Gaucher Disease: a multiorgan rare disease in Internal Medicine

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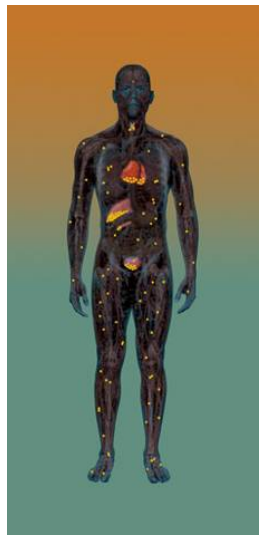
Rare Diseases

- Do I have as Internist the chance to deal with rare diseases?

YES

Rare Diseases: issues

- ✓ Multiorgans disorders
- ✓ Approached by “organ’s specialist” (Gastroenterologist, Hematologist, Reumatologist…)
- ✓ Inappropriate therapies



consequences

- ✓ Misdiagnosis/underdiagnosis
- ✓ Delay in diagnosis

- **Female 64 years old (b.1946)**
- **She experienced acute bone pains (diagnosed as osteomyelitis) between 10 – 14 years of age**

- At 20 years – diagnosed with chronic hepatitis referred to hepatologist
- **Splenectomy** because of splenomegaly of unknown aetiology
- 26 years: liver cirrhosis, slight hepatomegaly and cholestasis – no viral markers

- 58 years (2004): anaemia, haemorrhagic episodes – referred to haematologist BM biopsy: Gaucher cells. **No action taken**
- at age 60 (2006) further findings hepatomegaly (+14-19cm), Hg 6.0-8.0g/dL, mild leucopenia, normal thrombocytes, diffuse osteopenia and coxarthrosis

GD diagnosis confirmed with enzyme assay

- **Female 64 years old (b.1946)**
- **She experienced acute bone pains (diagnosed as osteomyelitis) between 10 – 14 years of age**

- She was misdiagnosed
- Spleen was removed although“splenomegaly of unknown aetiology”
- Diagnosis of Gaucher Disease was made 44 years after the initial symptoms
- She has a very poor QoL

Mr S.B, age 36 yrs,
officier in a library. Married

- Active sportman, had lack of energy, tiredness since few months leading to sport activity restriction

- No other symptoms but mild, occasional peripheral sensory loss
- Family History: southern italian origin. Parents apparently in good health. 3 brothers, 2 sisters

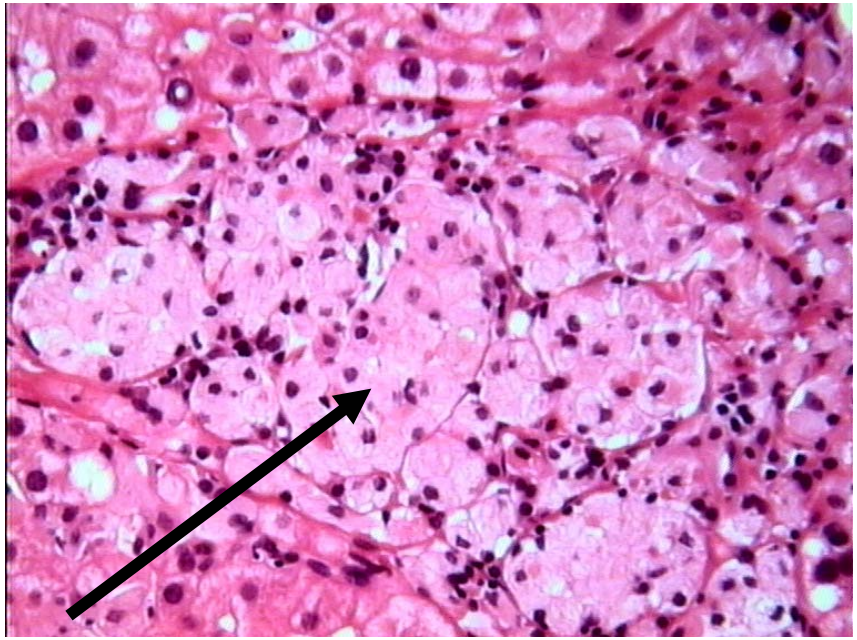
More clues……

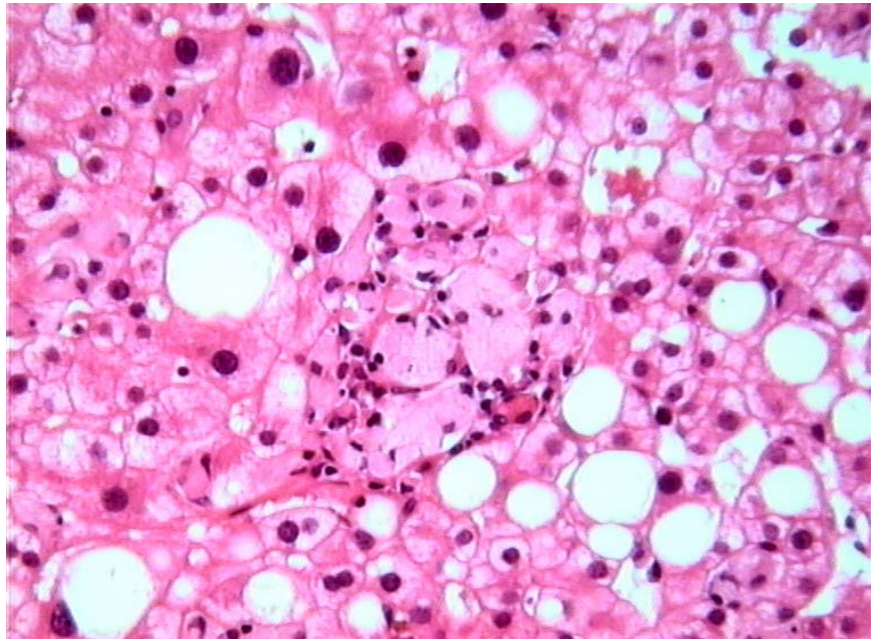
- Hb: 12.5 g/dl ; MCV: 81 fl
- WBC: 6.2/10^9l Neuts: 5.9; Lymph: 3.8
- Platelets: 88/10^9l
- AST: 37 U/L, ALT: 87 U/L, gGT: 35 U/L
- Tot. Bilirubin: 1.7 mg/dl, Unconj: 1.3 mg/dl
- Iron:84 mg/dl; Transferrin saturation:30 %;
- Ferritin: 1400 ng/ml;
- HCV, HbsAg: negative
- Blood film: normo/microcytic cells; poichylocitosis
- Hb pattern; G6PD activity: normal

