

CASE HISTORY

A fourteen years old boy from Skardu presented with a three weeks history of

- Pallor
- Fever
- Abdominal distention and
- Lethargy
- There was no history of jaundice, diarrhea, cough or bleeding from any site.

Past history

He gave a history of repeated bouts of fever for the past three years

Physical examination

- He was pale, but did not have jaundice and lymphadenopathy
- The skin showed patches of depigmentation over the face and the trunk
- His hair and left iris also showed depigmentation



- Liver was 3 cm and spleen 5 cm palpable below the costal margin

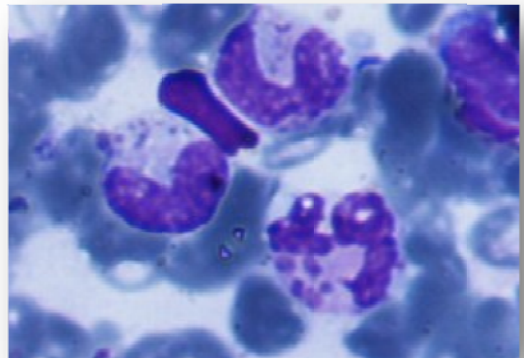
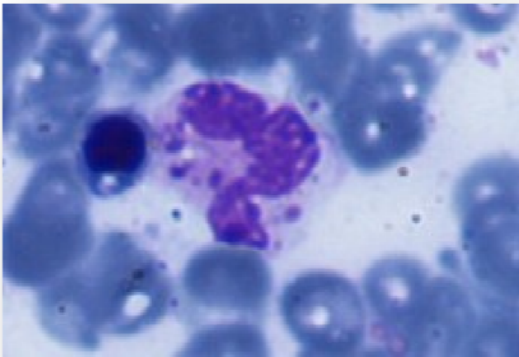
Peripheral blood counts

Hb	6.8 g/dl
White cell count	$3.8 \times 10^9/l$
Platelets count	$34 \times 10^9/l$
Red cell count	$2.60 \times 10^{12}/l$
Hct	21.0 l/l
MCV	81.1 fl
MCH	26.2 pg
MCHC	32.3 d/dl

Differential leucocyte count

Neutrophils	26 %
Lymphocytes	72 %
Monocytes	02 %

Neutrophils showed large dark-brown and pinkish inclusion bodies in the cytoplasm.



Reticulocyte count 2.0%

Red cell Morphology

Normocytic and normochromic

Biochemical Tests

Serum bilirubin	3.1 mg/dl
Serum ALT	82 u/l
Serum alkaline phosphatase	729 u/l
Serum urea	4.5 mg%
Serum creatinine	79 mg%

Clotting profile

Prothrombin Time	Patient	24 sec
	Control	14 sec
APTT	Patient	44 sec
	Control	32 sec

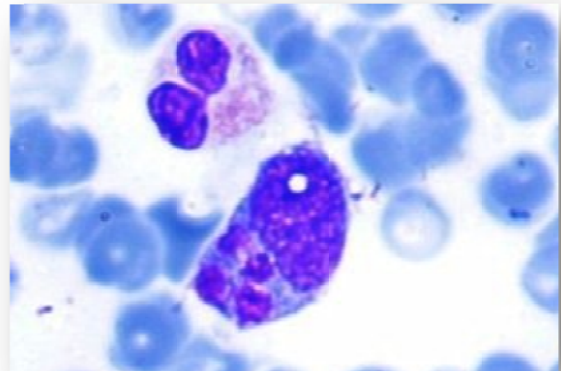
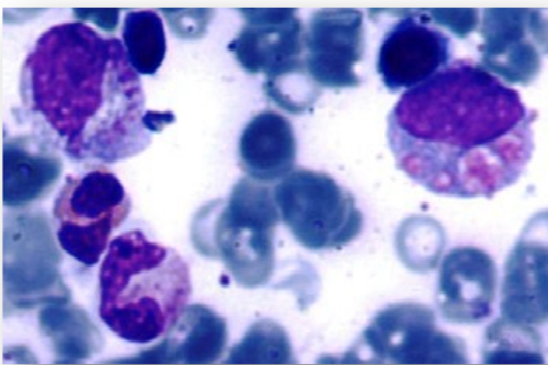
HBsAg Negative

