What Do You Need to Know About Bone Pathology?

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What’s Do You Need To Know About Bone Pathology?

• Reactive/pseudosarcomatous lesions of bone
  – Florid periosteal lesions
  – Fracture
  – Subchondral fracture

• Well differentiated cartilage tumors
  – Enchondroma vs Chondrosarcoma
  – “Borderline” lesions (atypical enchondroma)

• Pathological examination of bone and joint specimens
  – To see or not to see?
Sarcoma vs Reactive
Pseudosarcomatous Lesions

- **Reactive/benign masses**
  - Florid myofibroblast proliferations with mitotic activity, cellularity, atypia, tissue culture-like growth pattern.
- **Misdiagnosis as sarcoma = unnecessary treatment.**
- **Recognizing activated appearance of the cells is critical.**
- **Combinations of mitotic activity, cytological atypia, and/or necrosis as seen in sarcomas are not seen in pseudosarcomatous lesions.**
- **For bone lesions matrix architecture is helpful**
- **For bone lesions radiological correlation is helpful.**
Activated Cytology
Bizarre Parosteal Osteochondromatous Proliferation

- Florid proliferation of fibroblasts, cartilage and bone.
- Most common on the hands > feet > long bone.
- Long bone lesions clinically concerning for osteosarcoma.
- Imaging: calcified mass attached to surface of underlying bone by a broad base without destruction of the cortex, matures over time; confused with osteochondroma.
- Hypercellular cartilage with blue tinctorial change, endochondral ossification, fasciitis-like fibroblasts.
- Recurrent translocation t(1:17)(q32;q21), Inv(7)(q22q32)
Florid Reactive Periostitis

- Poorly defined mass/fusiform swelling around phalanx rather than a distinct nodular growth as seen in BPOP.
- Proliferating fibroblasts set in loose immature collagenous matrix. Foci of extravasated red cells and scattered chronic inflammatory cells may be present (reminiscent of nodular fasciitis) including mitotic activity.
- Fibroblastic tissue merges with immature trabeculae of woven bone forming by membranous-type ossification and lined by activated appearing osteoblasts.
- Most likely to be confused with osteosarcoma.
- Bone architecture – parallel intersecting trabeculae
Florid Periosteal Proliferations

Key Points

• Periosteal lesions contain fibroblastic proliferations similar to other pseudosarcomatous proliferations (nodular fasciitis).

• Matrix formation is well organized (eg. endochondral ossification of cartilage into mature bone in BPOP; parallel intersecting trabeculae of bone).

• Diagnosis rests on identification of morphological features and radiological correlation. Ancillary testing has little or no role (except possibly cytogenetics).

• Reactive periosteal lesions need to be distinguished from osteochondromas and osteosarcoma (reactive periosteal lesions are common in the hand where as osteochondromas and osteosarcomas are not).

• Histologically concerning to look at, but most often present as a clinically and radiologically benign tumor.
Osteochondroma:

- More “regular” cartilage with small chondrocytes.
- Endochondral ossification to mature bone with marrow.
- No fibroblastic component.
- Continuity with underlying bone.
Osteosarcoma of phalanx is rare, but well documented.

- Can have irregular calcified chondro-osseous matrix and fibroblastic stroma.
- Nuclear pleomorphism with dark irregular nuclei.
- Destructive mass on imaging
Neuropathic Joint and Fracture

• Neuropathic joint and fracture involving the foot seen in diabetics (may increase).
• Can present as a bone forming mass in the foot clinically worrisome for osteosarcoma or other bone tumor (osteosarcoma of foot is rare).
Fracture

- Distinguish fractures callus from sarcoma by the pattern and architecture of the matrix being formed, uniformity of the cytological appearance of osteoblasts, chondrocytes and fibroblasts (activated appearance), and growth pattern.
- Zonation phenomenon: fibroblastic areas merging with cartilage undergoing endochondral ossification into well formed bone.
- Correlation with imaging studies is imperative as they may reveal the fracture even in cases with exuberant fracture callus formation.
Fracture
Malignant Neoplastic Matrix
Primary Subchondral Fracture of the Femoral Head

- Elderly women with osteopenia and obesity
- Elderly patients
- Military trainees, runners
- Renal transplant patients
- Metabolic disease
- Others