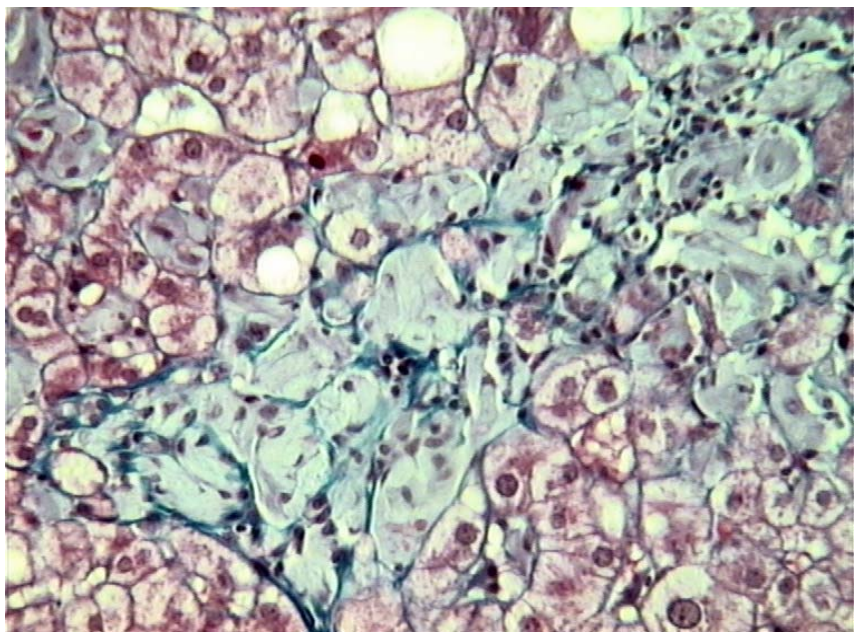
Liver enlargement (4 cm); spleen enlargement (3 cm)

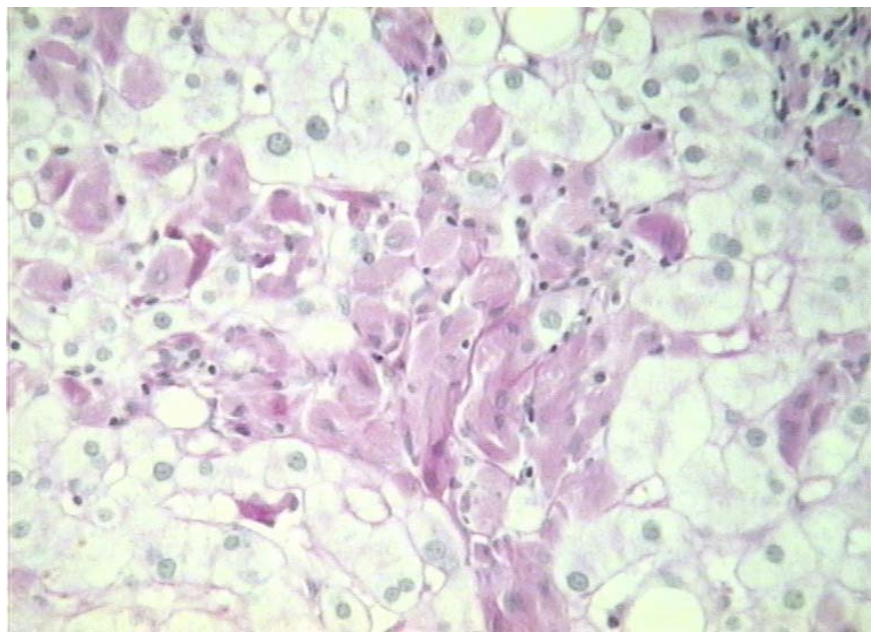
Suspected diagnosis

- Viral neurophaty (neurologist)
- Mononucleosis
- Viral Hepatitis/Cirrhosis (Hepatologist)
- Lymphoma (Hematologist)



