infections along with close surveillance of developing accelerated phase. HSCT offers a promising life-saving intervention however difficulties in finding suitable donors remains a problem for many of these young patients.

ACKNOWLEDGEMENTS

Clinical practitioners who have provided the necessary investigative and imaging reports used in this manuscript. We declare no funding or financial support in the production of this manuscript.

REFERENCES

1. Arulappan J, Thomas DS, Wali YA, Jayapal SK, Venkatasalu MR. A child with Chediak-Higashi syndrome-a case study. Curr Pediatr Res 2018;22:69-72.
2. Jayaranee S, Menaka N. Chediak-Higashi syndrome: a case report. Malays J Pathol 2004;26:53-7. PUBMED
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;31:31-6. PUBMED | CROSSREF
4. Siddiqui E, Hanif S. Chediak-Higashi syndrome. Pak J Med Sci 2008;24:328-30.
5. Helmi MM, Saleh M, Yacop B, ElSawy D. Chédiak-Higashi syndrome with novel gene mutation. BMJ Case Rep 2017;2017:bcr2016216628. PUBMED | CROSSREF
6. Patne SC, Kumar S, Bagri NK, Kumar A, Shukla J. Chédiak-higashi syndrome: a case report. Indian J Hematol Blood Transfus 2013;29:80-3. PUBMED | CROSSREF

7. Valente NY, Machado MC, Boggio P, Alves AC, Bergonse FN, Casella E, et al. Polarized light microscopy of hair shafts aids in the differential diagnosis of Chédiak-Higashi and Griscelli-Prunieras syndromes. Clinics (Sao Paulo) 2006;61:327-32. PUBMED | CROSSREF
8. Morimoto M, Nicoli ER, Kuptanon C, Roney JC, Serra-Vinardell J, Sharma P, et al. Spectrum of *LYST* mutations in Chediak-Higashi syndrome: a report of novel variants and a comprehensive review of the literature. J Med Genet 2024;61:212-23. PUBMED | CROSSREF
9. Abdollahpour H, Appaswamy G, Kotlarz D, Diestelhorst J, Beier R, Schäffer AA, et al. The phenotype of human *STK4* deficiency. Blood 2012;119:3450-7. PUBMED | CROSSREF
10. Nehme NT, Schmid JP, Debeurme F, André-Schmutz I, Lim A, Nitschke P, et al. MST1 mutations in autosomal recessive primary immunodeficiency characterized by defective naive T-cell survival. Blood 2012;119:3458-68. PUBMED | CROSSREF
11. Upton J. Immunodeficiencies with hypergammaglobulinemia: a review. LymphoSign Journal. 2014;2:150113084544003. CROSSREF
12. Boxer LA, Watanabe AM, Rister M, Besch HR Jr, Allen J, Baehner RL. Correction of leukocyte function in Chediak-Higashi syndrome by ascorbate. N Engl J Med 1976;295:1041-5. PUBMED | CROSSREF
13. Lozano ML, Rivera J, Sánchez-Guiu I, Vicente V. Towards the targeted management of Chediak-Higashi syndrome. Orphanet J Rare Dis 2014;9:132. PUBMED | CROSSREF
14. Aslan Y, Erduran E, Gedik Y, Mocan H, Yildiran A. The role of high dose methylprednisolone and splenectomy in the accelerated phase of Chédiak-Higashi syndrome. Acta Haematol 1996;96:105-7. PUBMED | CROSSREF
15. Sparber-Sauer M, Hönig M, Schulz AS, zur Stadt U, Schütz C, Debatin KM, et al. Patients with early relapse of primary hemophagocytic syndromes or with persistent CNS involvement may benefit from immediate hematopoietic stem cell transplantation. Bone Marrow Transplant 2009;44:333-8. PUBMED | CROSSREF
16. Tardieu M, Lacroix C, Neven B, Bordigoni P, de Saint Basile G, Blanche S, et al. Progressive neurologic dysfunctions 20 years after allogeneic bone marrow transplantation for Chediak-Higashi syndrome. Blood 2005;106:40-2. PUBMED | CROSSREF
17. Eapen M, DeLaat CA, Baker KS, Cairo MS, Cowan MJ, Kurtzberg J, et al. Hematopoietic cell transplantation for Chediak-Higashi syndrome. Bone Marrow Transplant 2007;39:411-5. PUBMED | CROSSREF
18. Sung JH, Meyers JP, Stadlan EM, Cowen D, Wolf A. Neuropathological changes in Chédiak-Higashi disease. J Neuropathol Exp Neurol 1969;28:86-118. PUBMED | CROSSREF