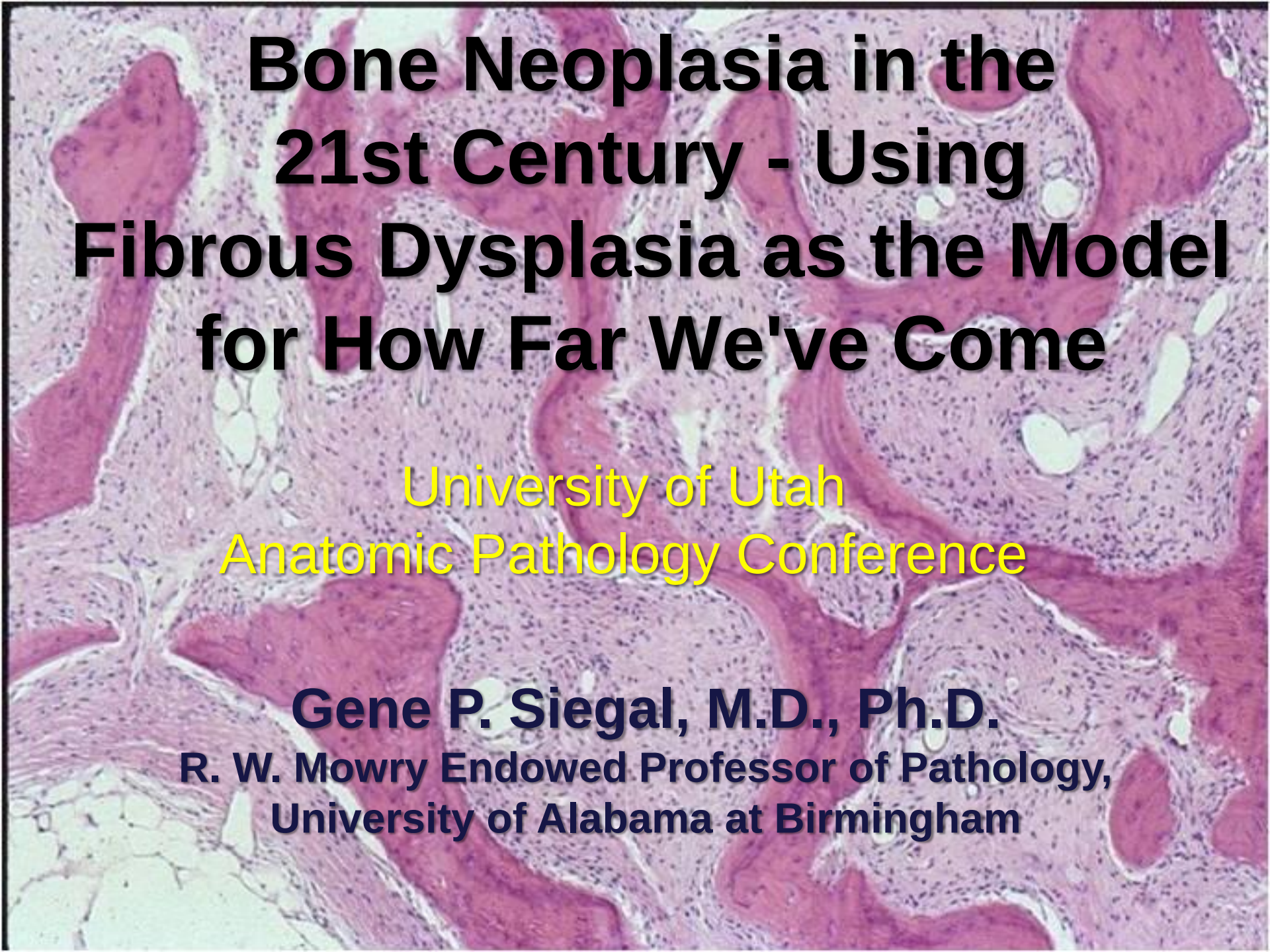

# Bone Neoplasia in the 21st Century - Using Fibrous Dysplasia as the Model for How Far We've Come

University of Utah
Anatomic Pathology Conference

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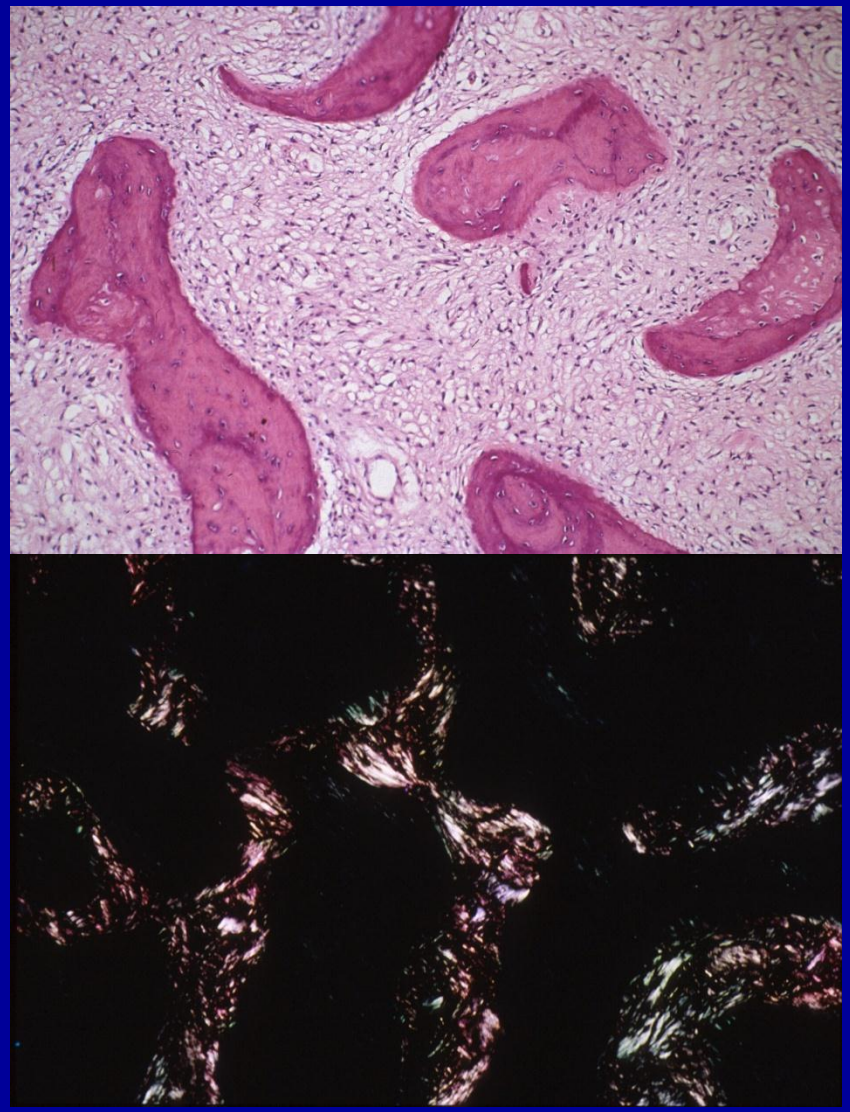
However, I declare no conflicts-of-interest with any topic discussed in my presentation today.