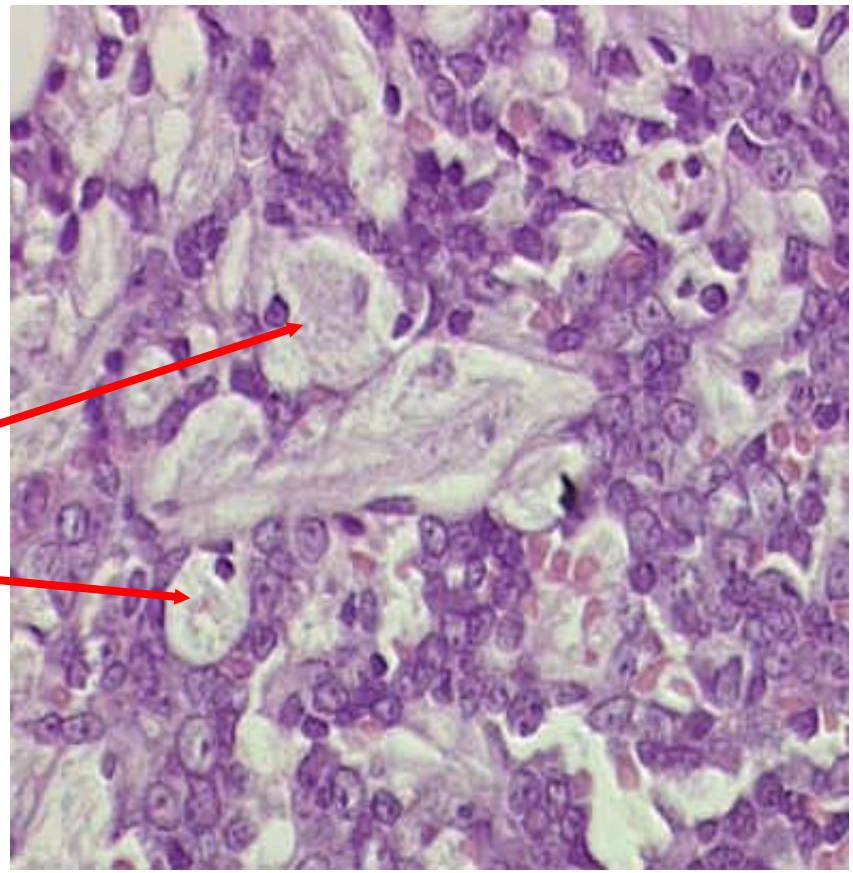




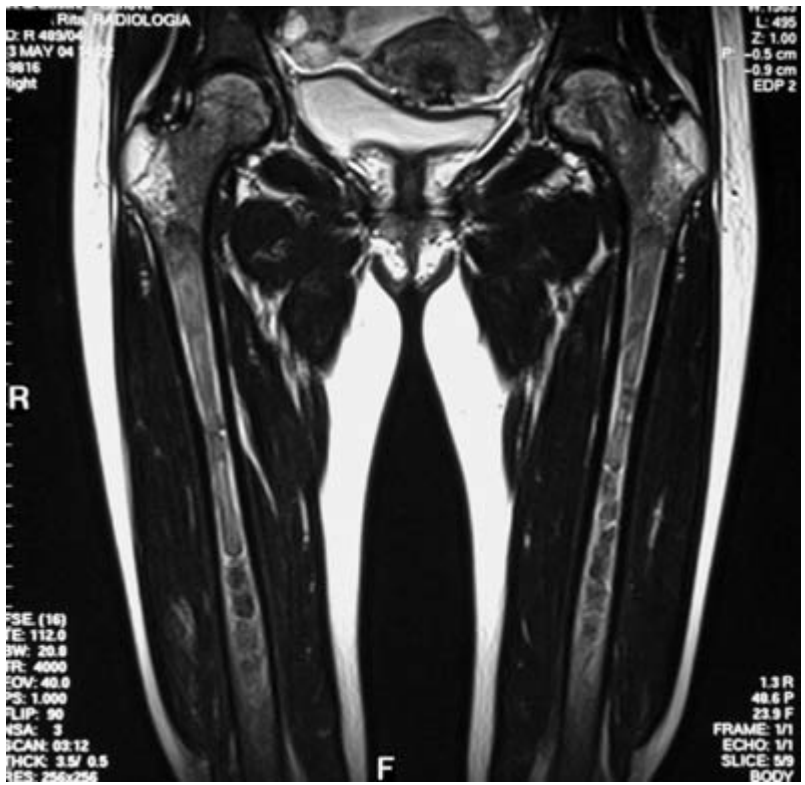


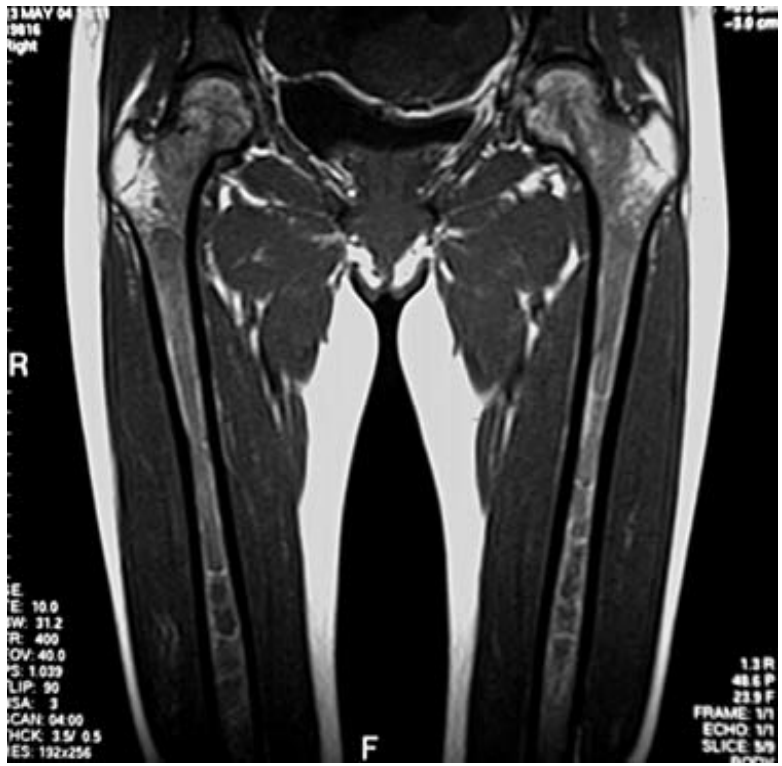
Bone marrow aspirate

Gaucher like cells?