- Radiological features are difficult to distinguish from AVN
Subchondral Fracture

- Given overlapping clinical and pathological features, PSF can be misinterpreted as “avascular necrosis” of the femoral head.
- Distinction has implications for patient treatment and management.
- Recognition of this lesion by pathologists will help better identify these patients and contribute to better clinical and radiological recognition of these patients.
- May grossly appear as “normal” femoral head.
Primary Subchondral Fracture of the Femoral Head
Primary Subchondral Fracture of the Femoral Head

Avascular Necrosis
Well Differentiated Cartilage Tumors

- Common
- WHO Classification:
  - Osteochondroma
  - Chondroma
  - Chondromatosis
  - Chondrosarcoma
- Central vs Peripheral
- Primary vs Secondary
Well Differentiated Cartilage Tumors

- Distinction between benign and malignant is difficult based only on histopathology.

- Enchondroma vs LG CHSA
  - Growth: Radiographic change
  - Invasion: Imaging features or identified histologically
  - Location
Well Differentiated Cartilage Tumors

• Clinical features

• Radiological features

• Pathological features
Clinical Features of Well Differentiated Cartilage Tumors
Enchondroma

- Painless or pain for other reasons
- Most patients in 2\textsuperscript{nd}-4\textsuperscript{th} decade (5-80 yo)
- 50\% occur in the tubular bones of the hands and feet, femur and humerus; rare in axial and flat bones
- Hands and feet – fracture
- Long bones – incidental
- Limited growth
Chondrosarcoma

- Second most common bone sarcoma
- Primary > secondary
- Typically occurs in older adults
- Pelvis, humerus, proximal femur
- May arise in enchondroma (low grade)
- Growth over time; pain from tumor
- Low grade (1/3) do not metastasize, but may recur and dedifferentiate
- Intermediate/high grade metastasize
Radiological Features of Well Differentiated Cartilage Tumors
Enchondroma Radiology

- Plain film/CT = gross pathology
- Metaphysis, diaphysis
- Lytic, variably mineralized – rings, arcs, stippled patterns
- Circumscribed, cortex intact, but can have cortical scalloping
- No periosteal reaction, loss of cortex or soft tissue mass
- Lack of growth on serial imaging (uncertain cases)
- Small tubular bones can have more aggressive features
Enchondroma Radiology
No calcifications
MRI useful to identify soft tissue mass
Chondrosarcoma Radiology

- Ill-defined areas of destruction
- Most mineralize, surrounding zone of radiolucency
- Endosteal scalloping with cortical thickening
- Loss of cortex and soft tissue mass
- Periosteal reaction (no fracture)
Chondrosarcoma
Change over time = Chondrosarcoma
Histopathology of Well Differentiated Cartilage Tumors
Enchondroma
Chondrosarcoma
Grading Chondrosarcoma
Role of Cytology

- Cytology generally not useful in distinguishing between enchondroma and CHSA except for high grade CHSA.
Enchondromatosis
Binucleated Chondrocyte
Invasion
What to make of this?
Needle Biopsy = Low Grade Hyaline Cartilage Tumor

Submit entire specimen for curettings
Necrosis in cartilage tumors
Enchondroma
Enchondroma with fracture
Atypical Enchondroma

- Bone entrapment
- Small bone of hand
- Benign imaging features
Atypical Enchondroma

- Long bone
- No aggressive imaging features
- No definite bone invasion
Atypical Enchondroma

- Long bone
- Some aggressive imaging features
- No definite bone invasion
Chondrosarcoma, grade 2/3

- Aggressive imaging features
- Bone invasion
- Cellularity
- Moderate cytological atypia
How to address “atypical enchondroma”?
How to address inter-observer variability?
Identifying Unique Genome Abnormalities that Distinguish Enchondroma from Chondrosarcoma

John Scarborough\(^1\), Robert Ricciotti\(^1\), Benjamin Hoch\(^1\), Yajuan Liu\(^1\), Eleanor Chen\(^1\)

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### Background

Distinguishing enchondroma from grade 1 and even grade 2 conventional chondrosarcoma based on histologic features can be a diagnostic challenge, but has strong implications for clinical management. Enchondroma, a benign cartilage neoplasm, is usually cured by simple curettage. By contrast, chondrosarcoma is a malignant neoplasm of bone which tends to locally recur and may metastasize. There remains a need for an ancillary molecular tool to help distinguish enchondroma from chondrosarcoma.

