

Case Presentation: **A 19 years old female presented with pallor, enlarged Liver and splenomegaly**

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CASE HISTORY:

A 19 years old female referred to the hematology department of HFH from medicine department for evaluation of Hemolytic anaemia. There was no history of fever, jaundice, bruising or bleeding any site and passage of dark colored urine. There is history of repeated admissions in the hospital for complaints of pallor in the past but was never properly investigated for that. There is history of developing Eclampsia during her first pregnancy two years back for she under went LSCS. She had also received multiple blood transfusions and was already receiving various haematinics by different doctors.

One of her sisters died at the age of 7 years for some undiagnosed transfusion dependent anaemia. She has a 9 month old male child who is healthy.

The labs carried out at that time were as follows:

Hb	8.8 gm/dl
TLC	8.8
Platelets	442
Retics	4.5%
Coombs test	Negative
Serum LDH	283 U/L
G6PD screening	Negative
Hb electrophoresis	Normal (post transfusion)
Osmotic Fragility test	was negative

Urine for hemosiderin	negative
Serum Bilirubin	1.2 mg/dl
ALT	66 U/L
ALP	283 U/L
Serum Albumin	3.6 g/dl
RFTs	Normal
HbsAg & AntiHCV	Negative
Serum Iron	340 ug/dl
TIBC	544 ug/dl
PT	17/12 sec
APTT	40/32 sec

Bone marrow examination was advised but she refused to undergo the procedure. (One year back)

Now she has presented with aggravated symptoms of anaemia for the last 10 days and was experiencing felt pain in the left hypochondrium for the last 08 days. Her examination has revealed marked pallor, an enlarged Liver, 1 cm and splenomegaly of 4 cm below right costal margin. She had pitting edema feet also.

Recent Laboratory investigations revealed

WBC	4.3 x 10 ³ /ul
Hb	6.3 gm/dl
Platelets	356 x 10 ³ /ul
RBC	2.01 x 10 ⁹ /l
MCV	74 fl
MCH	24 pg
Neutrophils	70% & dysplastic