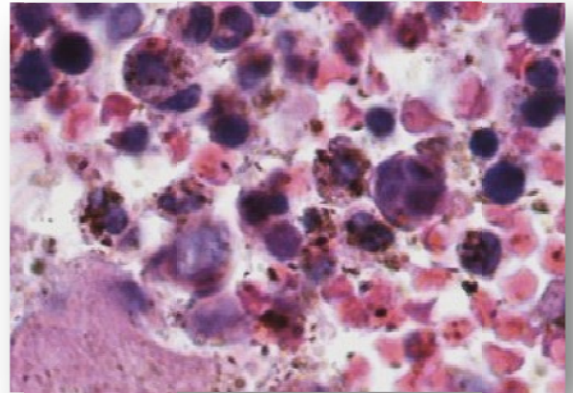
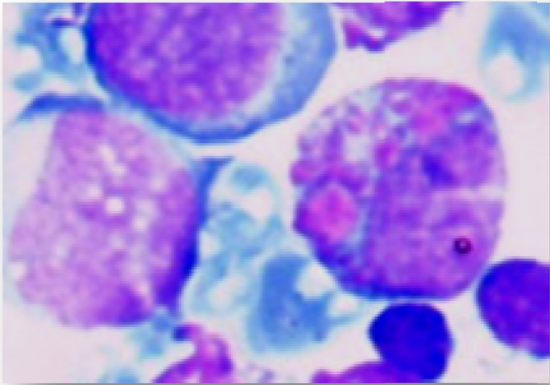
HCV Antibodies Negative

Coombs test: Negative

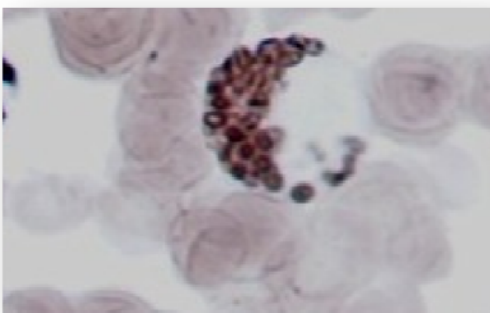
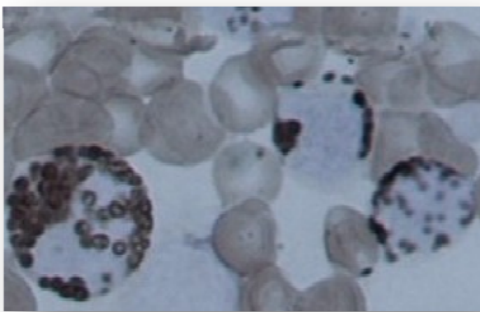
Bone marrow findings

- The findings revealed hypercellular bone marrow smear with myeloid hyperplasia
- Coarse dark brown granules were seen in the myeloid series cells
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These granules were strongly positive for Sudan Black stain



