Histological findings of femoral heads from patients with Gaucher disease treated with enzyme replacement

Ehud Lebel MD, Deborah Elstein PhD, Ari Zimran MD, Constantine Reinus MD, Ariel Peleg BA, Gail Amir MB ChB.

Dept. of Orthopaedic Surgery, Institute of Pathology, & Gaucher Clinic Shaare Zedek Medical Center, Jerusalem, Israel

EWGGD 6-2012 Paris FRANCE
Disclosure

Dr. Lebel has no financial or other constraints that may have impacted the results reported in this presentation.
Osteonecrosis (ON) in Gaucher disease

• A common problem, adversely affects QoL
• ~10% of int’l registry patients report ON
  [Khan et al, 2012]
• Most common joints:
  – Hip, Shoulder, Knee, Ankle
• Etiology: bone infarction
• Consequence: joint destruction

61y old, female
Approach to osteonecrosis

• Prevention?
  - Early ERT? YES [Mistry et al, 2009]
  - Core decompression? NO [Lebel et al, 2009]

• Post Osteonecrosis
  - Total hip arthroplasty? Beneficial [Goldblatt et al 1998 and others]
  - ERT to decrease complications? Questionable [Donaldson et al, 2011]
Can we do better?

**Risk reduction**
- Prone genotypes?
- Begin ERT early to protect from ON?
- Refrain from splenectomy? [Fleshner et al, 1991]

**Improve management of ON**
- Can ERT improve QoL after ON?
- Can ERT delay joint degeneration?
- Is ON reversible?
- Should we postpone THR until bony change is seen? [Bubbar et al, 2009]
Should we use histology-based evaluation?

- Bone biopsies
- Evaluation of retrieved specimens during THR

Sliced retrieved femur head
OR seek for other modalities?

**Imaging based workup**

1. Plain radiographs [Rossi et al, 2011]
2. Bone density [Pastores et al 1996]
3. MR based modalities
   - Rosenthal et al [1986]
   - Terk et al [2000]
   - Dusseldorf [Poll et al, 2001]
   - Vertebral Disc Ratio [Vlieger et al, 2002]
   - Bone Marrow Burden Score [Maas et al, 2003]
   - QCSI [Johnson et al, 1996]
What is new

• 2 years ago we presented our preliminary results
• (EWGGD 2010, Köln Germany)

• We know have an improved system for evaluation of bone specimens
Our revised approach

A new systematic histological evaluation using an expert pathologist’s pre-determined classification system of bony characteristics (Prof. Gail Amir, Unit of Bone Pathology)

• Systematic detection of:
  – Cellular components
  – Gross architecture
  – Necrosis
  – Signs of bone regenerative activity
Stage 1: bony milieu characteristics

% of surface with Gaucher cell infiltrate in bone
Stage 2: detection of necrosis & arthritis

1. Presence of necrotic bone (yes/no)
2. Evidence of arthritic changes (yes/no)
Stage 3: evidence of reparative activity 1

Osteoblastic rimming (grade 0-3)
Stage 3: evidence of reparative activity 2

Presence of remodeling lines (grade 0-3)
Stage 3: evidence of reparative activity 3

Apposition of new bone (grade 0-3)
What can we learn from bone biopsies?

1. Correlation with disease qualifiers
2. Correlation with treatment
Study cohort

Personal data

- 22 patients / 26 specimens
  - 2 pts had >1 specimen
- 9 Females; 13 Males
- Mean SSI=12.7 (range: 6-27)
- Age (at operation): 17-66 years
- N370S/N370S: 12 (55%)
- N370S/Other: 10 (45%)

Interventions

- Splenectomized: 17 (77%)
- ERT pre-surgery: 16 (73%)
- ON before start ERT: 6 (27%)
- ERT Duration: 1-16 years
- Dosage: 15-30Units/kg/EOW
Results
Results 1: Bony milieu characteristics

- **Osteonecrotic bone:**
  - 19/26 (73%) specimens
  - 7 (27%) specimens had no remnants of necrotic bone

- **Osteoarthritic changes:**
  - Evident in all specimens containing cartilage
Results 2: degree of Gaucher cell infiltration

- Infiltrate seen in 20%-95% of histological specimen

NO CORRELATION with
- age of patient
- type of mutation
- Splenectomy

A TREND was detected between duration of ERT and lesser % infiltrate (Spearman’s rho 4.07)
Results 3: Regeneration/reparative signs

- RIMMING
- REMODELLING lines
- NEW BONE apposition

These signs were not statistically correlated with severity of Gaucher disease or with duration of ERT.
Limitations of current study

• This is a retrospective study
  – Specimens were not prepared specifically for this study
  – Sampling of femoral head was limited to “regions of interest”
  – Special stains could not be used

• Femur head (esp. after osteonecrosis) may not be representative
  – The necrotic event might change bony vasculature
  – This region may be less reactive to ERT
  – There are known differences between regions of bone
What have we learned?
1. Universal description of bone histology is needed

A systematic evaluation score of bone biopsy in Gaucher-disease IS CRUCIAL for standardized description.

- Necrosis and OA
- Bone regeneration
- Infiltrate
2. Do not delay intervention!!

- There is no justification to postpone SURGICAL intervention until “IMPROVEMENT” occurs with ERT;
- We have seen virtually no complications post-surgery and rare loosening event
3. A non-invasive bone evaluation modality is needed

- An imaging study, that would be correlated to biopsy results should be sought
- This modality should help to monitor bony tissue reaction to ERT
- MRI-based modality is probably the most appropriate
Thank you

Ehud Lebel MD (Orthopedic surgeon)
lebel@szmc.org.il