# Definition

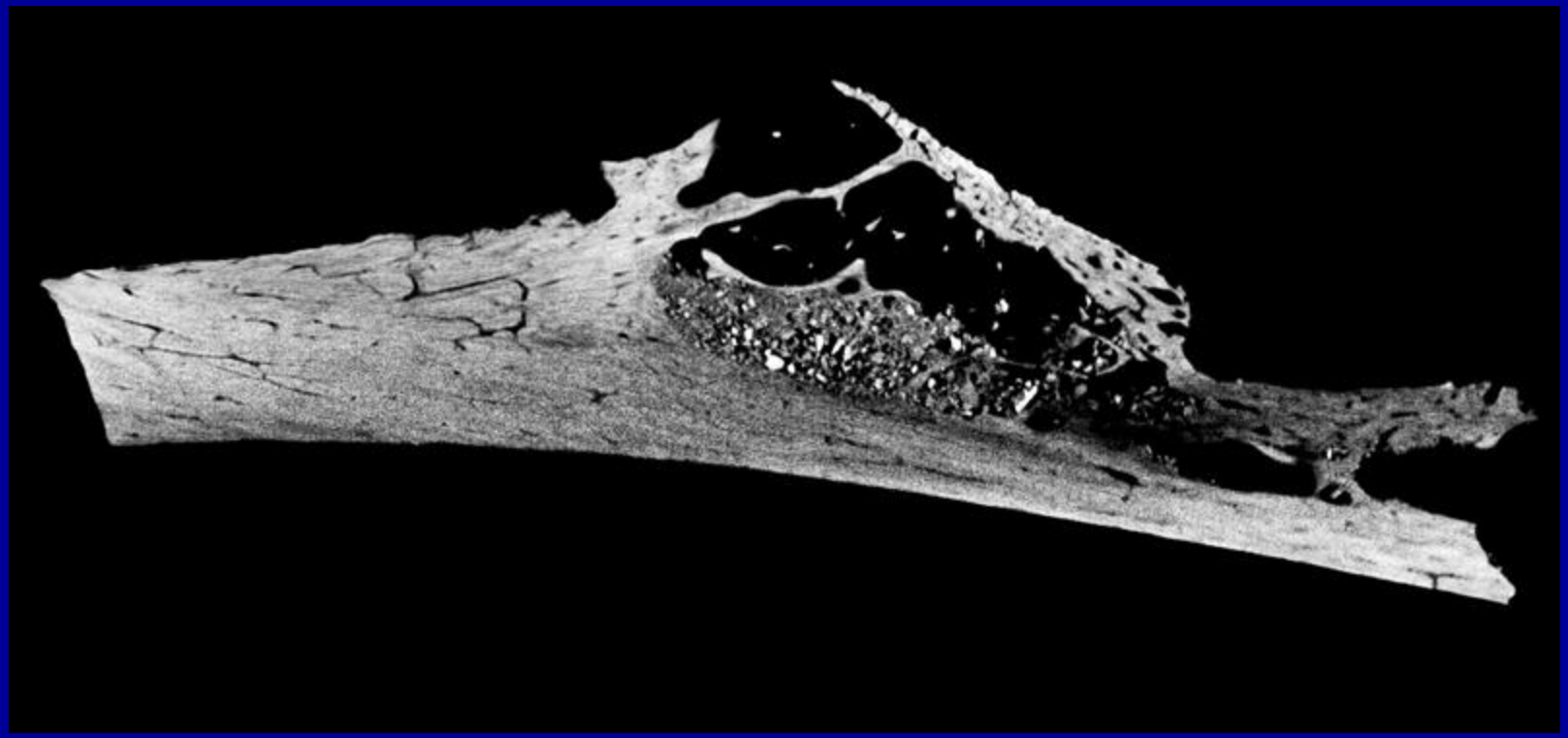
- FD is a neoplastic process involving primarily the intramedullary portion of from one to many bones.
- It is composed of randomly distributed spicules of woven bone, absent prominent osteoblastic rimming set in a background of swirling fibrous connective tissue.



# 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.

Monge J, et al. (2013) Fibrous Dysplasia in a 120,000+ Year Old Neandertal from Krapina, Croatia. PLoS ONE 8(6): e64539. doi:10.1371/journal.pone.0064539

# Suspected fibrous dysplasia from the rib of a Neandertal

- Essentially all bones reported
- Women favor long bone involvement
- Men favor ribs & skull

# Fibrous Dysplasia

**Monostotic** 6:1 **Polyostotic**

**Monomelic**
(1 extremity)

**Polymelic**
(diffuse)

**Hemimelic**
(1 side of body)

## Monostotic Form

1/3 Head & Neck
1/3 Femur & Tibia
1/3 Ribs

## Polyostotic Form

Femur
Pelvis
Tibia

Unni KK: Dahlin's *Bone Tumors* 369, 1996

Harris, WH et al. *JBJS* 44 (Am):207-2333, 1962

# 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

**Barbero, P. et al.: *Minerva Stomatol* 41:51-5, 1992**

**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**

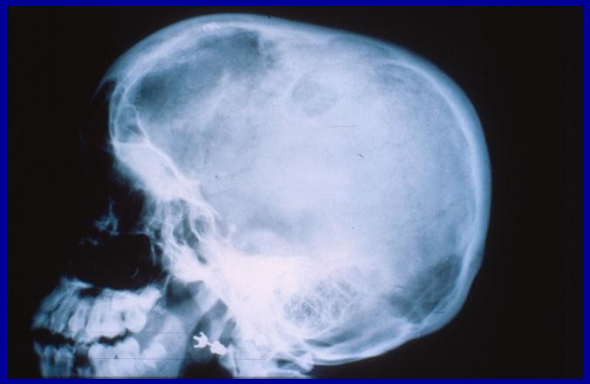
**Sakamoto, M. et al. *Otol Head Neck Surg* 125:563-4,2001**
**Joseph, E. et al.: *Pediat Neurosurg* 32:205-8, 2000**

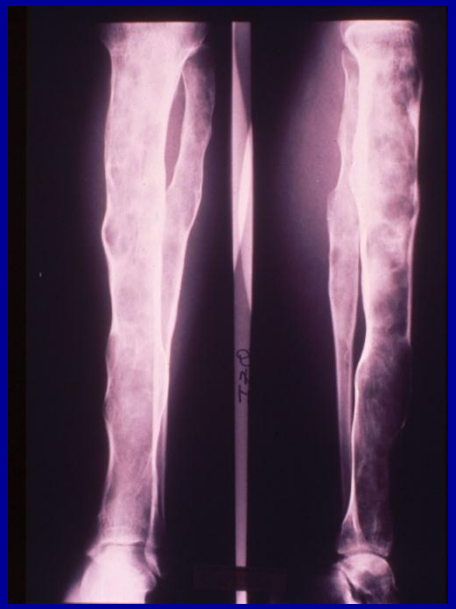
**Avimadje, A. et al.: Joint Bone Spine 67:65-70, 2000**
**Perlman, M. et. al.: J Foot Surg 26:317-21, 1987**

# Radiologic Imaging

## 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





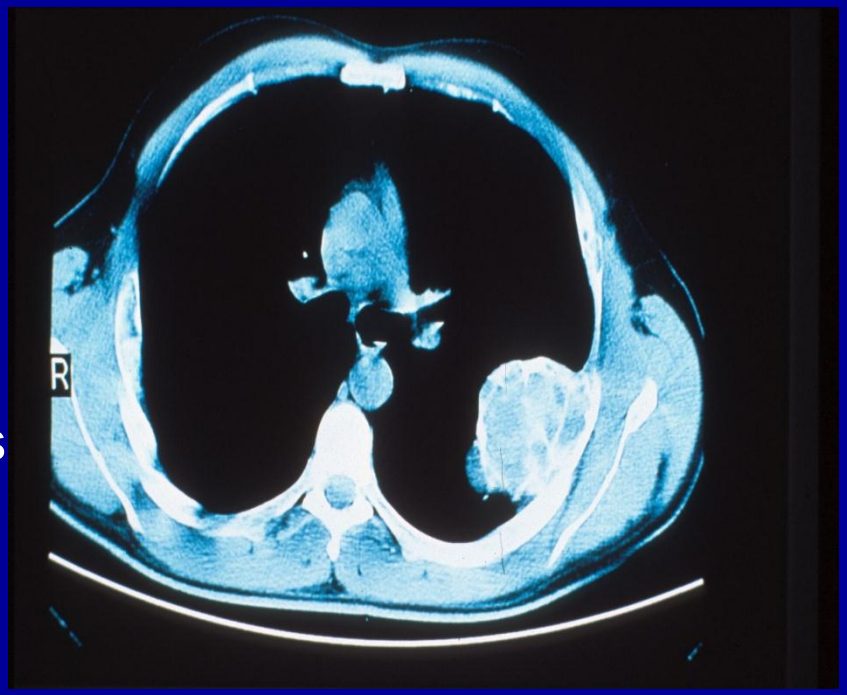
**Kransdor, F.M. et al.:** ***Radiographics*** **10:519-37, 1990**

