**BACKGROUND and AIM**

Gorham-Stout syndrome (GSD) is a rare disorder characterized by lymphangiomatosis, invasion of soft tissues, osteolysis associated with severe bone morbidity and potentially lethal in the presence of chylothorax. Although bone lesions are due to abnormal vessels proliferation, new lines of investigations point out the role of osteoclastogenic cytokines. As the management of GSD is not univocal and outcomes are unpredictable we build a multifaced protocol in order to study its natural history, biomarkers of disease severity and to treat the patients uniformly.

**SUBJECTS and METHODS**

n=7 patients (5M and 2F, 3 mts 26.0 yrs of age) with GSD (dgn by biopsy) underwent at baseline, after 6 months and than yearly:
1. clinical examination
2. imaging evaluations (Total Body-TB, and spine DXA and STIR Total Body MRI)
3. biochemical (Ck, BAP, PTH, 25OHD, D-Dimer).
4. karyotype, CGH-array
Based on clinical status they were treated with bisphosphonates (BP) and/or Interferon (INF).
1. Pam: 1 mg/kg for 3 di 4 mts (max 30 mg dose) or ZOL: 0.25 mg/kg TB and +6 w; then 0.05 mg/kg (m3max 4 mg/dose)
2. If chylothorax: INF/FA 2b 150000U/m² every other day

Table 1. Age at diagnosis, bone involvement, symptoms (*=chylothorax) and therapy in 7 patients with GSD

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age at diagnosis</th>
<th>Bone</th>
<th>Focal/ Multifocal</th>
<th>1st Signs/symptoms</th>
<th>C* Therapy</th>
<th>FU/re-activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>24,0/26,0</td>
<td>2 Ribs, clavicle</td>
<td>Focal</td>
<td>Cutaneous angroma swelling, Pain, Dyspnea</td>
<td>INF 1y+6m/ hipop. dext./ ZOL 6m</td>
<td>5 yrs/ C* n=3, last in 2012</td>
</tr>
<tr>
<td>M</td>
<td>15,8/16,3</td>
<td>Sternum, ribs</td>
<td>Focal</td>
<td>Toracic pain, Dyspnea</td>
<td>INF</td>
<td>4,8 y</td>
</tr>
<tr>
<td>M</td>
<td>12,0/17,5</td>
<td>Femur, ilion, pubis</td>
<td>Mult</td>
<td>Lameness, Pain, multiple fragile fractures (2005-2009), Hypertropnic L.Imb, Dyspnea</td>
<td>INF 2005-2007 PAM, 18 in 2009 PAM-ZOL, INF</td>
<td>5 y C* n=3, last in 12.2010</td>
</tr>
<tr>
<td>M</td>
<td>1,2/1,9</td>
<td>Ulna</td>
<td>Focal</td>
<td>Local swelling, Pain</td>
<td>PAM</td>
<td>3,5 y</td>
</tr>
<tr>
<td>F</td>
<td>10,8/12,4</td>
<td>Clavicle, 2 ribs, clavicum</td>
<td>Mult</td>
<td>Fracture, Dyspnea, Pain</td>
<td>INF 2011-2012 PAM 12 in ZOL 2013</td>
<td>4,5 y Ribs-clavicle n=1 07.2013 Cannian°</td>
</tr>
<tr>
<td>M</td>
<td>4,2/4,8</td>
<td>Scapula, humerus</td>
<td>Focal</td>
<td>Cutaneous angroma</td>
<td>-</td>
<td>2 y</td>
</tr>
<tr>
<td>M</td>
<td>0,0/0,6</td>
<td>Cranium</td>
<td>Focal/Multifocal</td>
<td>Latecrocervical swelling, local exema, artery, chest, dyspnea</td>
<td>ZOL</td>
<td>0,7 y</td>
</tr>
</tbody>
</table>

**DXA results**
- n=1M and 1F: reduced TB BMD for age/sex
- n=2M and 1F: reduced spine BMD (z-scores between – 2.8 and –1.1)
- subjects on BP displayed an increase in BMD of about 1 Z-score during therapy

**Figure 1. a. BMD TB and b. Spine BMD response to BP in 1 pts with multifocal GSD and femoral fragility fracture**

**TB STIR MRI studies**
- Non specific involvement of multiple skeletal sites far from the primary localization in 2 pts (Figure 2, panel a. and b)
- reduced/ increased during FU

**Figure 2. a. Hyperintensity in STIR (a) Hypointensity in T1(b)**

**Bone markers did not change during acute or re-activation of GSD; only the D-Dimer was increased during acute phases of GSD (Figure 4)**

**Genetic studies**: Karyotype and CGH-array were normal

**Responses to therapy**
- During BP: reduction of bone pain until resolution
- During BP+INF2b: Reduction/resolution of chylothorax

**Figure 3. a. Hyperintensity in STIR (c) TC (d)**

- 1 new focus of disease (c) in 1 pts with multifocal disease, confirmed by CT (d) (Figure 3, panel c. and d)

**CONCLUSIONS**

- In GSD, control of bone pain and chylothorax was obtained with BP and INF2b.
- New acute phases of GSD occurred in patients with extended focal forms of GSD (3 out of 4 pts)
- DXA showed reduced BMD in 3 out of 4 pts with severe forms of GSD (systemic bone reabsorption. Other factors?)
- D-Dimer might be useful during follow-up as a vascular malformation marker (bone markers seems not to have a prognostic role)
- The specificity of STIR MRI need to be confirmed; it still be useful in defining focality/multifocality of disease: different follow up?
- Exome Sequencing of the DNA of the lesions might be useful

**Subjects**
- n=7: osteolysis at baseline (clavicle n=1, ribs n=2, femur n=1, sternum n=1, humerus n=1, scapula n=2, ulna n=1, cranial basis n=1)
- 1 osteolysis lately (parietal bone)
- n=3 3 pathological fractures before therapy start (clavicle n=1F, hip and femur n=1M, rib n=1M), 44%
- n=4 chylothorax, 57%

**Figure 4. D-Dimer during 24 mts follow-up**

- 646-P3

**Poster presented at:**