Keck School staging :1a





Mr S.B, age 36 yrs,
officier in a library. Married

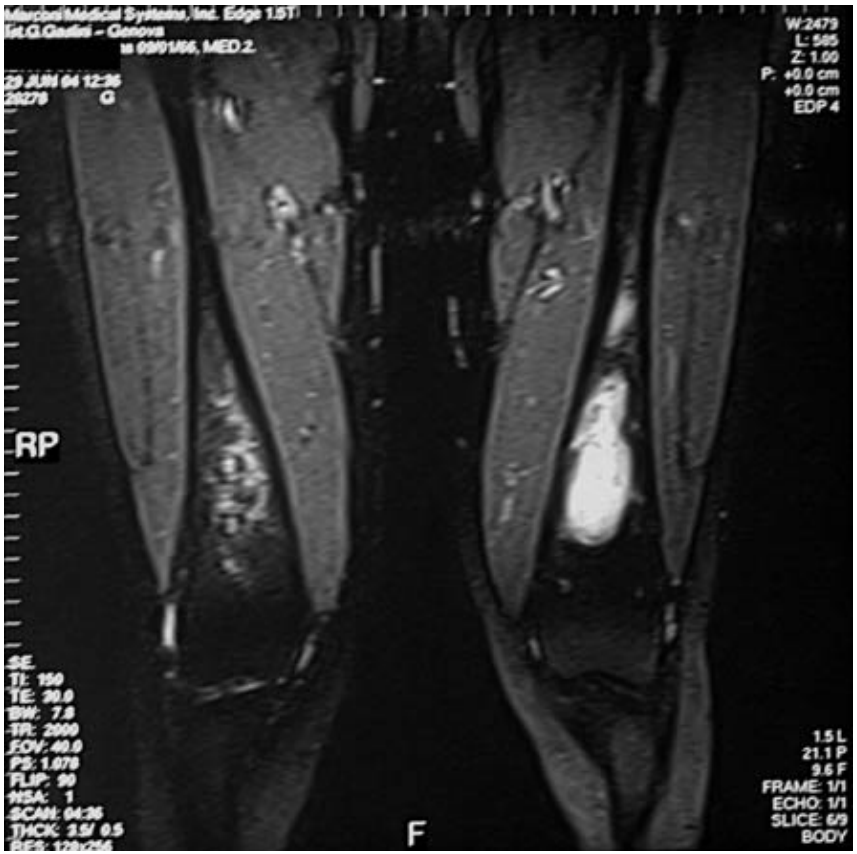
- More than 1 year before diagnosis was made
- He visited 4 different specialists
- He underwent 2 invasive exams (BM, Liver biopsy)
- The diagnosis in presence of splenomegaly, anemia, thrombocytopenia should have been suspected and made by enzyme measurement

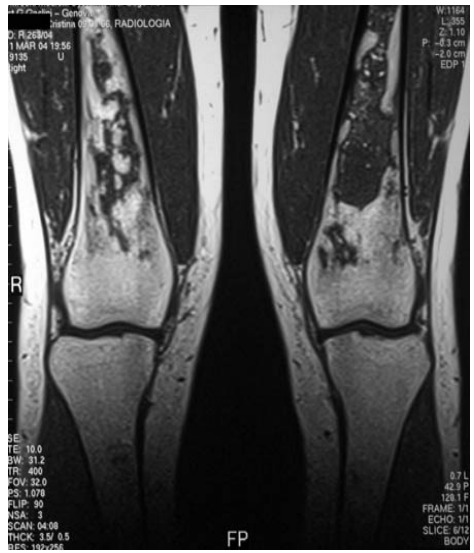
- **37 year old female**
- **She reported severe back pain at 11 years of age – wore body cast for 3 months**

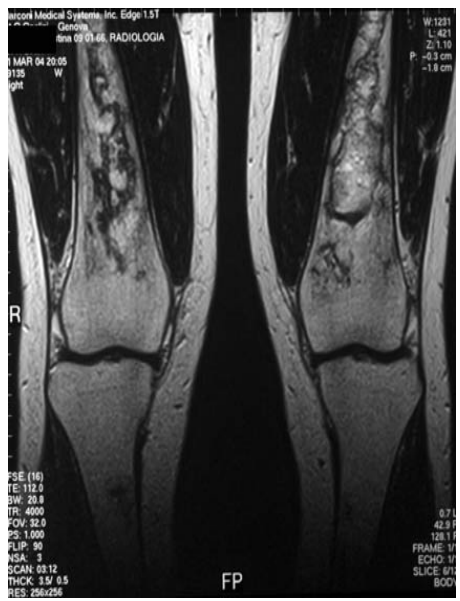
- When she was 26 year old one sister was diagnosed with symptomatic GD
- Family screen showed she had mild splenomegaly, Hg: 13.0g/dL, platelets: 135,000/uL
- Homozygous for N370S
- Informed – mild form of disease no need for further follow up

- At age 30 – bone crisis in distal femur : Hg 10.3g/dL, platelets: 121,000/uL, liver vol 1.4 x n, spleen 7.5 x n
- X-ray: AVN and compression fracture of T7 vertebra at site of previous back pain
- DEXA: severe osteoporosis T score: -2.8
- At age 30 years: enzyme replacement therapy initiated
- At 35 years: hip replacement surgery: bone marrow in left femur entirely destroyed by AVN

Kecking school staging : 3b







- **37 year old female**
- **She reported severe back pain at 11 years of age – wore body cast for 3 months**

- She had the diagnosis, but because of lack of knowledges she remained untreated