**Smith, S. & Kransdorf, M.:** ***Radiol*** **4, 73-88, 2000**

# Radiologic Imaging

## Computerized Tomography

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



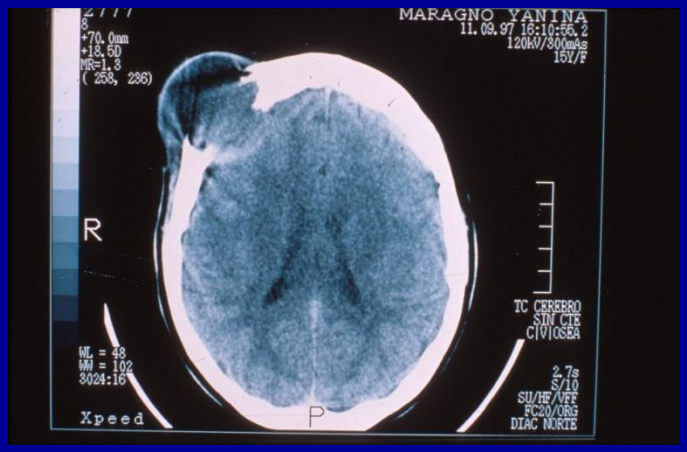

**Yao, L. et al.:** ***J Comput Assist Tomogra*** **18: 91-4, 1994**

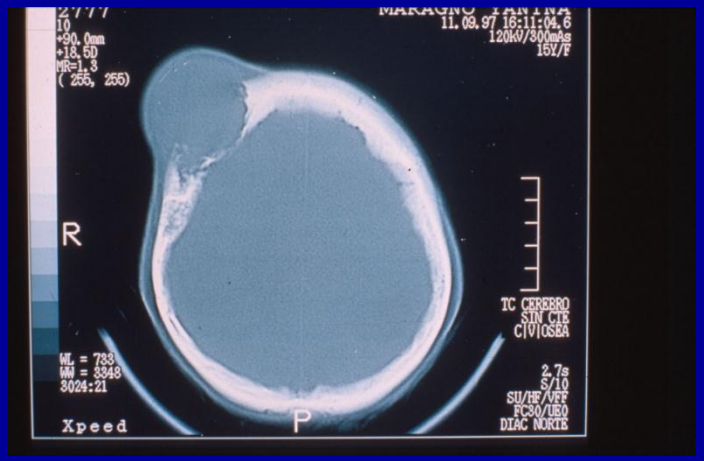
**Daffner, R. et al.:** ***AJR*** **139:943-8, 1982**

