Giant Cell Rich Tumors of Bone

Andrew Horvai, MD, PhD
Associate Clinical Professor, Pathology

Outline

- Principles: Definitions, biology
- Common giant cell rich lesions of bone
  - Giant cell tumor
  - Chondroblastoma
  - Aneurysmal bone cyst and variants
  - Giant cell rich osteosarcoma
- Pitfalls and controversies
  - Frozen section
  - Malignancy in “benign” lesions
  - Unusual locations / presentations

The osteoclast

- Predominant cell type in GC-rich lesions
  - Hematopoietic-derived (monocyte/macrophage)
  - Phagocyte
  - Normally responsible for bone resorption (acid and proteases)
  - Lytic lesions
- Differentiation/function tightly regulated by local and systemic mediators

Disclosures

This lecture discusses "off-label" uses of a number of pharmaceutical agents. The speaker is describing these effects to illustrate biological mechanisms and is not endorsing or promoting the use of these agents.

The author has no financial relationship with the manufacturers of these agents.
The osteoclast

- Analogy between normal and pathological mechanisms
- Giant cells are not the neoplastic population
- Attention to other components
  - Mononuclear cells
  - Matrix

“That’s a lot of giant cells”

- Giant cell tumor of bone (GCT)
- Aneurysmal bone cyst (ABC)
  - “Solid” aneurysmal bone cyst / giant cell reparative granuloma / brown tumor
- Chondroblastoma (CBL)
- Giant cell rich osteosarcoma (OGS)
A trimodal approach

- Clinical
- Radiology
- Pathology

Clinical

- Age
- Location
- Number of lesions
- Co-morbidities
  - Fracture
  - Hyperparathyroidism / renal failure

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>GCT</th>
<th>Chondroblastoma</th>
<th>ABC</th>
<th>GC rich osteosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain, swelling, often short duration</td>
<td>Pain, often long duration</td>
<td>Pain, short duration</td>
<td>Pain, swelling short duration</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>25%</td>
<td>6-20%</td>
<td>&lt;3%</td>
<td>N/A</td>
</tr>
<tr>
<td>Metastasis</td>
<td>2-4%</td>
<td>Case reports</td>
<td>Case reports</td>
<td>None*</td>
</tr>
<tr>
<td>Malignancy</td>
<td>&lt;-1% primary</td>
<td>Case reports</td>
<td>Case reports</td>
<td>&gt;80% 100%</td>
</tr>
<tr>
<td>Treatment</td>
<td>Curettage/cement</td>
<td>Curettage/cement</td>
<td>Curettage/cement</td>
<td>Neo-adjuvant chemo, resection</td>
</tr>
</tbody>
</table>
**Treatment: Giant cell tumor**

- **Denosumab**: Monoclonal antibody targets RANK-L
- 30/35 patients with tumor response (histologic or radiologic)

**Radiology**

- Plain films usually sufficient
  - 2 views
- CT and MRI
- What to look for
  - Is it intraosseous?
  - Location
  - Compartment
  - Opacity
  - Border
  - Periosteum

<table>
<thead>
<tr>
<th></th>
<th>GCT</th>
<th>Chondroblastoma</th>
<th>ABC</th>
<th>GC rich osteosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compartment</strong></td>
<td>Epiphysis</td>
<td>Epiphysis</td>
<td>Metaphysis</td>
<td>Metaphysis</td>
</tr>
<tr>
<td><strong>Opacity</strong></td>
<td>Purely lytic</td>
<td>Lytic + calcifications</td>
<td>Purely lytic</td>
<td>Lytic + sclerotic</td>
</tr>
<tr>
<td><strong>Border configuration</strong></td>
<td>Circumscribed</td>
<td>Marginated, sclerotic rim</td>
<td>Marginated, expansile</td>
<td>Permeative</td>
</tr>
</tbody>
</table>
Pathology

- Distinguishing features of classic examples
  - Distribution of giant cells
  - Matrix
  - Mononuclear cells
  - Atypia, pleomorphism

Case 1: 42 year old woman with distal radius mass

Giant cell tumor

Giant cell tumor
Case 2: 18 year old man with distal femoral mass

Giant cell tumor

Chondroblastoma: circumscription

Chondroblastoma: fibrochondroid matrix
Case 3: 23 year old man with distal tibia lesion

Chondroblastoma: chickenwire calcifications

Chondroblastoma: nuclear grooves

Aneurysmal bone cyst
Cysts in Solid Variant of Aneurysmal Bone Cyst

We read with interest the article titled “Solid Variant of Aneurysmal Bone Cyst in Long Tubular Bones: Giant Cell Reparative Granuloma” in AJR [1]. “Solid cyst” is a confusing term. In this article dealing with “solid variant of aneurysmal bone cyst,” the authors included two cases containing cysts with fluid levels, and one of them was shown in figure 11.