### Design

SNP-based cytogenomic microarray analysis (CMA) using the Illumina Infinium CytoSNP-850K platform was performed on genomic DNA isolated from archived formalin-fixed paraffin-embedded tissue of 5 cases of enchondroma and 8 cases of chondrosarcoma.

Chondrosarcomas were characterized by bone invasion/entrapment on microscopic examination and aggressive features on imaging. Enchondromas lacked invasive growth and were confined to bone. For each case, a log intensity ratio and allele frequency were generated to represent net copy number changes and regional genetic abnormalities (e.g. aneuploidy, deletion, amplification and loss-of-heterozygosity) within each chromosome. To represent genomic complexity of each case, a genomic index (GI) of (total number of alterations)\(^2\)/total number of involved chromosome was determined.

### Results

All enchondroma cases (5 short bones and 1 long bone; age range: 18-57; sex: 3 F/2 M) showed no copy number changes or regional genetic abnormalities. By contrast, all chondrosarcoma cases (1 grade 1, 6 grade 2 and 1 grade 3; 1 long bone, 1 vertebral column, 2 short bones, 4 flat bones; age range: 20-77; sex: 5 F/3 M) demonstrated complex genetic alterations with frequent chromosomal losses. Recurrent chromosomal alterations in at least 50% of cases include losses of 6q and 13 (100%), loss of 1p, 6p, 9p and 11 (83%), loss of 1q, 3, 4p, 9q, 10, and 22 (67%) and loss of 4q, 14, 16q, 17, and 21 (50%).

Chondrosarcoma cases demonstrated GI ranging from 4 to 20.06 and appeared not to correlate with grade.

### Table 1

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Normal Chromosome</th>
<th>One Loss</th>
<th>Two Losses</th>
<th>cnLOH</th>
<th>GENOMIC INDEX: A(^2)/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enchondroma</td>
<td>2n (XX)</td>
<td>(1-22,X) x2</td>
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<td></td>
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<td>Ambiguous cartilage neoplasm(^*)</td>
<td>2n (XX)</td>
<td>(1-22,X) x2</td>
<td>(1-22,X) x2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chondrosarcoma, grade 1</td>
<td>7,8,12,15q,16,17,18,19,20</td>
<td>2,3,4,6,11,15q,21,22,X,Y</td>
<td>1,4,9,10(UPD),13,14</td>
<td>17.07</td>
<td></td>
</tr>
<tr>
<td>Chondrosarcoma, grade 2</td>
<td>5,7,12,19,20</td>
<td>1,2,3,4,6,8,9,10,11,13,14,15,16,17,18,21,22,X</td>
<td>1,4,9,10(UPD),13,14</td>
<td>20.06</td>
<td></td>
</tr>
<tr>
<td>Chondrosarcoma, grade 2, Ollier's (dc: age 3)</td>
<td>6q, 9p, 13, 22</td>
<td>4</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chondrosarcoma, grade 2, Ollier's (dc: age 3)</td>
<td>6q, 9p, 13, 22</td>
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### Conclusions

- SNP-based CMA demonstrates complex copy number and regional genetic alterations, including recurrent loss of 6q and 13, in chondrosarcoma. In contrast, no abnormalities were detected in enchondroma.

- Stratification of genetic complexity by the genomic index clearly distinguishes enchondroma from chondrosarcoma, but does not differentiate low-grade from high-grade chondrosarcoma.

- SNP CMA is a useful molecular test to distinguish enchondroma from chondrosarcoma in diagnostically challenging cases.