# 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



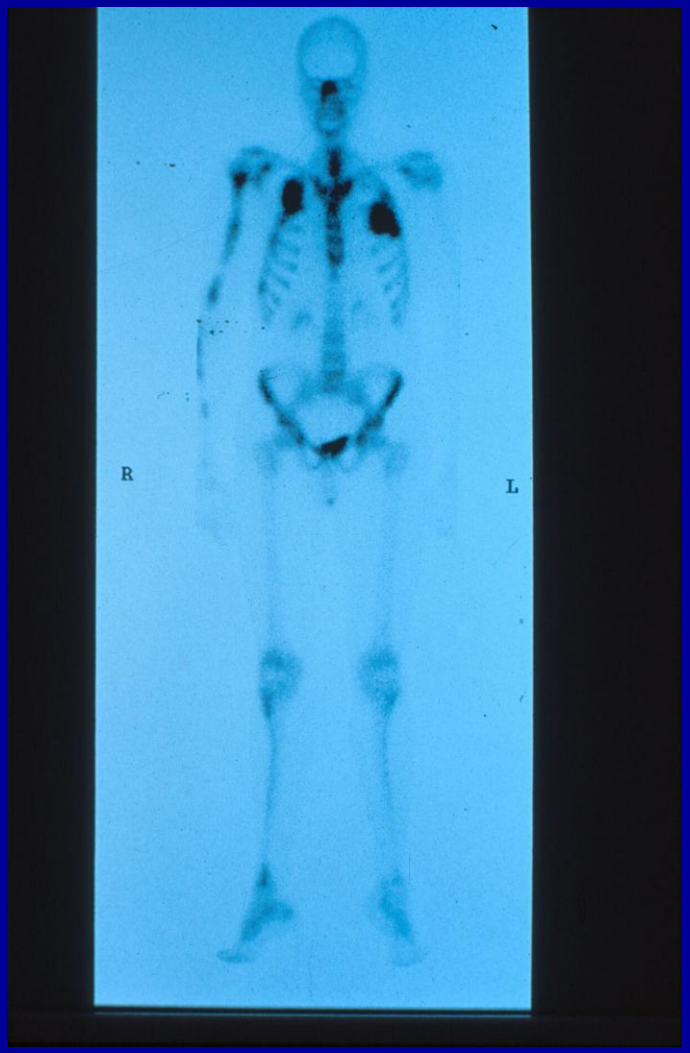




**Jee, W. et al.:** ***AJR*** **167:1523-7, 1996**

**Norris, M. et al.:** ***Clin Imaging*** **14:2 11-5, 1990**

# Scintography

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

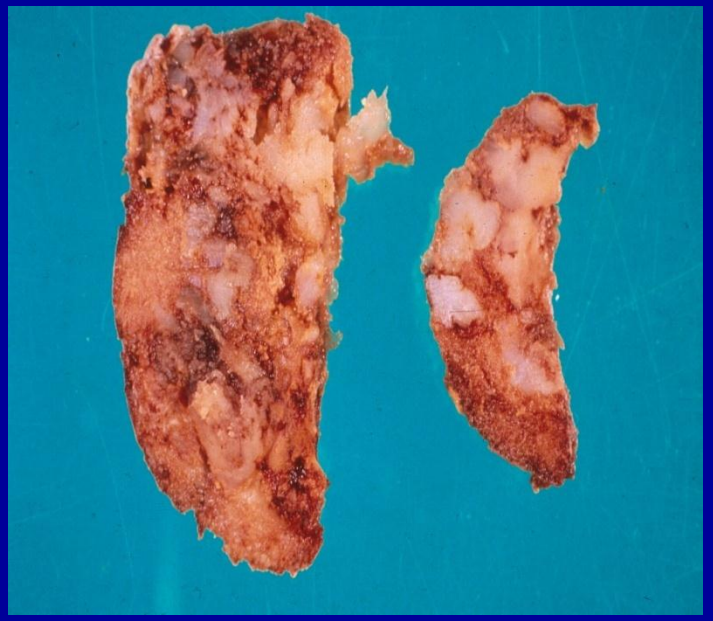



**Fukumitsu, N.: et al.: *Clin Nucl Med* 24:446-71, 1999**

**Hoshi, H. et al.: *Ann Nucl Med* 4:35-8, 1990**

# 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

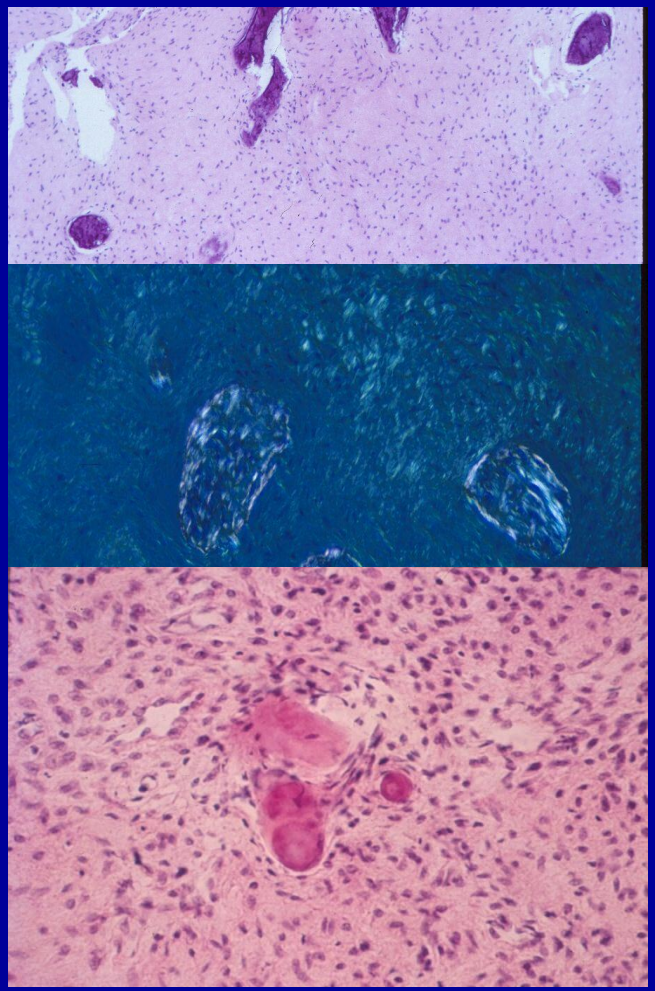


**Siegal, G. *Path of Solid Tumors in Children* 183-212, 1998**

**Dorfman, H. et al.: *Human Path* 25:1234-7, 1994**

# Histopathology

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

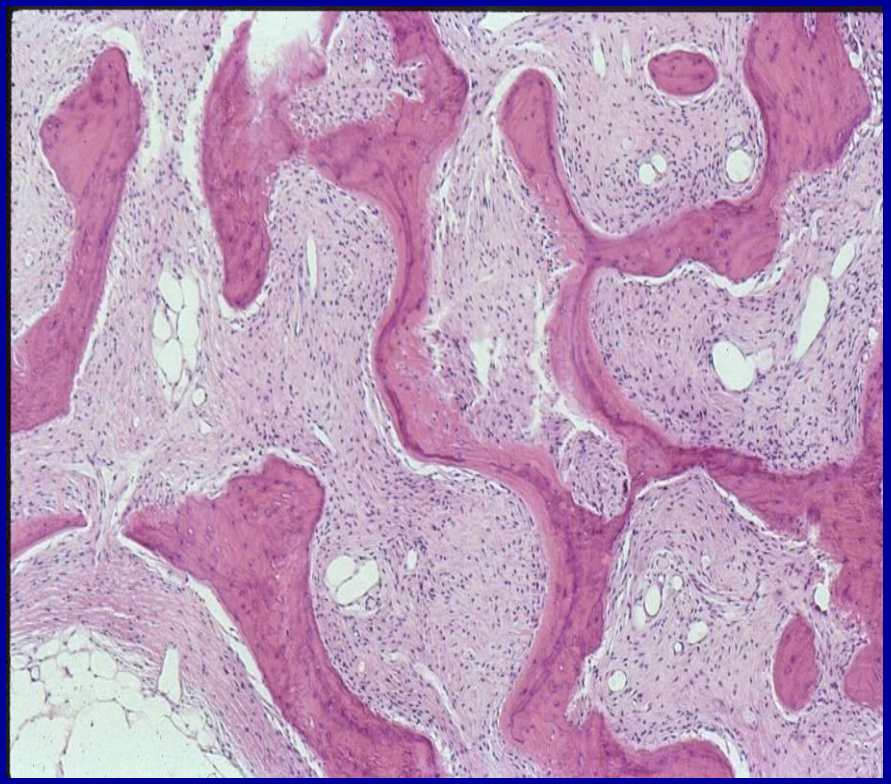


**Fechner, R. & Mills, S.:** ***Tumors of Bone & Joints*****, AFIP 147, 1993**

**Sissons, H. et al.:** ***Arch Path Lab Med*** **117:284-90, 1993**

# Histopathology – Con't

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



**Faure, C. et al.: *J. Radiol* 68:657-65, 1987; Asma, Z.: *Mod Path* 15:28A, 2002**

# Immunophenotype

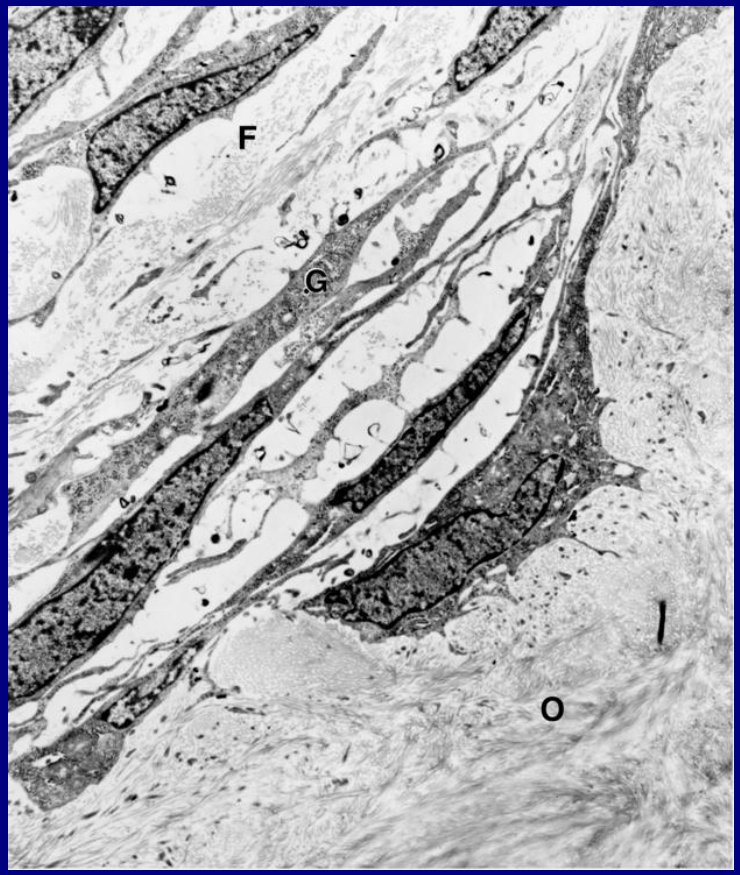
| Fibrous Component | BONE |
| --- | --- |
| VIM + | Osteonectin + |
| XIIIa + | Osteopontin + |
| BMP + | Osteocalcin + |
| | c-Fos +, c-Jun + |
| | Prostaglandin E-2 + |
| | ER+, PR + |
| | MIB-1 - Low |

