Skeletal Aspects of Gaucher Disease: Radiological Findings and Functional Use

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Image obtained from www.ADAM.com
We will begin with an overview of Gaucher disease. Knowledge of the disease on a cellular level will aid our understanding of how radiology plays a critical role in the diagnosis and on-going assessment of the skeletal components of Gaucher disease.
Gaucher Disease:
A lysosomal storage disease with a cascade of systemic effects

• Autosomal recessive inborn error of metabolism

• Defective β-glucosidase ⇒ accumulation of glucocerebrosid (lipid membrane component) in macrophages

• Macrophage behavior altered ⇒ Gaucher cells
  - Increased inflammatory behavior via cytokine release
  - Increased metabolic activity
  - Increased secretion of acid hydrolases

Gaucher cell with classic “tissue paper” appearance
Cellular level:
Pathologic link between lipid accumulation and altered cellular function remains unclear, however, aberrant behavior disturbs organ functioning by two mechanisms, as described below.

Organ/Systemic Level:
Primarily arises because of:
1. Space-occupying accumulation and lesions, such as in the marrow canal
2. Inflammation
PRIMARY ORGANS/SYSTEMS EFFECTED:

Liver
Kupffer cell accumulation
Hepatomegaly

Lung
Infiltration, Pulmonary Arterial HTN

Spleen
Splenomegaly
RES, platelet sequestration

Bone
Bone Marrow

Dependent upon the type of Gaucher disease, the brain may also be effected
While in this presentation we will focus upon the skeletal aspects of Gaucher disease, it is important to consider the other systemic ramifications in assessing bone involvement.

For example, splenectomy has been associated with increased bone involvement and destruction, as without splenic sequestration, Gaucher cells appear to accumulate more in the marrow cavities.
Three main forms

I: Non-neuropathic

II: Acute, neuronopathic → Neuronal damage
   Death in early infancy

III: Chronic, neuropathic → Neuronal damage
   Death in childhood, early adulthood

Autosomal Recessive

• 1q21
• Almost 200 known SNPs
• N370S is ~50% of mutations

www.bioethics.org
**TYPE I GAUCHER DISEASE**

Prevalence:
- 1 in 50,000 – 100,000
- Highly concentrated within the **Ashenazi Jewish** population, where prevalence can be as high as **1 in 500**

Estimated **20,000 individuals in the US**

Variable “penetrance”: Even amongst monozygotic twins, presentation is extremely varied in form and severity?
  - Environmental influence

Lab studies show increased chitotriosidase

**NOW ON TO OUR FOCUS**
Type I Gaucher Disease:
The role of radiology in diagnosis and disease assessment

Image obtained from www.ADAM.com
INDEX PATIENT: HISTORY AND PRESENTATION

CC/Identifying information: A 43 yo male with severe R knee pain and a history of Gaucher disease, as well as osteomyelitis and R below knee amputation

PMH:
• S/p splenectomy at age 15
• Ascites
• True and Pseudo-osteomyelitis
• Multiple bone infarcts and necrosis, s/p BKA

PE:
Significant for severe hepatomegaly without jaundice

Lab work-up: Elevated LFTs
PATIENT #1: AP RADIOGRAPH OF THE R KNEE

Even without a detailed knowledge of Gaucher disease, we can pick out many gross abnormalities of our patient’s knee film.

Can you find some?

Loss of joint space with severe destruction of the distal femoral and proximal tibial surfaces.

Complete misalignment of the joint.

Mottled bone with areas of lucency and sclerosis.
WHAT ARE TYPICAL GAUCHER FINDINGS?

We will come back later and discuss our patient’s findings in detail later.

For now, let’s take a step back and look at the characteristics of bone and marrow involvement in Gaucher and what we expect to see on radiographic imaging.
Gaucher Skeletal Disease: A Helpful Subdivision

Bone Marrow Disease

- Thrombocytopenia
  - Low platelets are a result of decreased production from out-crowding in the marrow, as well as increased destruction in the spleen. (The oft-seen anemia and leukocytosis are more a factor of splenic sequestration than marrow infiltration.)

Structural Involvement

- Avascular Necrosis
- Sclerosis
- Pathological Fractures
- Deformity
- Cortical Thinning

These are the radiologic findings we will look for on plain films.
These two modalities are the mainstays of imaging, with MR being the gold standard of assessing disease severity and plain films used for pathologic assessment.

3. **Nuclear medicine: Tc-99m-Sestamibi**

4. **Dual Energy X-ray Absorptiometry (DEXA)**

There are other imaging modalities, as well.