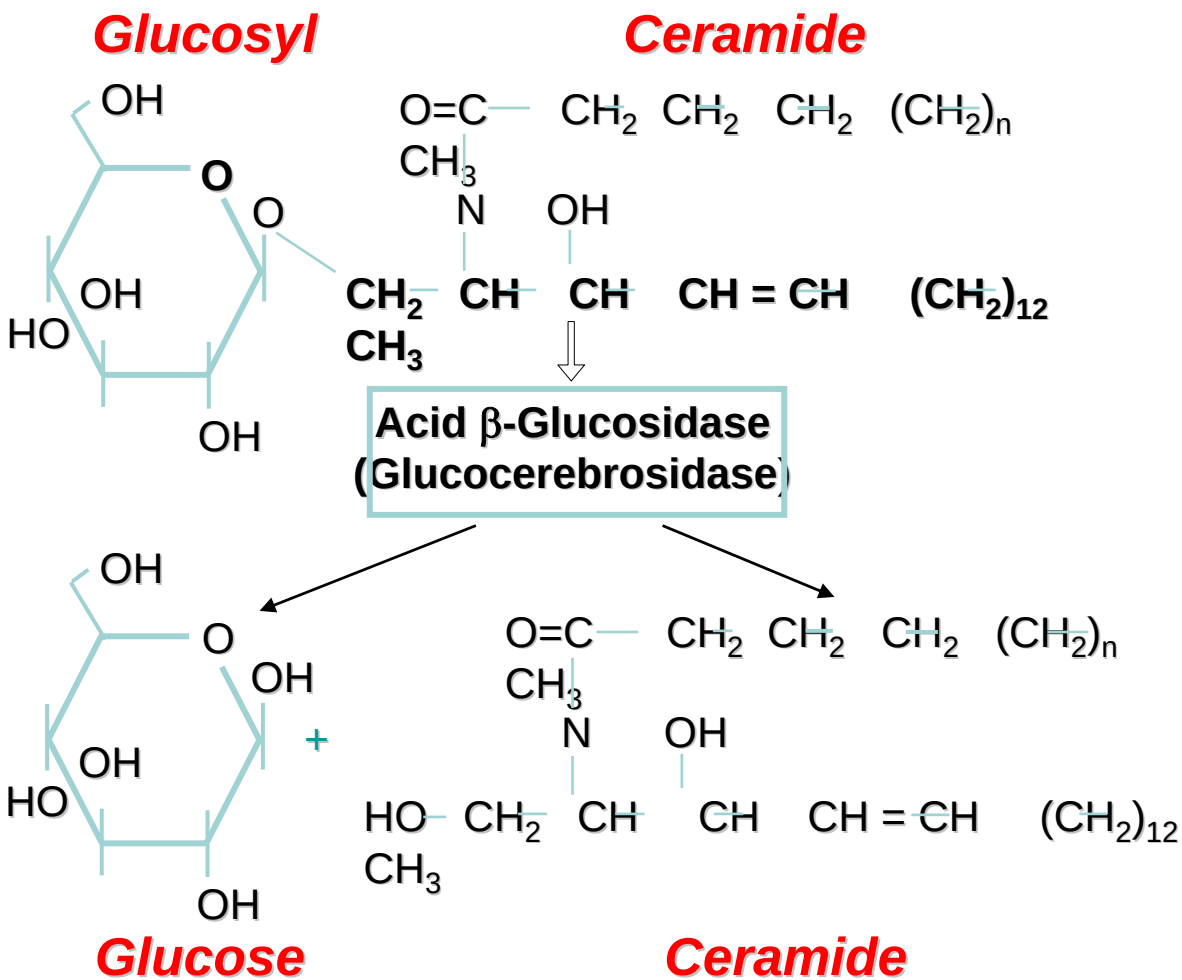
- The consequences are life-long limiting