**Table 1.** Summary genetic alterations detected in cases of enchondroma, one morphologically-ambiguous case\(^*\) and chondrosarcoma. *The morphologically ambiguous case\(^*\) was readily distinguished by molecular analyses and assigned as enchondroma.
Conclusions

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• SNP CMA is a useful molecular test to distinguish enchondroma from chondrosarcoma in diagnostically challenging cases.
Well Differentiated Cartilage Tumors

• Small bones of hand
  – Vast majority benign but can recur
  – Distinguishing fracture from true invasion
  – Some aggressive features can be seen
  – Cytology and cellularity can range from benign/low grade to intermediate grade
  – Chondrosarcoma of hand is large and destructive
Chondrosarcoma of Hand
Well Differentiated Cartilage Tumors

• Long bones
  – Bone invasion defines chondrosarcoma
  – Cytology and cellularity can range from benign/low grade to intermediate grade
  – Some aggressive features now acceptable (not enough to call chondrosarcoma)
Well Differentiated Cartilage Tumors

• Atypical enchondroma/low grade cartilage neopasm
  – Hand: limited bone invasion without large destructive mass, or with fracture
  – Long bones: cellular/intermediate grade appearing tumors without bone invasion
  – Aggressive radiological features without bone invasion on histological examination
  – Be sure entire specimen is examined
Well Differentiated Cartilage Tumors

- Microscopic examination of curetting specimens remains a challenge
- Must have radiological correlation
- Inter-observer variable remains
- Most true CHSA are at least grade 2
- Molecular markers needed (cellular enchondroma vs grade 3 CHSA)
Orthopedic Surgery Announcement

"With the recent shift towards bundled payment and cost cutting, and evidence based medicine, we are no longer sending specimens for our routine total joint arthroplasty to pathology, unless clinically indicated. Several studies have shown that this practice has a very low yield and rarely adds anything significant in the future management of the patients."
Pathologic Examination of Joints

To see or not to see?

- Clinically significant and curable diseases may not be detected without histopathologic exam
- Information from exams used for QA purposes, outcomes and other research, and education
- Information not considered in previous analyses despite vital, if intangible, benefit to patients and society
- Regulatory requirements
- Previous studies are old, had small numbers of patients, and exam performed by pathologists with minimal bone pathology expertise
Hospital for Special Surgery Study

- 16,587 cases (largest ever)
- Routine processing of specimens
- Experienced pathologists
- Only looked at concordant vs discordant diagnoses (discordant result = difference between clinically reported and pathologic diagnosis)
- 7 most common conditions were analyzed
- Secondary DJD cases classified in primary condition when possible

<table>
<thead>
<tr>
<th>Pathologic Diagnosis</th>
<th>Hip, %</th>
<th>Knee, %</th>
</tr>
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<tbody>
<tr>
<td>Degenerative joint disease</td>
<td>75.8</td>
<td>89.5</td>
</tr>
<tr>
<td>Subarticular fracture</td>
<td>10.9</td>
<td>6.5</td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>5.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Trauma/fracture</td>
<td>3.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Rapidly destructive disease</td>
<td>2.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Inflammatory arthritis</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>0.2</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>
Hospital for Special Surgery Study
Concordant vs Discordant Diagnoses

- 81.2% concordance for hips
- 90.6% concordance for knees
Greatest concordance occurred for DJD and the least concordance for subarticular insufficiency fractures.
In addition 5.4% of hips and 1.4% of knees contained additional discrepant pathology.

Most were not suspected.

Most common malignancy was CLL/SLL, known in 50%, but not considered relevant to be mentioned on req form.

Metastatic tumors not known or considered irrelevant at time of surgery.
To See Or Not To See?

• HSS study refutes the view that the difference between clinical and pathologic diagnoses is insignificant (0-10% in previous studies vs 19% discordance in HSS study).
• DJD clinically diagnosed 20% more than could be pathologically confirmed (most over-diagnosed disease).
• Discordance was very high in subchondral fracture and rapidly destructive disease.
• Additional findings in 5% hips and 1% knees (most unexpected, including malignancies).
To See Or Not To See?

- Gold standard for verification of clinical diagnosis is histopathologic diagnosis by properly trained pathologists.
- Discordance rate between clinical and pathologic diagnoses is much higher than previous published literature (difference related to experience).
- Examination provides opportunity for discovery of new conditions, research into known conditions, QA measures (accuracy of clinical diagnoses), type of disease related to implant survival, and educational endeavors; all factors not previously considered.
- 0.5% cost savings by eliminating histologic examination
- Change in clinical management and cost-effectiveness not specifically analyzed.
Cost containment (Accountable Care Organization model of care) will require all involved to analyze what are the true benefits to patients, both tangible and intangible.
Thank You!

Questions and Comments

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