In the original description of solid variant of aneurysmal bone cyst, Sanerkin et al. [2] excluded lesions with cystic components, although macroscopically they allowed “scattered blood-filled sinuses.” On the other
Case 4: 19 year man with distal femoral mass

Giant cell rich osteosarcoma
Pathology summary

<table>
<thead>
<tr>
<th></th>
<th>GCT</th>
<th>Chondroblastoma</th>
<th>ABC</th>
<th>GC rich osteosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution of giant cells</td>
<td>Uniform</td>
<td>Heterogeneous</td>
<td>Heterogeneous</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>Matrix</td>
<td>Absent</td>
<td>Fibrochondroid plaques + calcification</td>
<td>Osteoid, sometimes abundant</td>
<td>Osteoid</td>
</tr>
<tr>
<td>Mononuclear cells</td>
<td>Ovoid, uniform, nuclei similar to GC</td>
<td>Ovoid, eccentric nuclei, grooves</td>
<td>Spindled, fibroblastic/&quot;fibrohistiocytic&quot;</td>
<td>Polygonal to spindled, hyperchromatic</td>
</tr>
<tr>
<td>Mitosis</td>
<td>Abundant</td>
<td>Rare</td>
<td>Variable</td>
<td>Abundant, atypical</td>
</tr>
<tr>
<td>Atypia</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Marked</td>
</tr>
</tbody>
</table>

Ancillary tests: p63 Immunohistochemistry

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Precent cases positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giant cell tumor</td>
<td>De la Roza 87</td>
</tr>
<tr>
<td></td>
<td>Lee 90</td>
</tr>
<tr>
<td></td>
<td>Dickson 100</td>
</tr>
<tr>
<td>ABC</td>
<td>De la Roza 63</td>
</tr>
<tr>
<td></td>
<td>Lee 20</td>
</tr>
<tr>
<td></td>
<td>Dickson 29</td>
</tr>
<tr>
<td>Chondroblastoma</td>
<td>De la Roza 83</td>
</tr>
<tr>
<td></td>
<td>Lee 50</td>
</tr>
<tr>
<td></td>
<td>Dickson 30</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>De la Roza 50</td>
</tr>
<tr>
<td></td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>?</td>
</tr>
</tbody>
</table>

Giant cell rich tumors

Giant cell rich osteosarcoma

ABC GC rich osteosarcoma

Chondroblastoma

Giant cell tumor of bone express p63

Ancillary tests: Immunohistochemistry

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Panel</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giant cell tumor</td>
<td>RunX2+ Twist-</td>
<td>90</td>
<td>83</td>
</tr>
<tr>
<td>Chondroblastoma</td>
<td>RunX2- Sox9+</td>
<td>53</td>
<td>99</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>RunX+ Twist+</td>
<td>82</td>
<td>86</td>
</tr>
</tbody>
</table>

Pitfalls/uncommon presentations

- Frozen section, scant material
- Trimodal approach still applies
- Exclude osteosarcoma or other malignancy
- “Giant cell rich-lesion, no malignancy” is acceptable if distinction cannot be made between GCT, ABC and CBL
- Treatment will be curettage with follow-up
**Pitfalls: Giant cell tumor**

- Exceptions to “no matrix”
  - Cartilage: healing pathological fracture
  - Bone: Capsule, residual cortex, secondary ABC change

**Pitfalls: Giant cell tumor**

- Spindle cell rich areas
  - Fascicular or storiform growth
  - GC rich areas invariably present if sufficient material obtained

**Malignancy in GCT**

- “Benign” GCT
  - Necrosis
  - Abundant mitotic activity (>20 mf / 10 hpf)
  - Intravascular invasion
  - Lung metastases in 2-4%
  - Metastases can spontaneously regress
**Malignant giant cell tumor**

- **Primary malignant GCT**
  - Typical GCT adjacent to high grade sarcoma (often osteosarcoma)
  - Transition gradual
  - Atypical mitotic figures diagnostic
  - Abnormal osteoid matrix should prompt careful search for cytological atypia

- **Secondary**
  - 10+ year interval after initial diagnosis
  - Radiotherapy
  - Histological types: osteosarcoma, fibrosarcoma

---

**45 year old woman with distal radius mass and pain**

---

**Pitfalls: Chondroblastoma**

- Only ~30% of cases demonstrate all characteristic features
  - Fibrochondroid matrix, chicken wire calcifications, nuclear grooves
**Pitfalls: Chondroblastoma unusual sites**

- Temporal bone
- Talus

**Pitfalls: Chondroblastoma**

- Chondroblastoma with secondary ABC
  - 30% of cases
  - Bone, hemorrhagic cavities, fibrous septae

**Take home messages**

- Pathologic diagnosis of giant cell rich lesions requires careful correlation with radiographic and clinical findings
- The benign lesions in this category (GCT, ABC, CBL) are treated similarly, so the most important consideration is to exclude malignancy, especially giant-cell rich osteosarcoma
- RANK – RANK-L interactions likely mediate the accumulation of giant cells in these lesions and may be a therapeutic target