Diagnosis: Chediak-Higashi Syndrome

- Chediak-Higashi syndrome is a rare autosomal recessive disorder characterized by: recurrent pyogenic infections (usually skin, respiratory tract and mucous membrane)
 - partial oculo-cutaneous albinism
 - Nystagmus, photophobia and progressive neurologic abnormalities
 - Mild coagulation defects, and
 - Hepatosplenomegaly.
- However, a definitive diagnosis can only be made when the pathognomonic abnormal large granules are noted in the leucocytes and other granule-containing cells.
- The exact incidence of disease is unknown. Less than 500 cases have been reported worldwide in the past 20 years.
- **Pathogenesis:** The underlying defect in Chediak-Higashi syndrome (CHS) is abnormal organellar protein trafficking that leads to aberrant fusion of vesicles and failure to transport lysosomes to the appropriate site of action.
- The defect is due to a mutation in the lysosomal trafficking regulator (CHS1/LYST) gene at 1q42. This gene effects protein synthesis or/and maintenance of storage & secretory granular lysosomes of leukocytes and fibroblast, dense bodies of platelets, azurophils granules of neutrophils and melanosomes of melanocytes all are involved.¹
 - The large granules within the neutrophils result from abnormal fusion of primary (azurophilic) granules with secondary (specific) granules.^{2, 3}
 - The fusion of the giant granules with phagosomes delays phagocytosis, contributing to the impaired immunity.
 - The same defect is seen in melanocytes resulting in partial oculo-cutaneous albinism due to impaired delivery of melanin from melanocytes to keratinocytes .
 - There may be reduced dense bodies in platelets, which may explain the easy bruising and prolonged bleeding time found in some patients.

- The susceptibility to recurrent infections is explained by the defects noted in T-cell cytotoxicity and natural killer (NK) cell function as well as in chemotaxis and bactericidal activity of granulocytes and monocytes leading generalized cellular dysfunction .⁴
- Affected patients are more susceptible to bacterial and fungal infections, but have a normal resistance to viral infections.
- Majority of patients are diagnosed in infancy due to the severity of the infection or the unusual presentation of the organism. Some escape the diagnosis until adulthood.
- Majority of patients enter the “accelerated phase” of the disease characterized by massive lympho-histiocytic infiltration of virtually all organ systems, like liver, spleen, lymph nodes, bone marrow and central nervous system. Such patients present with persistent fever, hepatosplenomegaly, lymphadenopathy, abnormal liver function tests, pancytopenia, coagulation disorder, ataxia and seizures and more profound immune deficiency.⁵
- The accelerated phase may occur shortly after birth or several years later. If left untreated, the disease proves to be invariably fatal.
- Death among patients with CHS is often due to sequelae of infection.⁶
- **The diagnosis of Chediak-Higashi syndrome is suspected in individuals with any of the following**
 - Partial oculo-cutaneous albinism
 - Pigment dilution of the skin and hair. It may be appreciated at birth on physical examination. However, complete ophthalmologic examination may be necessary to identify the diagnostic finding of reduced iris pigment. Associated findings of nystagmus and decreased retinal pigmentation may also be present.
 - Recurrent infections, especially with *Staphylococcus aureus* and *beta haemolyticus streptococcus*
 - Pancytopenia with hepatosplenomegaly and lymphadenopathy
 - WBC giant granules: The finding of giant granules in polymorphonuclear neutrophils (PMNs) and in other granules containing cells, is the most reliable diagnostic criterion.

- **Mild bleeding tendency:** This is due to deficiency of platelet-dense bodies which are required for the secondary wave of platelet aggregation and is confirmed by platelet aggregation studies.
- Molecular genetic testing of *LYST*, the only gene known to be associated with CH.⁷

Treatment options for CHS patients are limited.

- Previously, the mainstay of treatment has been mainly symptomatic with antibiotics and Vitamin C for bacterial infections and blood product replacement for bleeding complications.
- Subsequently when accelerated phase occurs, etoposide , steroids and intrathecal methotrexate have been tried.
- Splenectomy has been used with some success in the accelerated phase.⁶
- Only recently has allogeneic bone marrow transplantation become a viable option for these patients. However, though transplantation has been shown to correct the hematologic and immunologic complications of CHS thus halting the inevitable grim prognosis, it has not been shown to reverse or prevent further neurological deficit.⁸
This is probably because once the degenerative changes in the axons and myelin sheaths occur in the course of the disease, it cannot be reversed.⁹
- It is important to offer allogeneic bone marrow transplant at an early stage of the disease since the prognosis is uniformly fatal once the disease progresses to the accelerated phase.

References

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