Bone Neoplasia in the 21st Century - Using Fibrous Dysplasia as the Model for How Far We've Come

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Definition

• FD is a neoplastic process involving primarily the intramedullary portion of from one to many bones.

• It is composed of randomly distributed spicules of woven bone, absent prominent osteoblastic rimming set in a background of swirling fibrous connective tissue.
Epidemiology

- Occurs in children & adults
- Neither favors nor spares any racial or ethnic group
- Equally prevalent in both sexes (monostotic form – slight increase in women)
- Found in antiquity
- Found in many vertebrates (apes, dogs, iguanas, etc.)
What do these 4 animals have in common?
Suspected fibrous dysplasia from the rib of a Neandertal, age 120,000 + years.

Suspected fibrous dysplasia from the rib of a Neanderthal.
- Essentially all bones reported
- Women favor long bone involvement
- Men favor ribs & skull

### Fibrous Dysplasia

- **Monostotic**
  - Monomelic (1 extremity)

- **Polyostotic**
  - 6:1
  - Polymelic (diffuse)

- **Polyostotic Form**
  - Femur
  - Pelvis
  - Tibia

- **Monostotic Form**
  - 1/3 Head & Neck
  - 1/3 Femur & Tibia
  - 1/3 Ribs

Unni KK: Dahlin’s *Bone Tumors* 369, 1996
Clinical Features

- Congenital forms exist
- New disease may occur in the elderly
- Usually discovered in late childhood (polyostotic earlier than monostotic)
- Monostotic form may stop progressing at puberty
- FD usually spares the epiphysis before puberty
- Extends to ends of bone after maturity

Latham et al: Arch Ortho Trauma Surg 111:183-6, 1992
Bones of the Head & Neck

- Temporal Bone
- Tympanic Bone
- Orbit
- Paranasal Sinuses (Including Sphenoid)
- Skull Base

RELATIVELY RARE SITES

- Spine (Cervical to Sacrum)
- Hands & Feet
- Fingers and Toes


Conventional Radiography

- Six types of patterns
- (“Peau d’orange” stippling, plaque-like, cyst-like, etc.)
- May be sclerotic, lytic or mixed
- “Ground-glass” texture with sclerotic rim
- Cortical thinning & bony expansion

Radiologic Imaging

Computerized Tomography

- Measure extent of disease
- Amorphous ground glass appearance
- May be sclerotic, lytic or mixed
- Presence of cortical perforations

Daffner, R. et al.: *AJR* 139:943-8, 1982
Radiologic Imaging

Magnetic Resonance Imaging

- Low signal intensity on T-1
- 1/3 hypotense; 2/3 hypertense on T-2
- ¾ hypotense rind
- ¼ internal septation
- Soft tissue extension (after Gadolinium-contrast)
- ¾ inhomogeneous intensity

Scintography

- ↑ Uptake on bone scintography (thought secondary to ↑ skeletal blood flow)
- ↑ Uptake of tracers (99mTc-MDP, Gallium-67)

Macroscopy

- Firm to gritty consistency
- Gray-brown
- May be cystic, hemorrhagic
- Can occur on bone surface (exophytic variant)
- When cartilage is pressed blue-tinged and translucent

Siegal, G. *Path of Solid Tumors in Children* 183-212, 1998
Histopathology

- Bizarre “C”-shaped metaplastic bone
- Naked bone spicules with central mineralization
- Both woven & lamellar bone often present in the jaws
- Hyalinization, hemmorhage, xanthomatos reactions & cystic change
- Calcific sphericals may be present in extragnathic skeleton

Histopathology – Con’t

• Fibroblastic spindle cells predominate
• Cells are without hyperchromasia or increased mitosis
• Density highly variable
• Cartilaginous differentiation is common
• Stromal variants common

Immuneophenotype

Fibrous Component
VIM +
XIIla +
BMP +

Bone
Osteonectin +
Osteopontin +
Osteocalcin +
c-Fos +, c-Jun +
Prostaglandin E-2 +
ER+, PR +
MIB-1 - Low

Ultrastructure

- Myofibroblasts, fibroblasts
- Mastocytes
- Woven bone with abnormal spindled osteoblasts
- Hyaline-cartilage-like foci
- Cells with microfibrillar cytoplasmic brush borders

FD & Other Genetic/Morphologic Conditions

A. Coincidental
- Gout
- Liver adenomas
- Peutz-Jeghers Syndrome
- Langerhans cell granulomatosis

B. Benign lesion probably secondary to cyst-like change
- Frontal sinus or ethmoid mucoceles
- Simple or empty cysts
- Aneurysmal bone cysts

FD & Other Genetic/Morphologic Conditions - Con't

C. **Other Benign Conditions**
- Osteoid osteoma
- Enchondromata with annular calcification
- Myositis ossificans progressiva
- Osteochondromatosis
- Desmoplastic fibroma

D. **Multi-organ & Malignant Conditions**
- McCune-Albright Syndrome
- Both M-AS & Mazabraud’s Syndrome
- Malignant Transformation