**Kaplain, et al.:** ***New Engl J Med*** **319: 421-5, 1988**

**Jin, Y. & Yang, L.:** ***Clin Orthop*** **233-8, 1990**

# Ultrastructure

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




Ohira, O.: *Nippon Seikigeka Gakkai Zasshi* 55:497-507, 1981

# 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

**Fontana, et al.:** ***Minerva Chir*** **51:167-9, 1996; Atasoy, C. et al.:** ***Clin Imaging*** **25:388-91, 2001**

**Gateway, O. & Esterly, J.:** ***Am J Roent Rad Ther Nuc Med*** **97:110-117, 1966; Burd, T. et al.:** ***Orthopedics*** **24:1087-9, 2001**

# 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

**Sanerkin, N. & Watt, I: *Br J Radiol* 54:1027-33, 1981; West, R. et al.: *Am J Clin Path* 79:630-31, 1983**
**Ruggieri, P. et al.: *Orthopedics* 18: 71-5, 1995; Iwasko, N. et al.: *Skel Radiol* 31:81-7, 2002**

# Syndromes Associated with FD

## Mazabraud's syndrome

**Mazabraud, A. et al.: Apropos de l'association de fibromyxomes des tissus mous a la dysplasie fibreuse des os. *Presse Med 75:2223, 1967.***

**Henschen,F.: Fall von osteitis fibrosa mit multiplen tumoren in der umgebenden muskulatur. *Verh. Dtsch Ges. Pathol* 21:93-97, 1926**

## 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

**Ruggieri, P et al.: Cancer 73:1411-24, 1994; Pack, S. et al.: *J Clin Endocrinol Metab* 85:3860-5, 2000; Huvos, A. et al.: *J Bone J Surg* 54 [Am]: 1047-56, 1972; Fukuroky, J. et al.: *Anticancer Res* 19:4451-7, 1999;**

***Beyerlein, M. 35 al.: Arch Otolaryngol Head Neck Surg* 123:106-9, 1997;Cheng, M & Chen, Y.: *Ann Plast Surg* 39:638-42, 1997**

# 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.

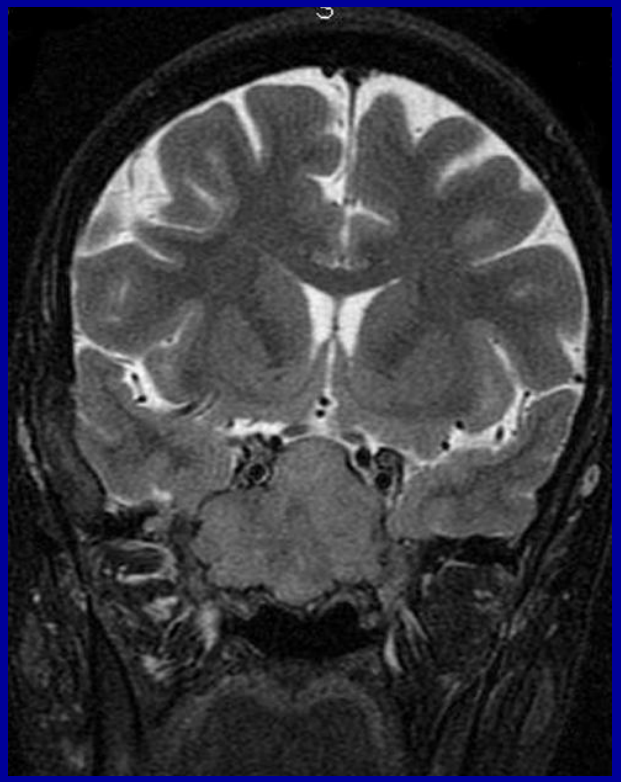
# Clinical History

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

# Clinical History

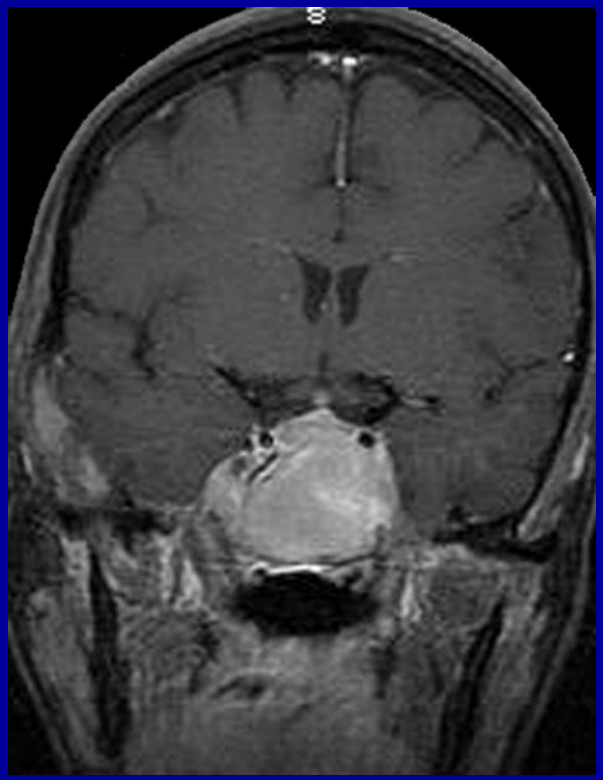
- On physical examination she appeared healthy but with ptosis of her left eyelid with inhibition of both lateral and medial gaze.
- An MRI and CT examination were performed.

# MRI Examination
# T1 Weighted Image



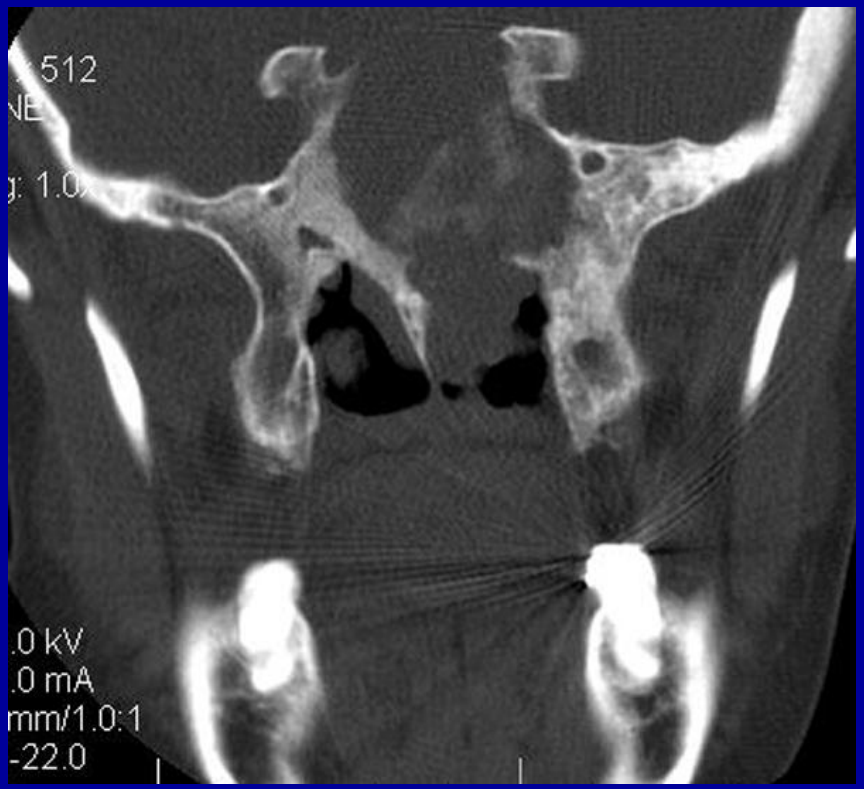
- 4cm mass replacing sphenoid sinus extending into nasopharynx
- Signal intensity isointense to muscle but heterogenous