Pathophysiology of Gaucher disease

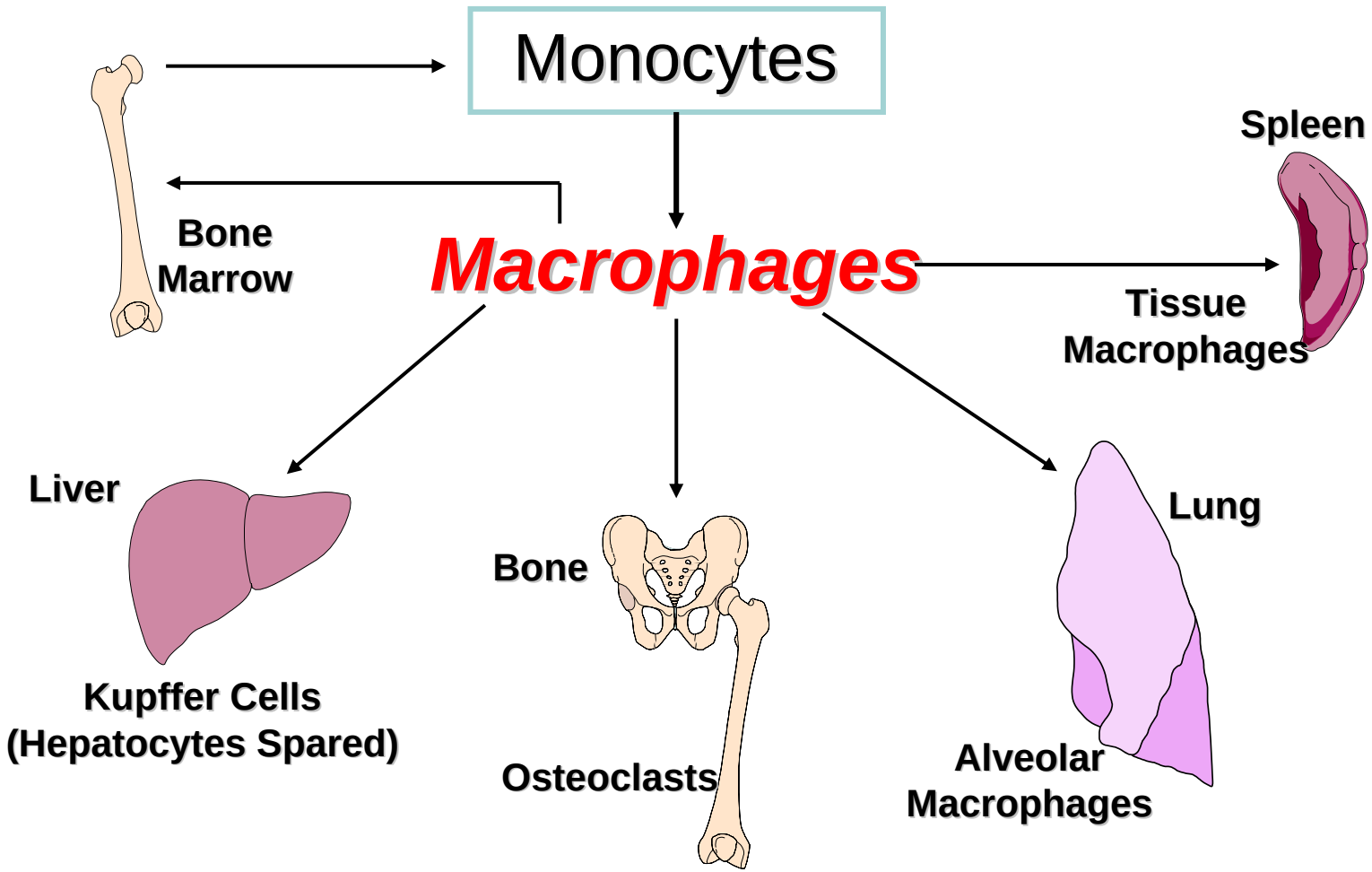
- GD caused by inherited deficiency in acid beta-glucosidase (glucocerebrosidase, GBA)
- Leads to glucocerebroside accumulation in lysosomes of macrophages
- Glycolipid laden cells (Gaucher cells) infiltrate organs to cause multisystem disease
  - Most commonly: spleen, liver, bone marrow,
  - Less commonly: lungs, lymphatic system, skin eyes, heart, kidneys, nervous system

Beutler & Grabowski 2001. In: Scriver et al eds The metabolic and Molecular Bases of Inherited Disease. 8th Ed NY: Mc Graw-Hill: 3635-3668

The Enzymatic Defect in Gaucher Disease



The Pathophysiology of Gaucher Disease



Pathophysiology of Gaucher disease

- Classified into 3 subgroups:
  - Type 1 – non neuronopathic (94%)
  - Type 2 – acute neuronopathic (1%) (death in infancy)
  - Type 3 – chronic neuronopathic (5%) (death in childhood/early adulthood)

- Phenotype affected by numerous mutations/genetic modifiers

Beutler & Grabowski 2001. In: Scriver et al eds The metabolic and Molecular Bases of Inherited Disease. 8th Ed NY: Mc Graw-Hill: 3635-3668

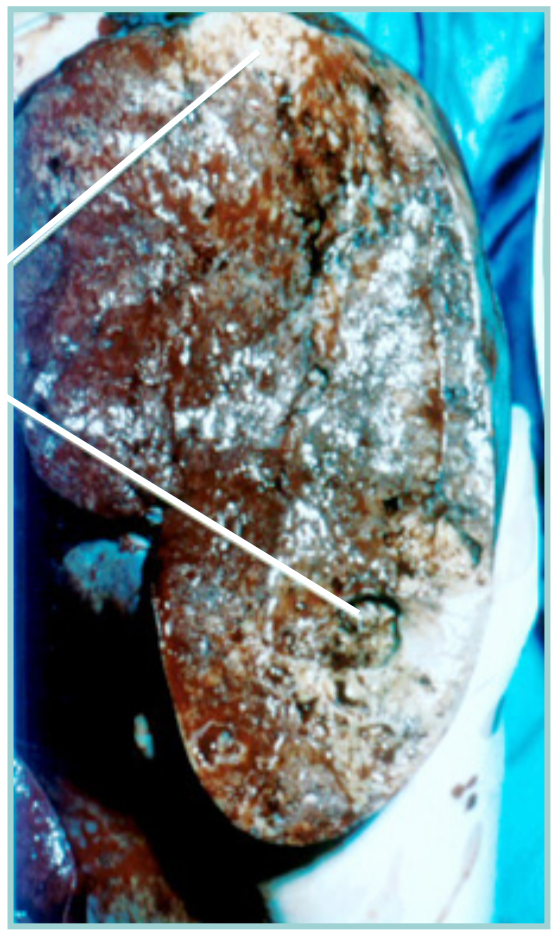
Why a delay in diagnosis?