Syndromes Associated with FD

**Mazabraud’s syndrome**


**McCune-Albright Syndrome:**

Syndrome characterized by Osteitis Fibrosa Disseminata, Areas of pigmentation and endocrine dysfunction with precocious puberty in females


Fuller Albright, Allan M. Butler, Aubrey O. Hampton, and Patricia Smith: *N Engl J Med 216:727, 1937*
Malignant Tumors Arising in FD

- Osteosarcoma
- Chondrosarcoma (including dediff & mesenchymal)
- Fibrosarcoma

Rarer Malignant Tumors Associated with FD

- Ewing’s Sarcoma
- Malignant Mesenchymoma
- MFH
- Angiosarcoma
- Leiomyosarcoma


Representative Example of a Patient with a Malignant Tumor Arising in Fibrous Dysplasia

• A 55 year old Caucasian woman presented with headache and neck pain of three months duration.
• She was otherwise in excellent health without known major illnesses or surgeries.
• A course of antibiotic therapy did not relieve her pain.
• A subsequent trial of steroids was similarly unsuccessful in alleviating her symptoms.
Clinical History

Three weeks prior to admission to our institution she developed blurred vision and “double vision” with drooping of her left eyelid.
Clinical History

• On physical examination she appeared healthy but with ptosis of her left eyelid with inhibition of both lateral and medial gaze.

• An MRI and CT examination were performed.
MRI Examination
T1 Weighted Image

- 4cm mass replacing sphenoid sinus extending into nasopharynx
- Signal intensity isointense to muscle but heterogeneous
MRI Examination
T2 Weighted Image

- Homogenous enhancement following intravenous contrast injection
- Replacement of cavernous sinuses
- Left wing of sphenoid was enhanced as was the tuberculum sella
- Brain parenchyma was normal
Maxillofacial CT

- Marked hyperostosis of the posterior ethmoid sinus
- Mass effect on nasal septum
Radiologic Diagnosis

• “We favor the diagnosis of meningioma filling the sphenoid sinus and pituitary fossa”.
ENT Evaluation

- Nasal endoscopy demonstrated a mass in the superior portion of the nasopharynx which was smooth and mucosally-covered.
- The neck was free of adenopathy and no lesions were appreciated in the oral cavity.
- Following endoscopic evaluation she underwent biopsy of the mass.
Gross Pathology

- White
- Fleshy
- Minimal Vascularity
Histopathology

- Woven bone without osteoblastic rimming
- Spindle cell neoplasm with osteoid formation
- Significant cellular pleomorphism
- Increased mitotic activity (1-3/HPF)
Immunophenotype

- Vimentin (+)
- Cytokeratin (-)
- EMA (-)
- S-100 protein (-)
Subsequent Course

- Accepted three courses of chemotherapy (Cisplatin, Adriamycin and Methotrexate)
- Except for modest marrow suppression patient did well
- Regained function of left eye and felt clinically improved
- She refused further preoperative therapy
Subsequent Course

• She refused plan of: resection + post surgical gamma knife
• Sought radical resection at multiple other institutions
• Died nine months following initial diagnosis presumably of her disease or its sequela
Final Diagnosis

Osteosarcoma arising in a background of Fibrous Dysplasia

(involving the sphenoid bone, pterygoids and extending into the right nasal cavity)
A 40-year-old woman presented with a 2-month history of an enlarging mass of her right proximal forearm.

She had first come to medical attention due to an abnormal gait and a bowing deformity of her forelegs 35-years earlier.
She was of short stature with features suggesting deformities of her maxilla and zygomas bilaterally.
Multiple café-au-lait pigmented macules were present on her neck and back, predominantly left sided
A scar over her left buttock was secondary to an intra-muscular myxoma removed 10 years prior.
• There was a tender mass palpated over her right proximal radius.

• No epitrochlear or axillary lymph nodes were clinically enlarged.
Radiologic Findings

• Conventional radiographs demonstrated typical features of fibrous dysplasia in the pelvis, femurs, and humeri
Radiologic Findings

Radiographs of the right proximal radius demonstrated aggressive lytic destruction of bone with a modest periosteal reaction.
Radiologic Findings

MR of the elbow depicted the extent of the large proximal radial mass.
Three well-marginated intra-muscular masses were identified by MR in the left gluteus maximus
Pathologic Findings

On initial biopsy, a cellular spindle cell lesion in a background of skeletal muscle was seen.
A second biopsy was performed 4 days later. Pleomorphic spindled cells producing tumor osteoid was noted. There was a high mitotic rate but no necrosis.
Note the osteoid
Additional History

The patient underwent pre-operative radiation therapy, ifosfamide containing four-drug chemotherapy and subsequent surgical resection.
The patient had a surgical resection of her proximal radius and ulna, distal capitulum of the humerus and surrounding soft tissues and skin.