# 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”.

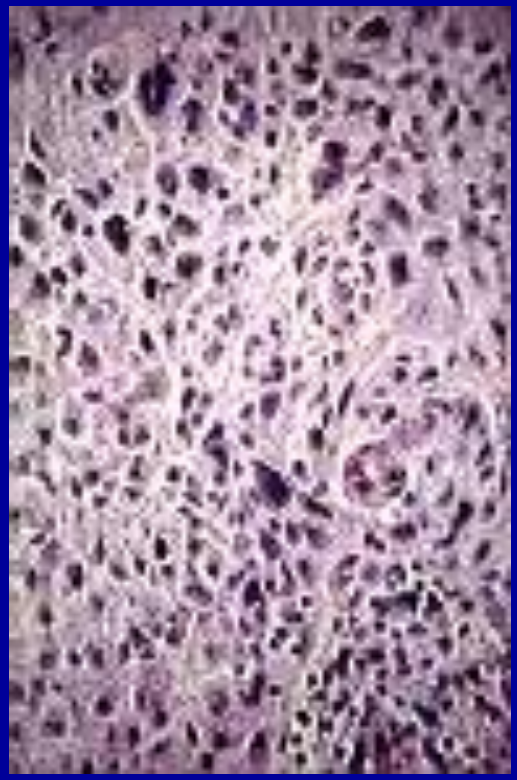
# ENT Evaluation

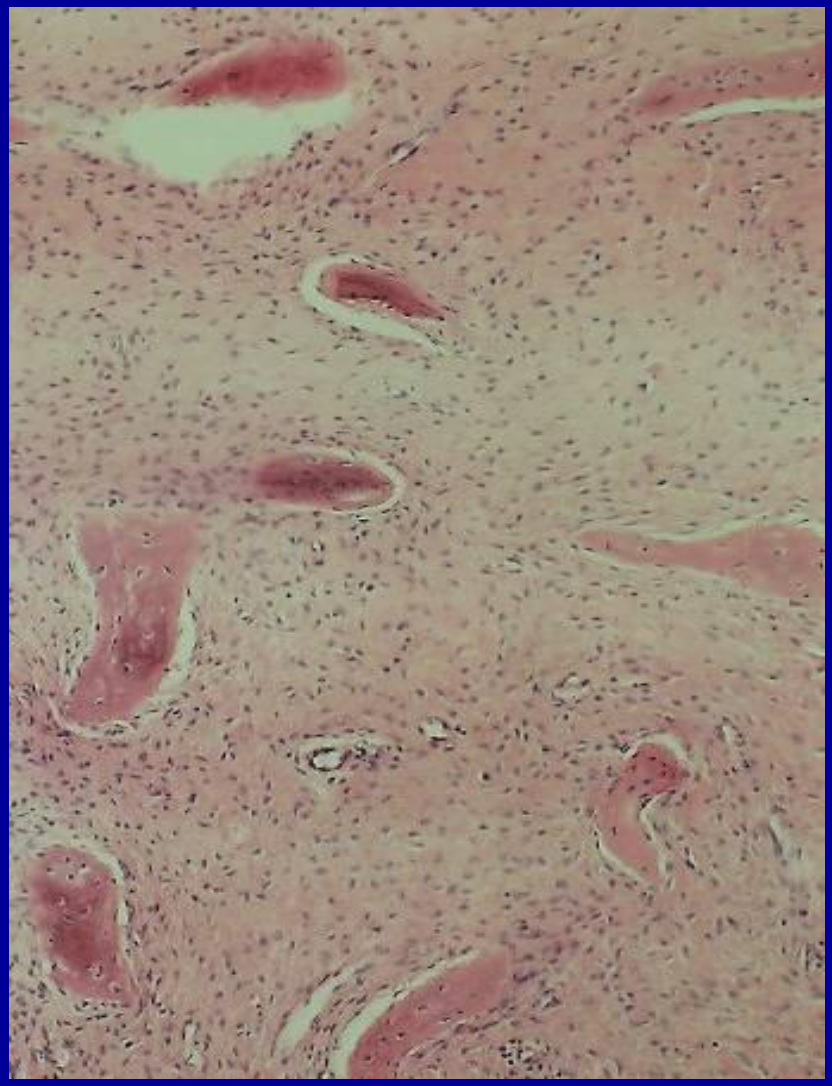
- Nasal endoscopy demonstrated a mass in the superior portion of the nasopharynx which was smooth and mucosally-covered.
- The neck was free of adenopathy and no lesions were appreciated in the oral cavity.
- Following endoscopic evaluation she underwent biopsy of the mass.

