Case 1: You will never ever guess what this is because I neglected to upload the whole slide or digital images due to a peculiar combination of ignorance and possible, though entirely unintended, incompetence likely exasperated by lethal procrastination in the reading of instructions.

31st ECP; Nice, France
SS-14: STB in your eye; 11 September 2019
Alexander Lazar MD/PhD
Professor
Departments of Pathology & Genomic Medicine
Section of Soft Tissue & Bone Pathology
Sarcoma Research Center
Alexander Lazar MD/PhD
Tuesday 11 September 2019
(I am lecturing internationally in a beautiful city on my wife’s birthday)

31st ECP: Nice, France
SS-14: Joint Session Soft Tissue and Bone Pathology / Ophthalmic Pathology: More than meets the eyes

I have the following financial relationships to disclose:


(mostly scientific advisory boards, clinical trials, research / travel support and business / financial strategy consulting)

These relationships are NOT relevant to the educational content of this lecture.
Male, aged 40
LLE pain with Army training
Diagnosis

Monostotic fibrous dysplasia
History

• Lichtenstein & Jaffe: 1938 & 1942 (FD)
• Osteitis fibrosa or generalized fibrocystic disease of bone (renal osteodystrophy and hyperparathyroidism)
• Craniofacial lesions = leontiasis ossea or cherubism.
• Albright-McCune syndrome (1937), osteitis fibrosa
  – Polyostotic (1942), L & J
• Mazabraud syndrome (1967); FD with myxomas
Fibrous Dysplasia in a 120,000+ Year Old Neandertal from Krapina, Croatia

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Abstract

We describe the first definitive case of fibrous dysplastic neoplasm in a Neandertal rib (120.71) from the site of Krapina in present-day Croatia. The tumor predates other evidence for these kinds of tumor by well over 100,000 years. Tumors of any sort are a rare occurrence in recent archaeological periods or in living primates, but especially in the human fossil record. Several studies have surveyed bone diseases in past human populations and living primates and fibrous dysplasias occur in a low incidence. Within the class of bone tumors of the rib, fibrous dysplasia is present in living humans at a higher frequency than other bone tumors. The bony features leading to our diagnosis are described in detail. In living humans effects of the neoplasm present a broad spectrum of symptoms, from asymptomatic to debilitating. Given the incomplete nature of this rib and the lack of associated skeletal elements, we resist commenting on the health effects the tumor had on the individual. Yet, the occurrence of this neoplasm shows that at least one Neandertal suffered a common bone tumor found in modern humans.
Fibrous dysplasia

A benign, medullary, fibro-osseous lesion, which may involve one or more bones.
Fibrous Dysplasia

- Historically: developmental; benign fibro-osseus proliferation
- Now: neoplastic disease of bone-forming mesenchymal cells with genetic basis
FD Complications

• Bone pain

• Pathologic fracture

• Deformity

• Osteosarcomatous transformation (1 %)
FD Definitions

• Monostotic
  – Single site involving one bone
  – Proximal femur, skull, jawbone, ribs

• Polyostotic
  – Multiple sites
  – Monomelic
    • single extremity or region
    • humerus, radius, phalanges or pelvis, proximal femur, tibia
  – Polymelic
    • widespread skeletal involvement
    • face/skull & proximal thigh most common; but ribs, scapula, pelvis and arm/hand and leg/foot bones
FD Syndromes

- **Albright-McCune**: polyostotic (polymelic), FD with endocrine hyper-reactivity leading to
  - precocious puberty in females
  - +/- hyperthyroidism, hyperparathyroidism, acromegaly and Cushing syndrome

- **Mazabraud syndrome**: vanishingly rare association of polyostotic FD and intramuscular myxomas

- **Jaffe-Lichtenstein syndrome**: polyostotic FD and cutaneous café-au-lait spots
FD Types

Monostotic fibrous dysplasia (around 60% of patients).

Polyostotic fibrous dysplasia (around 40% of patients), including McCune-Albright syndrome.

McCune-Albright syndrome with precocious puberty (<5% of patients).

McCune-Albright syndrome with other endocrine abnormalities (1-2%).
Osteoblast development

- Mesenchymal cells
- Preosteoblasts
- Functional osteoblasts
  - Synthesize EC bone matrix proteins (osteoid)
  - Produce calcification machinery
  - Induction and regulation of osteoclasts

- FD: inability to produce mature lamellar bone from woven bone.
FD Molecular Pathology

- GNAS mutations
- encodes α-subunit of heterotrimeric G-protein
- physiologically activated by associated ligand-bound seven transmembrane receptor (G-protein coupled receptor; GPCR)
- Activates adenylyl cyclase
- Increase in intracellular cAMP & PKA activity
GNAS

- Required for efficient formation and migration of osteoblasts into the marrow space
Molecular Analysis

**GNAS R201H**

- Uncut 144 bp
- Digest 113 bp

**Codon 201 WILDTYP**

**Codon 201 MUTANT**
## Summary of GNAS mutations - FD

<table>
<thead>
<tr>
<th>MO #</th>
<th>Diagnosis</th>
<th>GNAS point mutation</th>
<th>Restriction Digestion</th>
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Myxoma (intramuscular)

Lots of other benign and malignant lesions as well; combined with additional mutations in malignancies.
Low-grade central osteosarcoma

A low-grade malignant bone-forming neoplasm, that arises within the medullary cavity of bone.

- *MDM2* amplification!
- *GNAS* mutation rare, but described in low grade fibroblastic osteosarcoma.
FD Radiology

- Medullary lesion
- Ground glass appearance
- Shaft and metaphysis of long bones
- Opacity related to degree of woven bone present
  - Craniofacial- more radiopaque; dense trabeculae
- Bone contour often expanded
- Femur, tibia, humerus: cortical thinning and endosteal scalloping
Male, aged 26
Broke R arm twice pitching in baseball
FD Gross

- Central in bone
- Tan to grey
- Gritty
- Sharply marginated
- Thinned cortex
- Cartilage (blue-white)
- Hemorrhage (ABC)
- Cystic change
- Xanthomatous (yellow)
Male, aged 26
# Old School: Chinese Characters

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<th>大</th>
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<th>二</th>
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<td>vegetable</td>
<td>bean</td>
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<td>river</td>
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<td>is</td>
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<td>like</td>
<td>happiness</td>
<td>live</td>
<td>die</td>
<td>strength</td>
<td>sickness</td>
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New School: Hebrew Characters!

Cheth Zain Vau He Daleth Gimel Beth Aleph

Ain Samech Nun Mem Lamed Caph Yod Teth

Point Tau Shin Resh Koph Tzade Pe

Extended forms of

Tau Mem Lamed He Aleph

Final forms of

Tzade Pe Nun Mem Caph
Male, aged 68
Right rib
Fibroblastic OS in FD
Male, aged 68
Right rib
Fibroblastic OS in FD
The Nobel Prize in Physiology or Medicine 1994 was awarded jointly to Alfred G. Gilman and Martin Rodbell "for their discovery of G-proteins and the role of these proteins in signal transduction in cells"
10 October 1994

*Momento mori.* (L., remember you will die)
Conclusion

• FD has characteristic radiologic and histologic features

• G-protein signaling important in bone biology

• GNAS1 mutations seen in both syndromic and sporadic FD
Thanks!