RBC morphology was dimorphic with tear drop cells and Retics were 1.0%

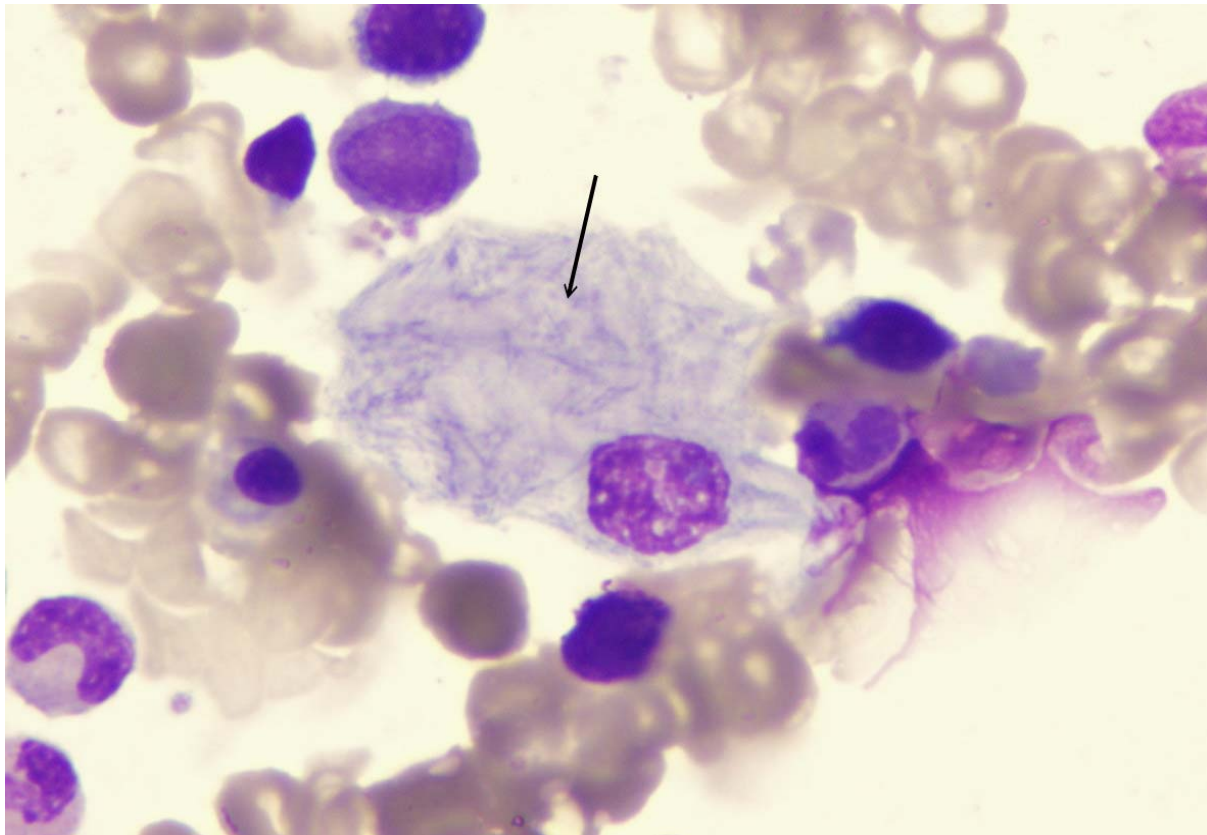
PT	20/13 sec
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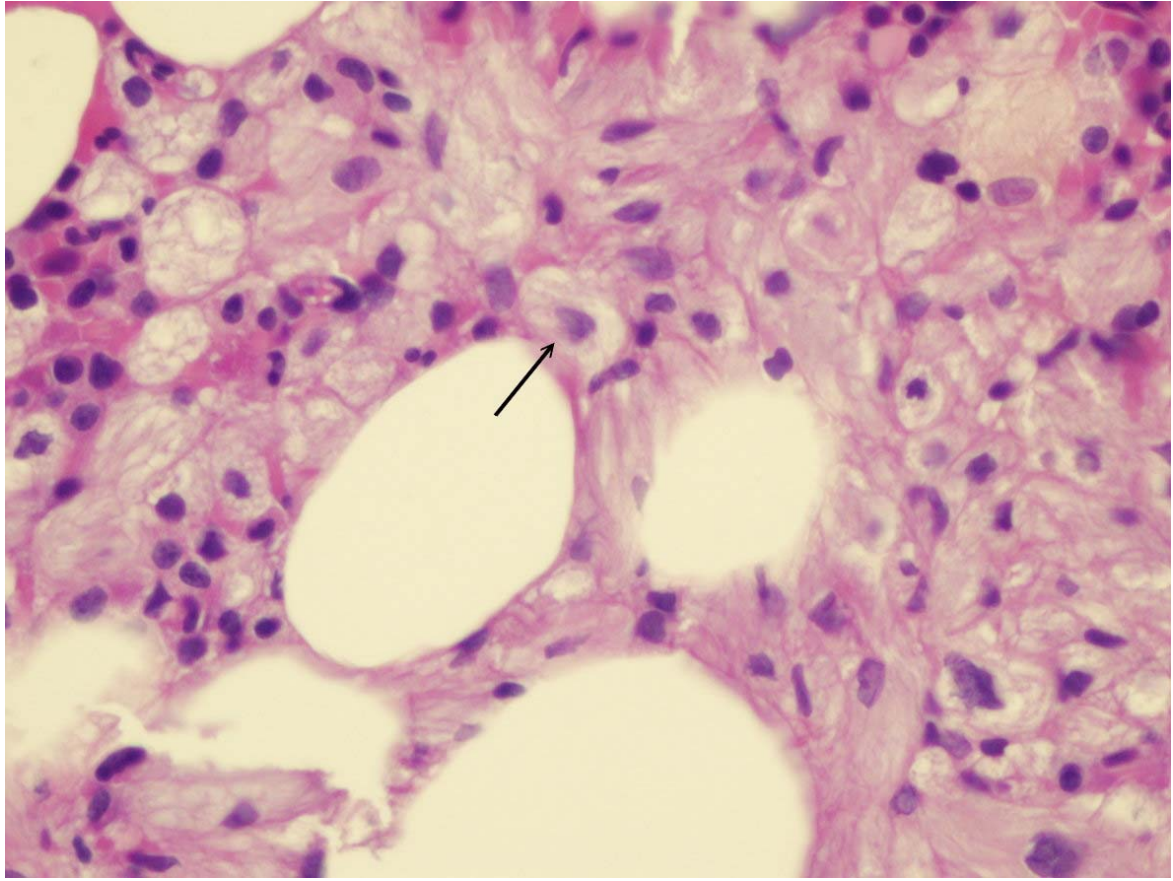
APTT	42/32 sec
Serum Iron	340 ug
TIBC	601 ug
% saturation Transferrin	56%
Hb Electrophoresis	Thalassaemia Trait
PCR	Hetreozygous with Frameshift 8-9 mutation.

Ultrasound abdomen revealed splenomegaly & an adnexal cyst

Bone marrow examination was done this time after taking consent. Findings of aspiration are shown in Fig- 1

Trephine biopsy is seen in Fig- 2





DIAGNOSIS

GAUCHER'S DISEASE TYPE – 1

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BETA-THALASSAEMIA TRAIT

Gaucher disease is a progressive, heterogenous, autosomal recessive disorder that represents a serious health problem. It is the most common lysosomal storage disorder. It is an inherited deficiency of lysosomal enzyme glucocerebrosidase (GC). The enzyme hydrolyses glucosyl ceramide to glucose and ceramide. Incidence is 1 in 60-80,000 individuals.

Pathogenesis basis of disease:

Mutations within GC gene located on chromosome 1q21.

Commonest mutations are N370S in Type – 1 and L444P in Type – 2. These result in mutant enzyme with reduced activity.