- Gaucher disease is a phenotypically heterogeneous disease
- There is enormous variation in:
  - Age of onset
  - Rate of progression
  - Organs affected
  - Disease severity across individuals
  - Severity of disease across organs in one individual
  - Presenting symptoms
- Even in individuals of same genotype

Amato et al 2004: J Inherit Metab Dis:27(5):659-69

Gaucher Disease Type 1

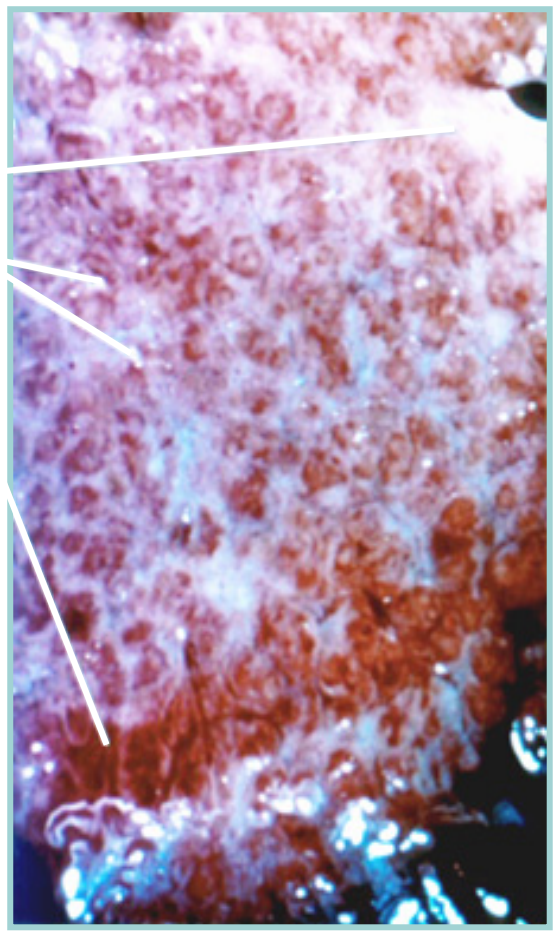
Splenic Accumulation (Gross)



- White-yellow streaks show accumulated Gaucher cells and fibrotic scarring

Hepatic Gaucher Cells

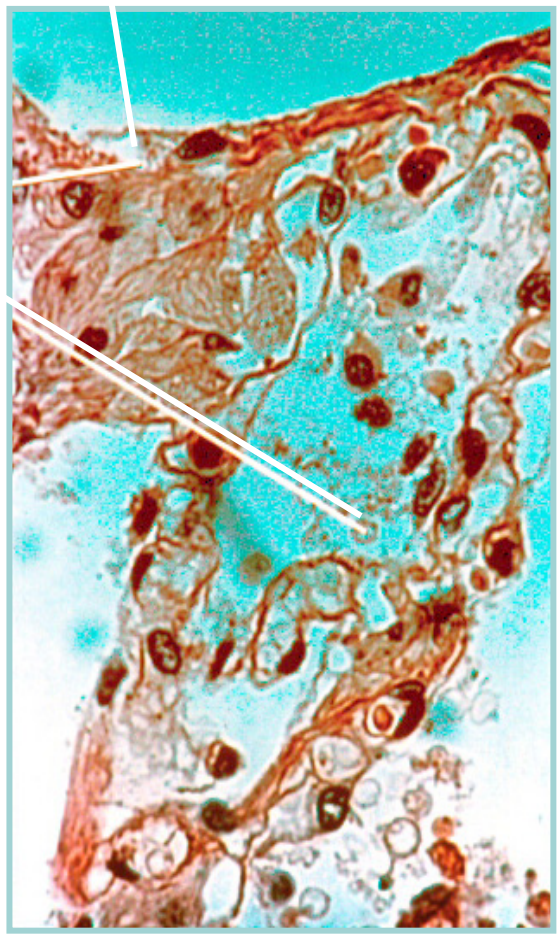
- Kupffer cells engorged with glucocerebroside. Hepatocytes (red staining cells) do not store glucocerebroside.
- Fibrosis and scarring are frequently present in affected livers.



Lung Gaucher Cells

Interstitial macrophages

Alveolar macrophages



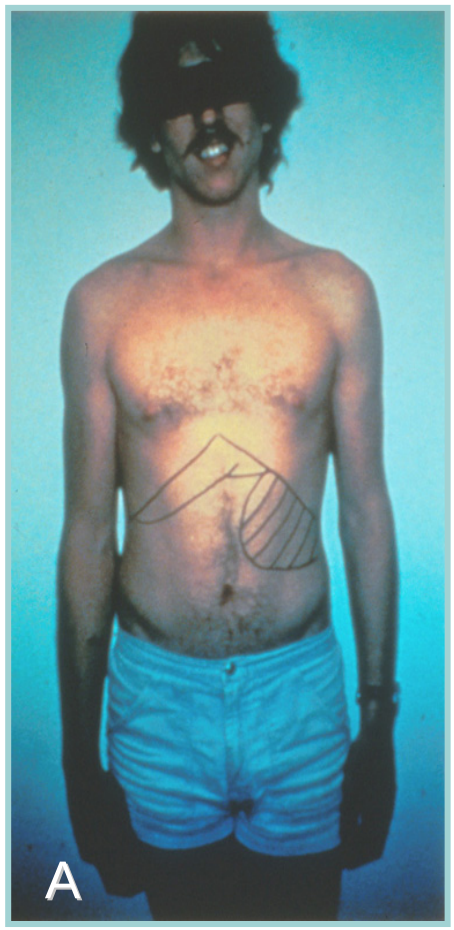
- Significant lung involvement, shown here, is unusual
- Gaucher cells are present as interstitial and alveolar macrophages
- Pulmonary involvement indicates a poor prognosis

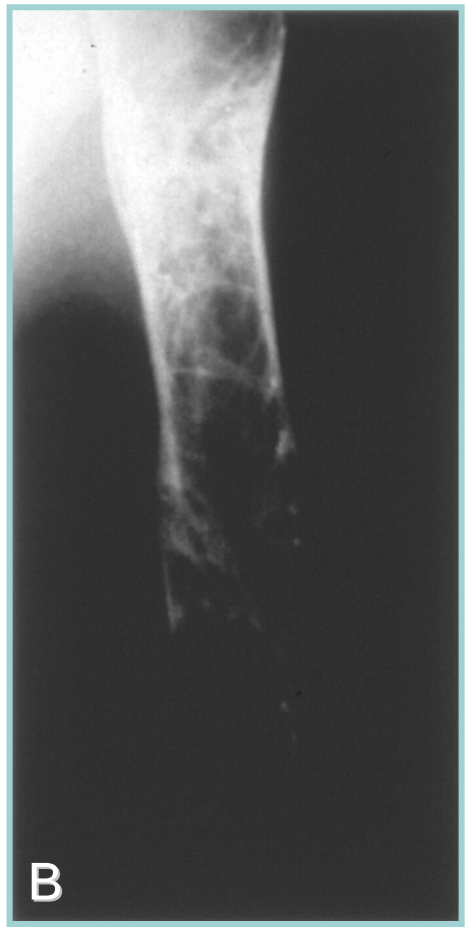
Gaucher Disease Type 1

Are you Missing the Diagnosis?