5. **Less frequently used nuclear medicine studies:**

Bone scans, Xe uptake
• Osteolytic destruction of both cortical and trabecular bone is often seen when destruction exceeds 50% of matrix

• Can also see sclerotic lesions

• Often useful in advanced disease or as an initial assessment of gross orthopedic pathology

• Should not be sole method of assessing orthopedic involvement

Let’s look at some other patients to view typical findings.
COMPANION PATIENT #1: HISTORY

CC:

A 40 yo female with Gaucher disease about to start enzyme replacement therapy with no current MSK complaints, here for a skeletal survey.

This patient’s films will show us examples of local involvement (again, think FORM).
Erlenmeyer flask deformities (flared metaphyseal regions) are commonly of the distal femur and proximal tibia.

Results from an impaired remodeling process.

Image courtesy of Dr. Ferris Hall.

COMPANION PATIENT #1:
PLAIN FILM OF THE L DISTAL FEMUR

Local Involvement

Cortical Thinning

Thought to arise from marrow canal expansion and impaired remodeling.
COMPANION PATIENT #1:
PLAIN FILM OF THE PROXIMAL L FEMUR

Local involvement

Widening of the marrow canal
COMPANION PATIENT #2: HISTORY

A 62 yo woman with known Gaucher disease now presents with sudden onset of wrist pain. PCP sends for films to r/o fracture.

In contrast to patient #1, this patient’s films will show us examples of focal and generalized involvement.
COMPANION PATIENT # 2: PLAIN FILMS OF THE R WRIST

Focal and General Changes

Avascular Necrosis and Collapse of the Lunate

Diffuse osteopenia

Paracrine effect on osteoblasts and osteoclasts

AP film

Oblique film
LATER IMAGING OF COMPANION PATIENT #2

R and L lateral plain films of the distal femur and proximal tibia

**Osteopenia**

**Cortical thinning**

**Sclerotic lesions 2° to infarcts**

**Note that this lesion was read as probable sclerosis, though enchondroma could not be definitively ruled out. It is crucial to remember that patients with Gaucher dz can also manifest other, unrelated bone pathology.**
COMPANION PATIENT #3: A HOST OF FINDINGS

Sclerosis secondary to bone infarcts

Compression of the vessels from outside the wall by Gaucher cells leads to ischemia. (As explained by Dr. Ferris Hall.)

Erlenmyer flask deformity

Widening of marrow canal

Hip replacement after numerous fx

Frontal plain film of the R femoral shaft

Images from PACS
SEVERE PROGRESSION

Sclerotic lesions and deformity within the lumbar spine

Replaced femoral head

Cropped plain film AP view of the lumbar spine and pelvis
COMPANION PATIENT #4

An 18 y.o. man with Gaucher disease undergoing skeletal survey

Image courtesy of Dr. Hall

AP plain film of the pelvis
A mere two years later...massive hip joint degeneration

Loss of joint space

Unlike osteoarthritis, the destruction to the joint space and loss of cartilage is the result of bone death first, which leads to cartilage damage secondarily from a poorly matched femoral head and acetabulum.
Complete loss of joint architecture

Sclerotic and lucent areas

BKA

No soft tissue gas

Therefore, less likely to be osteomyelitis.
LIMITATIONS OF PLAIN FILMS

But what about early disease?
Can it be caught before destruction occurs?
PLUS…

**Radiographs are a poor indication of response to treatment!**
AN IMPORTANT NOTE ON THERAPY

Parental enzyme replacement
- An “ideal” disease for enzyme replacement because of phagosome fusion with the lysosome
- Genzyme, FDA approved 1991
- Now standard of care

Rapid response seen in visceral organs

MSK response may be delayed
- Damaged bones may not heal with enzyme replacement alone

Alternative: Substrate reduction
If plain films are not sensitive enough to detect enzyme therapy response, but therapeutic dosings are often based upon bone involvement, how else can bone disease of Gaucher be assessed?
The gold standard for assessing bone marrow involvement

- Useful in quantifying marrow replacement by Gaucher cells
- Traditionally, femur, spine, and pelvis are imaged
  - T1 weighted MR shows reduced fat signal (decreased signal intensity); T2 shows reduced water signal OR increased inflammation
1. **Bone Marrow Burden Score**: Semi-quantitative evaluation of marrow loss; indirectly represents Gaucher cell invasion
   - Higher score (max 15) is indicative of more severe disease

2. **QCSI (Dixon)**:
   Uses a specific fat-sensitive sequence algorithm to quantify marrow replacement as a “fat fraction”
   - Lower score ➔ more infiltration

**Advantages**: Sensitive modality to determine early therapy response

**Caveats**: Not widespread, technology not included on standard MR packages.
BONE MARROW BURDEN SCORING

• Developed in 2003 as a more easily applied assessment
• Validated to be accurate in representing bone disease severity in comparison with Dixon scoring even with radiologists not specifically trained in Gaucher disease
• Images of femur and spine assessed and scored

Femur rubric

<table>
<thead>
<tr>
<th>T1</th>
<th>Fat appears Hyperintense</th>
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<tr>
<td></td>
<td>Isotense/Hyperintense (Normal)</td>
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<tr>
<td></td>
<td>Slightly hypointense</td>
</tr>
<tr>
<td></td>
<td>Hypointense</td>
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</tbody>
</table>

*Decreasing fat
*Decreasing marrow
*Increasing Gaucher infiltration

Table adapted from Maas, et al.
BONE MARROW BURDEN SCORING:

Companion Patient #5

Mildly reduced marrow intensity in the femoral necks.