Accumulation of Glucosylceramide within the lysosomes of reticuloendothelial cells cause disproportion of cellular organization and disturbance of normal function.

Host reaction to abnormal cells results in cytokine release (IL-1, IL-6, TNF).

Cellular proliferation and increase of other enzyme levels.

Clinical features:

Caused by the accumulation of glucocylceramide laden macrophages (Gaucher cells) in the spleen, liver and bone marrow.

Anaemia	CNS
Splenomegaly	Pulmonary
Hepatomegaly	Renal

Bone pain

Skin

Manifestations	Type 1	Type 2	Type 3
Hepatosplenomegaly	++	+/-	+
Bone disease	++	-	+/-
Cardiac valve disease	-	-	+
CNS disease	-	+++	+/-
Oculomotor apraxia	-	+	+/-
Corneal Opacities	-	+/-	+/-
Age at death	60 – 90 yrs	< 5 yrs	< 30 yrs

Laboratory Investigations:

Blood CP

Cytopenias (uni or trilineage)

Coagulation profile

- Bleeding time prolonged
- D-dimers elevated
- Factors II, VII, X, XII reduced
- Platelet function abnormal

Bone marrow examination

Ferritin	elevated
Acid phosphatase	elevated
LFTs	deranged

Lipid profile

■	Cholesterol	reduced
■	LDL	//
■	HDL	//

Immunoglobulins	elevated
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Paraproteins	//
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IL-1, IL-6, IL-8,	//
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IL-10 and TNF-

Confirmatory tests:

PCR for genetic mutations

■	N370S
■	L444P

Enzyme assay

■	Glucocerebrosidase (absent or very low levels)
■	Chitotriosidase (normal 4-76 nmol/ml)
■	CCL18/PARC

Other investigations:

Skeletal survey

Abdominal Ultrasound

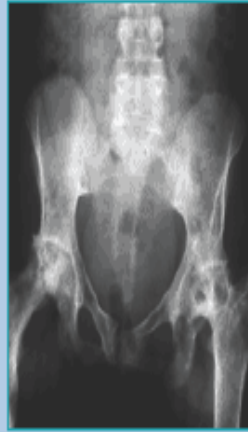
CT Scan

MRI

Gaucher Disease: Bone Manifestations



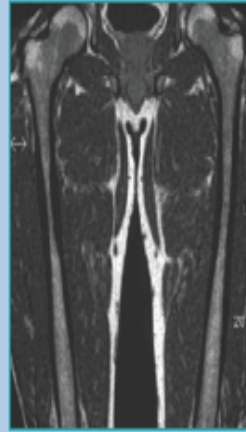
Osteopenia



Avascular necrosis
(AVN)



Erlenmeyer flask
deformity



Bone Marrow
Infiltration

Staging

Gaucher's Disease Severity Score Index (SSI).

Max score 42

<u>Skeletal domain</u>	Score 11	<u>Hematological domain</u>	Score 10
Bone marrow infiltration based on MRI		Hemoglobin concentration	
		> 12 g/dl (male) > 11.5 (female)	0
absent/minimal	0	between 10-12 g/dl	1
mild	1	< 8 g/dl or need for blood transfusion	3
severe	3		
		White blood cell count	
Osteonecrosis		> 4x10 ⁹ /L	0
None	0	2.5 - 4 x 10 ⁹ /L	1
medullary infarction	1	< 2.5 x 10 ⁹ /L	2
osteonecrosis	2	< 1.9 x 10 ⁹ /L	3
		Platelet count	
Pathological fractures		> 150 x 10 ⁹ /L	0
Reported	2	60-100 x 10 ⁹ /L	2
		< 60 x 10 ⁹ /L	3
		Bleeding time	
		< 8 min	0
		> 8 min	1

Biomarker domain **Score 3**

Serum chitotriosidase or CCL18	
Chitotriosidase < 600 nmol/ml x h	0
Chitotriosidase > 15,000 nmol/ml x h	3
CCL18 <72 ng/mL	0
CCL18 > 1000 ng/mL	3

Visceral domain **Score 11****Spleen**

no MR/US lesions	0
MR/US lesions	3
no splenectomy	0
splenectomy	2
volume < 5 N	0
between 5-9 N	1
between 10-15 N	2
volume > 15 N	3

Liver

no hepatic disease	0
hepatic disease	3
volume < 1.25 N	0
between 1.25 - 2.5 N	1
volume > 2.5 N	2

Lung domain **Score 4**

Pulmonary hypertension	
absent	0
moderate	1
severe	2

Respiratory failure	
absent	0
moderate	1
severe	2

Neurological domain **Score 3**

No signs/symptoms	0
Peripheral neuropathy	1
Parkinson's disease/parkinsonism	3

Treatment:

Supportive treatment

- Transfusion
- Biphosphonates

Enzyme Replacement Therapy (ERT)

- Imiglucerase

Substrate Reduction Therapy (SRT)

- Miglustat

Bone Marrow Transplant

Gene Therapy

Monitoring:

Chitotriosidase

CCL18/PARC

Annual skeletal MRI