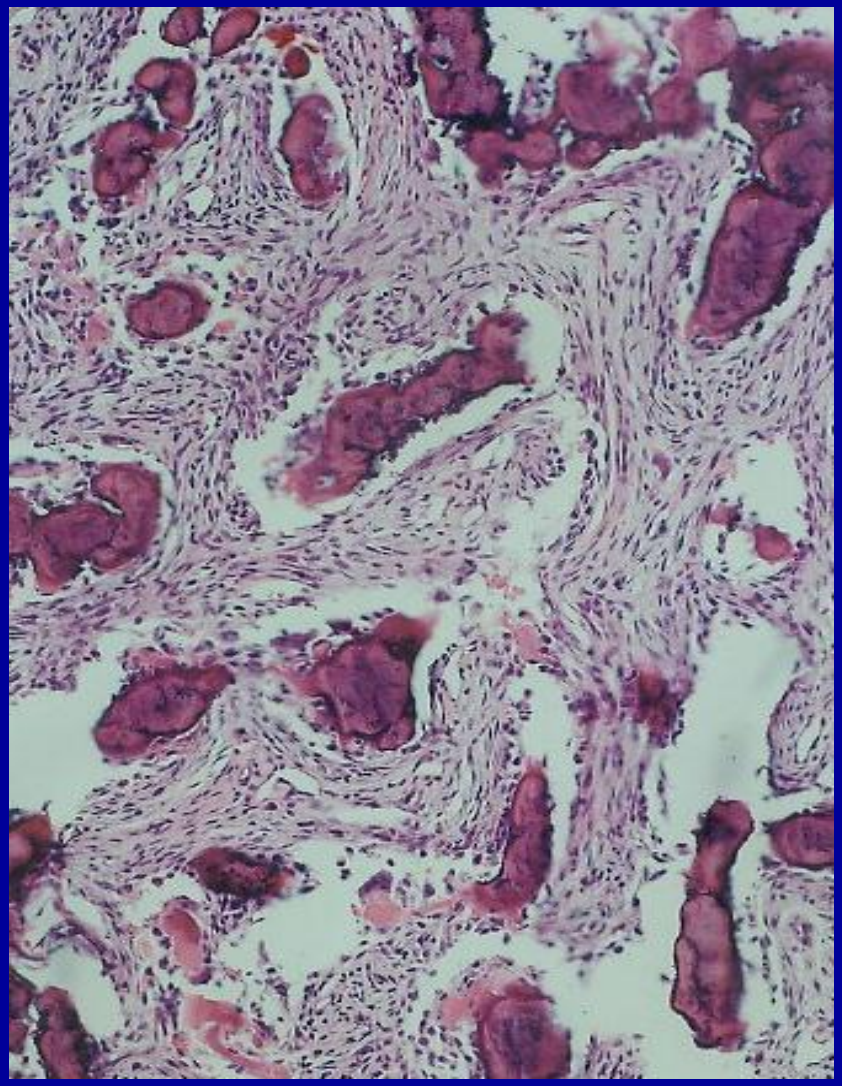
# Gross Pathology

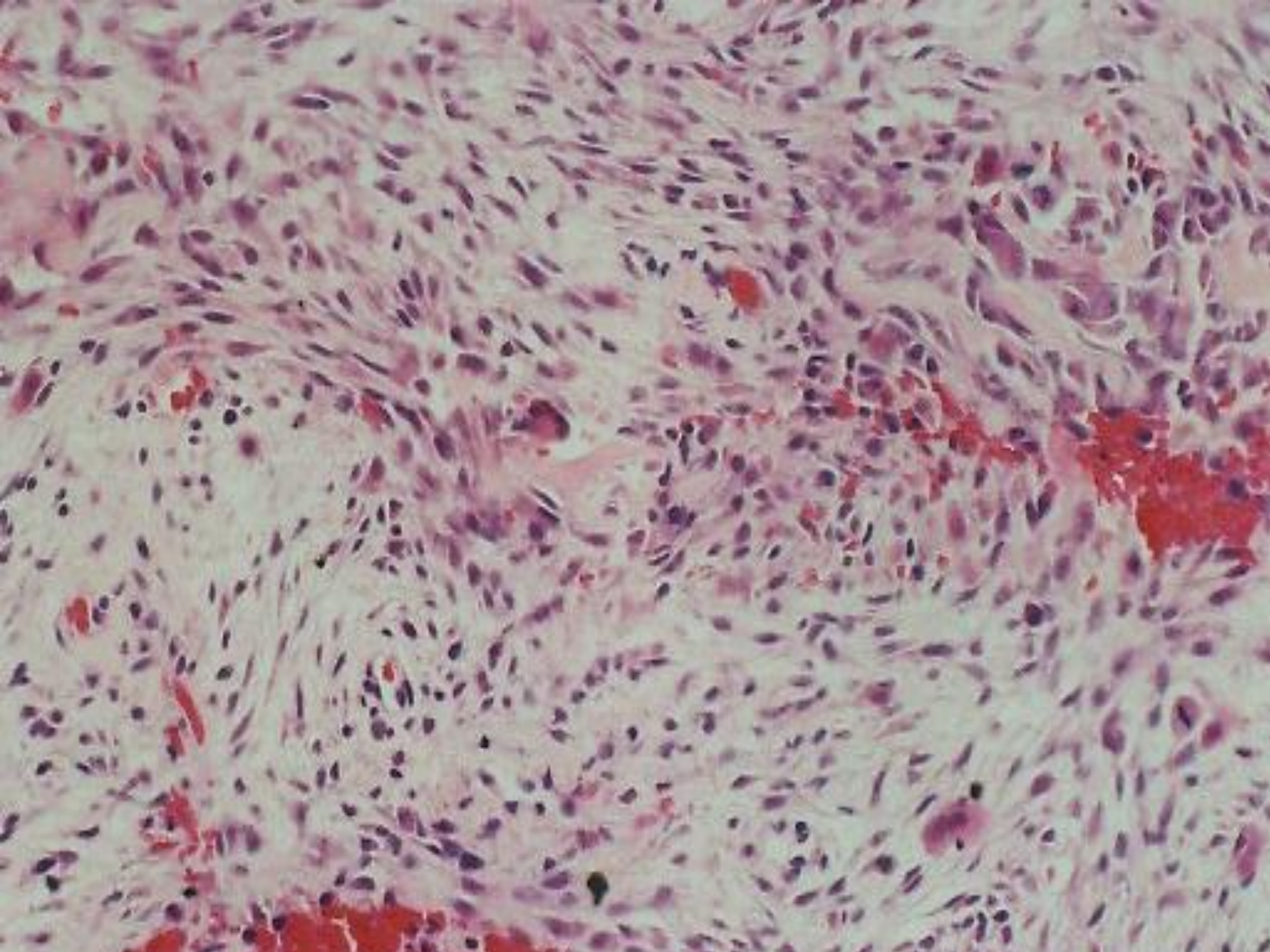
- White
- Fleshy
- Minimal Vascularity