Slightly hypointense = 1

T1 weighted coronal MR of the femur

Image from Maas, et al.
Significant loss of marrow intensity in multiple areas, including the femoral neck, diaphysis and distal epiphysis.

Severe Hypointensity = 2

T1 weighted coronal MR of the femur

Image from Maas, et al.
Lateral T1 Weighted MR of Spine

Mild hypointensity of the spinal marrow.

Severe

Nearly complete lack of marrow intensity.

Images from Maas, et al.
## BONE MARROW BURDEN SCORING: T2 Rubric

<table>
<thead>
<tr>
<th>Type</th>
<th>Score</th>
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<tbody>
<tr>
<td>Hyperintense</td>
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</tr>
<tr>
<td>Slightly hyperintense</td>
<td>1</td>
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<tr>
<td>Isotense (Normal)</td>
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<tr>
<td>Slightly hypointense</td>
<td>1</td>
</tr>
<tr>
<td>Hypointense</td>
<td>2</td>
</tr>
<tr>
<td>Mixed type (femur only)</td>
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</tbody>
</table>

- **Acute inflammation, infarction**
- **Decreased healthy marrow, fibrosis**

*Note double-tailed scale*

Increased intensity and/or mixed intensity is believed to represent a more active presentation of destruction.

Table adapted from Maas, et al.
Mildly reduced fluid intensity in the femoral necks and shaft.

**Mild Hypointensity = 1**

Coronal T2 weighted MR of the femurs

Image from Maas, et al.
Significant areas of both increased and decreased fluid intensity throughout the L femur.

Mixed type

ACUTE

Also note distal involvement

Coronal T2 weighted MR of the femurs

Image from Maas, et al.
**BONE MARROW BURDEN SCORING:**

**OTHER KEY MODIFIERS**

Femur: Location of Involvement

<table>
<thead>
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<tr>
<td>Diaphysis</td>
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<tr>
<td>Proximal epiphysis</td>
<td>2</td>
</tr>
<tr>
<td>Distal epiphysis</td>
<td>3</td>
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</table>

Lumbar Spine: Infiltration Pattern

<table>
<thead>
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<th>Score</th>
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<tbody>
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<tr>
<td>Proximal epiphysis</td>
<td>2</td>
</tr>
<tr>
<td>Distal epiphysis</td>
<td>3</td>
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</table>

Tables adapted from Maas, et al.
MR assesses reduction in normal marrow presence, not an increase in pathological function

In addition, bone response to enzyme therapy may be slow to visualize

What other imaging modalities exist?
EARLIER DETECTION: TC-99M SESTAMIBI

- Tc-sestamibi taken up by cells based upon cellular metabolism, retained in mitochondria (commonly used for myocardial perfusion studies)

- Mariani, et al. showed high correlation with uptake and disease severity; effective in assessing therapeutic improvement

E = Extension
I = Intensity

Images from Mariani, et al.
Caveats:
- Not advised in pediatric patients
- Poor resolution
- Confounding of bone thickness

Focus on femur and tibia to avoid diffuse uptake of Tc-sestamibi in abdomen, obscuring spine and pelvic involvement
OTHER IMAGING MODALITIES

DEXA

Dual Energy X-ray Absorptiometry may be used to assess for osteopenia, however, it is of little use in pediatric patients.

Xenon-scanning

Inhaled radioactive agent shows increased uptake in areas of Gaucher cell activity.
Bone scan from Patient #1 prior to his amputation

• Can be used to evaluate osteomyelitis in a patient with Gaucher disease

• Increased uptake in the L distal tibia and distal condyles of the L femur

Image courtesy of Dr. Kevin Donohoe
SUMMARY: PRIMARY ROLES OF RADIOLOGY IN GAUCHER DISEASE MANAGEMENT

1. Immediate stabilization and diagnosis of structural disease

2. Assessment of long-term therapeutic goals
   a) Bone marrow burden and response to enzyme replacement
   b) Serial MRs reveal semi-quant dec in BMB score w/ tx

3. Thorough MSK evaluation every 2 years to assess change

4. MSK events – fracture, pain, bone crisis, r/o infarct ➔ use of plain films
References:


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