A. Type 1 patient with what appears to be mild disease expression.

B. Bone films of the same Type 1 patient demonstrating significant bone involvement.

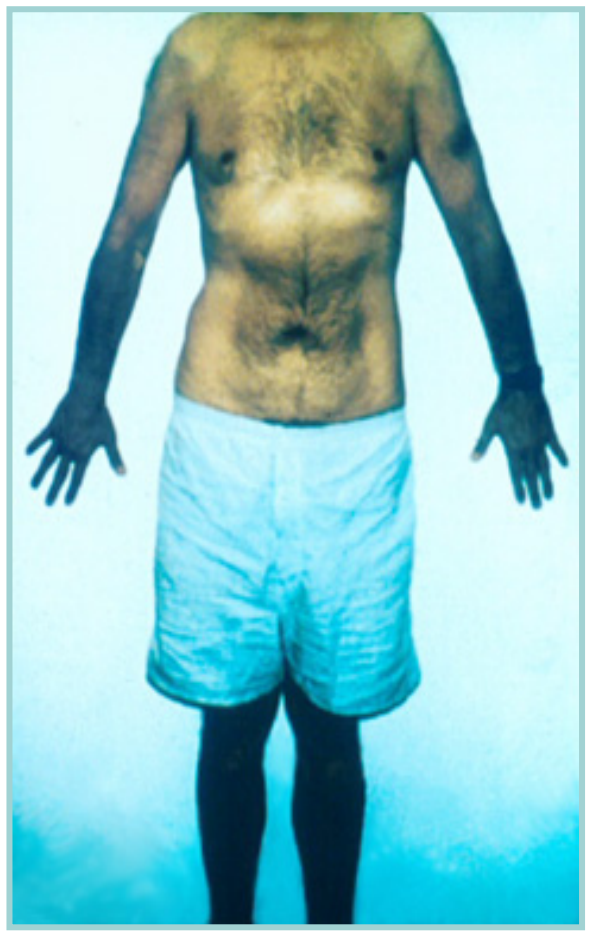




Gaucher Disease Type 1

Asymptomatic
60-Year-Old Male

- Patient exhibits minimal signs.
- Disease should be monitored regularly for signs of progression.
- He has a high risk to develop myeloma



Gaucher Disease – Type 1

Common Presentations of Gaucher Disease - Type 1

- Painless spenomegaly, usually with hepatomegaly
- Anemia, thrombocytopenia
- Fatigability
- Easy bruising
- Excessive postoperative or postpartum bleeding

- Menorrhagia
- Aseptic necrosis of hips or humeri
- “Growing Pains” - children
- Legg-Calve-Perthes disease - children
- Growth failure - children
- Spontaneous fractures
- Bone disease

Hematological malignancies in Gaucher disease

- ✓ The relative risk of cancer in patients with Gaucher disease is 3.6
- ✓ Moreover the relative risk of a hematoligic malignancy is 14.7
- ✓ The most frequent hematologic malignancy are: myeloma, chronic lymphocytic leukemia, Hodgkin's disease, acute leukemia, non-Hodgkin's lymphoma

Treatment of Gaucher Disease

- ✓ Enzyme replacement Therapy (ERT)
- ✓ Substrate inhibition therapy (SIT)
- ✓ Small molecules (chaperone)
- ✓ Bone marrow transplantation
- ✓ Gene therapy
- ✓ Adjunctive medication or intervention

Treatment of Gaucher Disease

- Gaucher disease
  - Chronic
  - Multisystemic
  - Highly variable (pattern, severity, progression)
- Disease heterogeneity→management cannot be homogeneous
- Patient-centered
- Goal-oriented approach is critical for individual tailoring of therapy

At Diagnosis

- Hb: 12.5 g/dl ; MCV: 81 fl
- WBC: 6.2/109l Neuts: 5.9; Lymph: 3.8
- Platelets: 88/109l
- AST: 37 U/L, ALT: 87 U/L, gGT: 35 U/L
- Tot. Bilirubin: 1.7 mg/dl, Unconj: 1.3 mg/dl
- Iron:84 mg/dl; Transferrin saturation:30 %;
- Ferritin: 1400 ng/ml;

After 1 year of treatment

- Hb: 13.5 g/dl ; MCV: 83 fl
- WBC: 6.7/10^9l Neuts: 5.7; Lymph: 3.4
- Platelets: 137/10^9l
- AST: 27 U/L, ALT: 27 U/L, gGT: 35 U/L
- Tot. Bilirubin: 1.0 mg/dl, Unconj: 0.7 mg/dl
- Iron:118 mg/dl; Transferrin saturation:28 %;
- Ferritin: 475 ng/ml;

Spleen and liver reduced by 40%

Take home messages

- Rare diseases affect in Europe more than 35 million people
- Rare diseases must be suspected by internists
- Early diagnosis save lifes
- Rare diseases are orphan: urgent needs for improving knowledges and for investing in research