A 5 x 2.5 x 2.5 cm lobular tan tumor mass was identified within the proximal radius. The consistency varied from soft to “bone hard.”
Microscopic Features

Residual osteoblastic osteosarcoma was identified with a Huvos histologic response grade of III. (< 5% viable tumor)
Microscopic Features

All margins were free of tumor but all 3 bones demonstrated fibrous dysplasia
Follow-Up

The patient subsequently underwent resection of 2 of the larger gluteal masses. Gross and histologic evaluation revealed intramuscular myxomas.

Karyotyping showed a normal 46,XX
Additional History

2 years later, the patient re-presented with an enlarged mass on the lateral aspect of her elbow.

Radiology

Conventional radiographs of the humerus, radius & ulna showed changes typical of FD.

MRI of the distal right humerus demonstrated a heterogenous mass with ↑ T2-weighted signal.
A cell block showed markedly atypical cells with high pleomorphism was noted as were bizarre mitosis.
The patient underwent a right above-elbow amputation and a 10 x 6.5 x 3.7 cm soft tissue, cystic, red-brown mass was removed.
Histologic evaluation verified recurrent osteosarcoma
Cytogenetic studies using GTG banding techniques showed a normal female karyotype (46,XX) in the FD portion of the spectrum which was confirmed by FISH in 98% of the cells.
The 0GS demonstrated a 48,XX,+5,+7 karyotype
FISH carried out by us using probes for CH 5 (D5S23) & CH 7 (ELN, Link 1) showed trisomy 5 & 7 in ~66% of 0GS cells, 2% of FD cells & 0% of “normal” cells
Comparative Genomic Hybridization Findings

+Xp11.2-p22.1, +1p12-p31, +1q21-q25(1q23), -1q31-q44,-2,+3q, +4q, +5q11.2-q23, -5q31-q35, +6p11.2-p21.3, -6p22-p25, -6q, +7q, -8p, +8p, +8q11.1-q23, +9p, -10q, -11, -12q22-q24.3, +13q, +14q, -16, -17, -19, -22.
Etiology

- Clonal structural aberrations
  CH 3, 8, 10, 12, 15
- Trisomy 2
  - McCune-Albright Syndrome
  - Polyostotic FD
  - Monostotic FD
  - Pituitary adenoma
  - Intra-Muscular Myxomas

All have the same genetic abnormality
GNAS 1 mutation in the alpha subunit of stimulatory G protein
(CH 20 {20q13})

Schwindinger, W. et al.: *PNAS* 89: 5152-6, 1992
Activated Adenylyl Cyclase

GTP

α

Activated Adenylyl Cyclase

GDP

γ β


Protein Kinase C (PKC) Pathway

Activating mutations in \( G_\alpha \)

Arg201Cys
Arg201His
Activated Adenylyl Cyclase (ON)

GTP

GTP

ATP

cAMP + Ppi

L

R

PKA Pathway

PKC

DAG

PIP₂

PLC

PKA

RS CS

RS CS

RS

RS

PKA

STK

ATP

P

Mobilization of intracellular Ca²⁺

IP₃

Arg201Cys

Arg201His

Activating mutations in $G_s$α

PKC Pathway

ATP

ADP

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Siegal, G. et al., WHO Classification of Tumours of Soft Tissue and Bone, 2012
Activating Missense Mutations in the GNAS gene

- R201H  57%
- R201C  38%
- Q227L  05%

R = Arginine  Q = Glutamine
H = Histidine  L = Leucine
C = Cysteine
Etiology

c-Fos is also overexpressed in FD thereby:

- Activating mutations in GNAS 1 → ↑ Adenylyl cyclase
- Neoplastic progression & transformation → ↑ c-Fos
- Activation of PKC & PKA Pathways
Etiology – Con’t

• Why do mutations in one gene (GNAS 1) cause different diseases?

• Why are clinical manifestations variable in distribution and appearance?
Etiology – Con’t

- Mutations occur post-zygotically in a somatic cell
- Expression depends on size of the cell mass during embryogenesis
- Where in the cell mass the mutation occurs determines the phenotype

Sarcomatous changes are RARE in:

**Fibrous Dysplasia**
- 0.4 – 0.5% in fibrous dysplasia
- 4% in McCune-Albright syndrome

**Mazabraud’s Syndrome**
- 3/36 patients (includes current patient developed sarcoma (8.3%)
- Of these 36 patients, 11 had McCune Albright
- 2 of these 11 patients developed osteosarcoma (18.2%)

Prognosis and Treatment

- Spontaneous resolution has been reported
- Curettage, cryosurgery &/or bone grafting if symptomatic
- In polyostotic disease often osteotomies or internal fixations are required
- Radiation should be avoided
- Bisphosphonates in therapy & glucocorticoids may have a role

Conclusions

• FD is a benign neoplasm susceptible to malignant transformation
• Its molecular etiology is beginning to be understood
• It has a myriad of clinical, radiological, & pathological presentations
• It proper recognition leads most often to a non-aggressive treatment plan and a long life
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