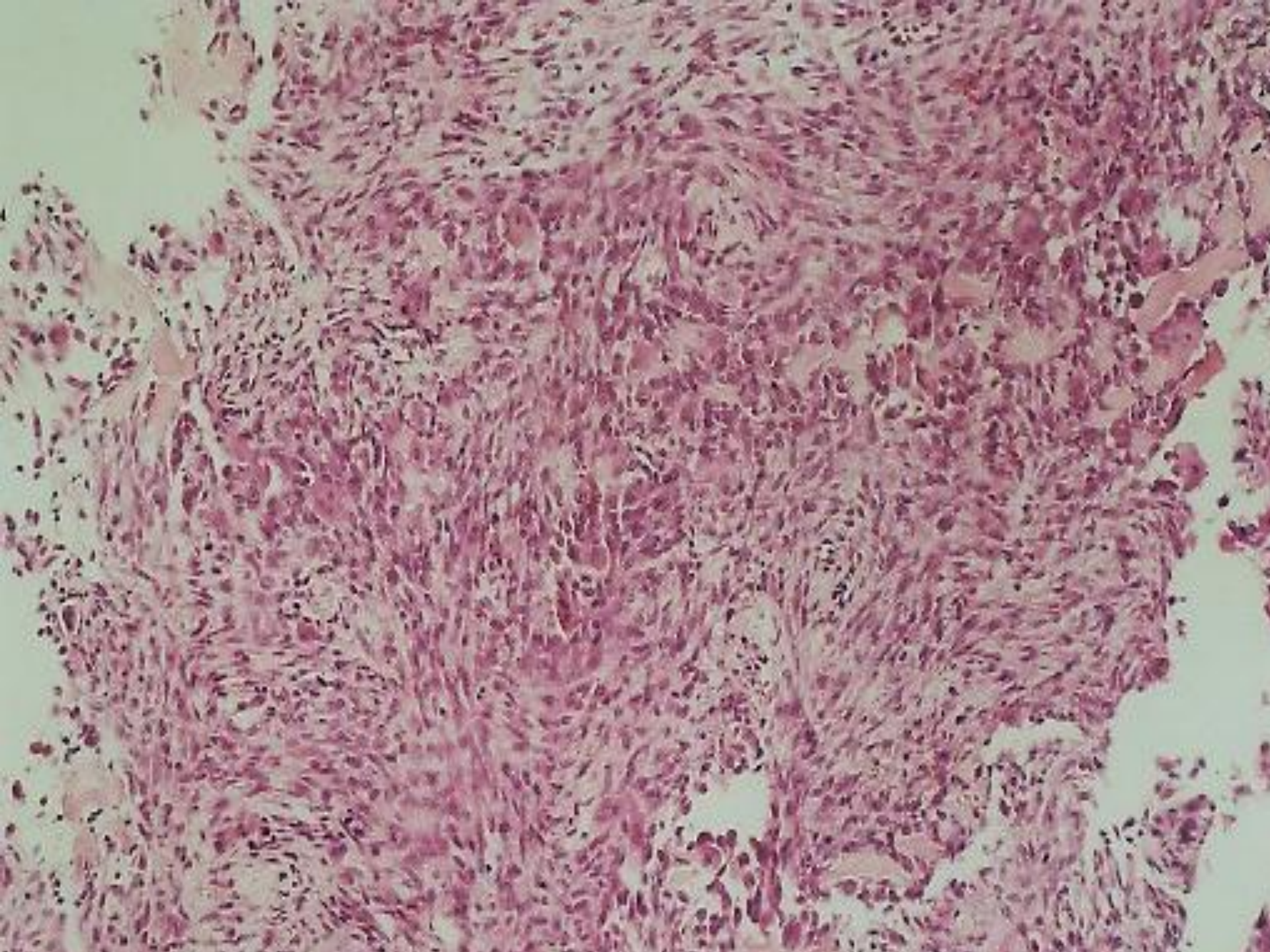


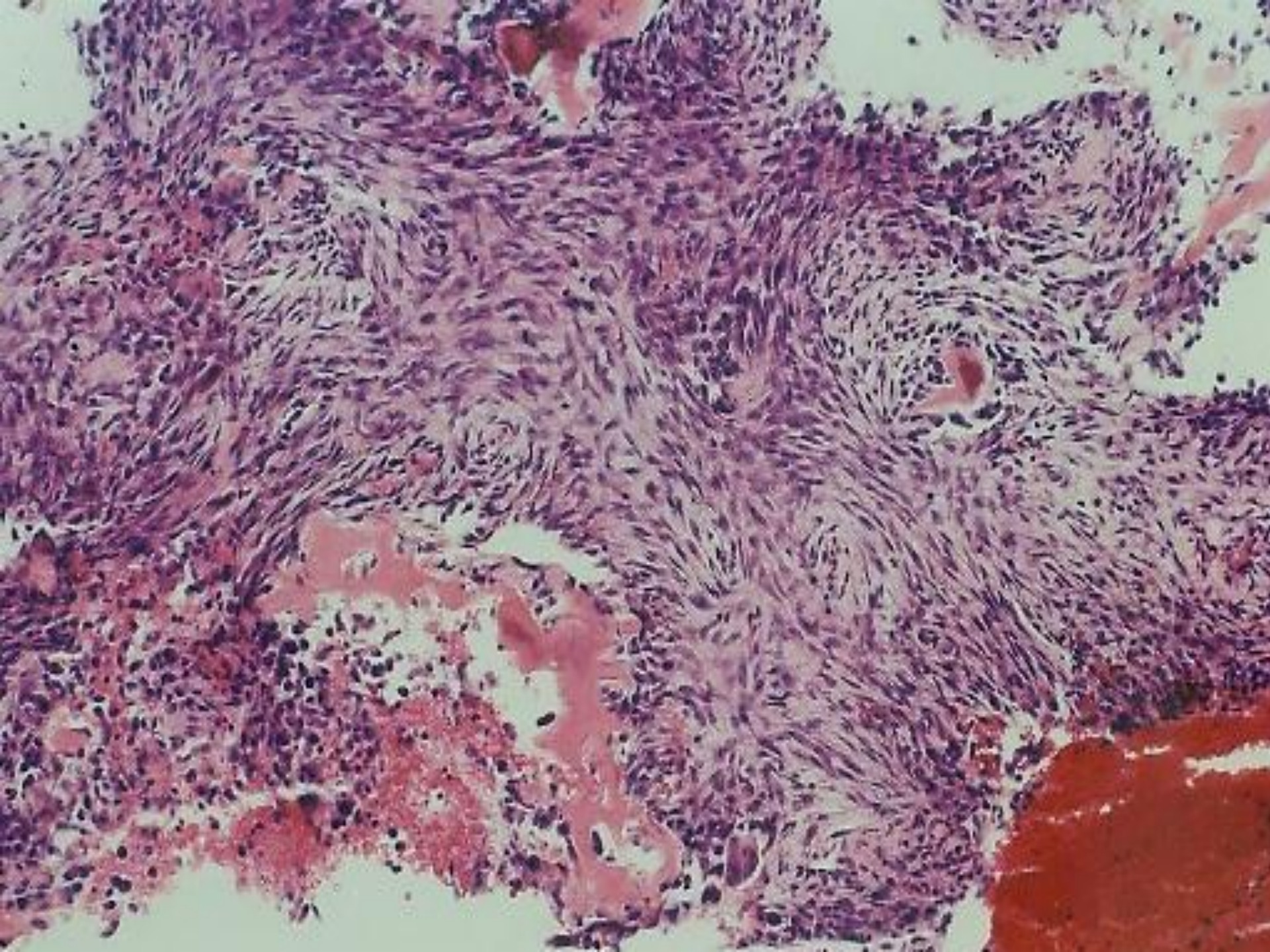


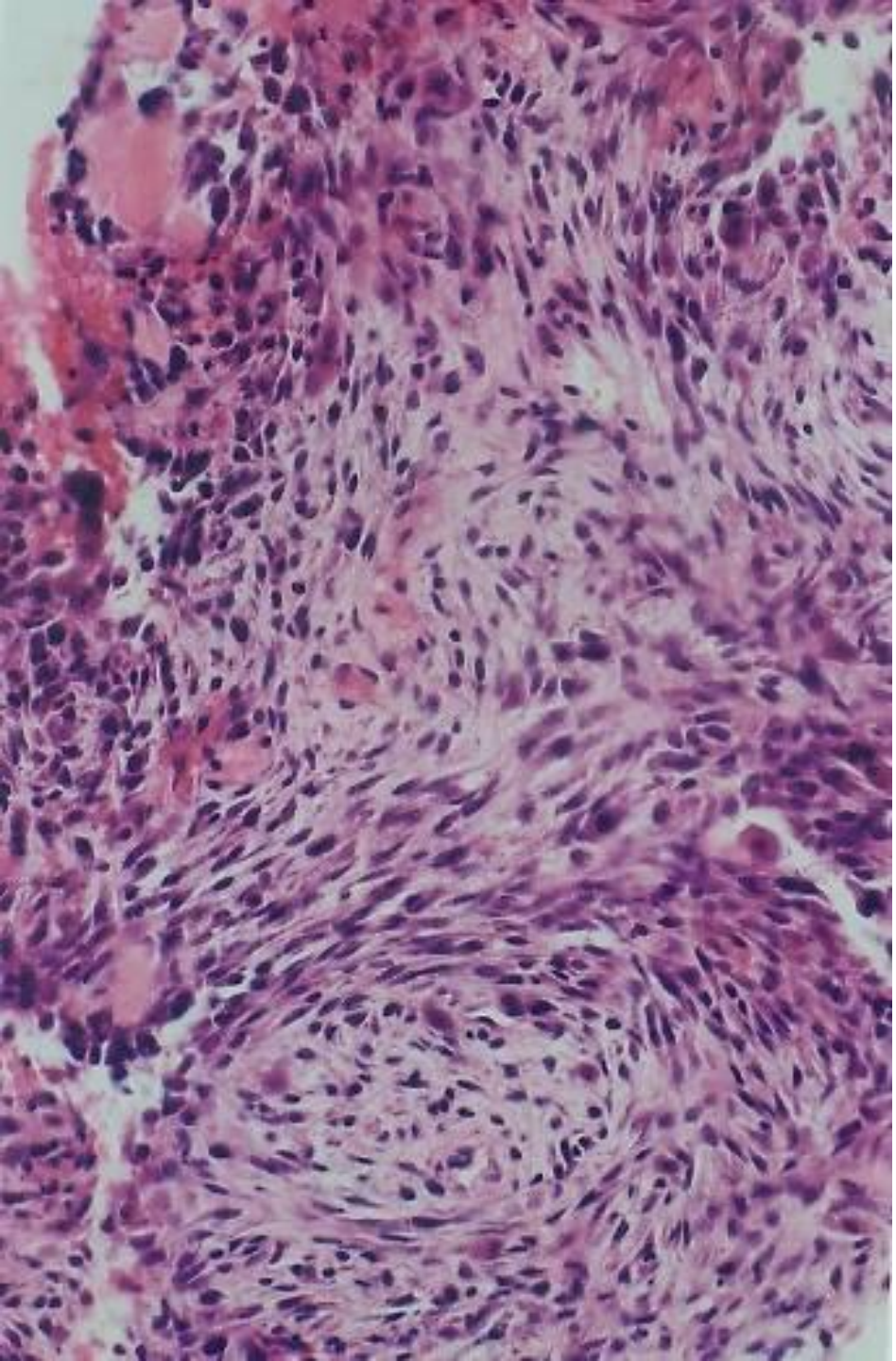
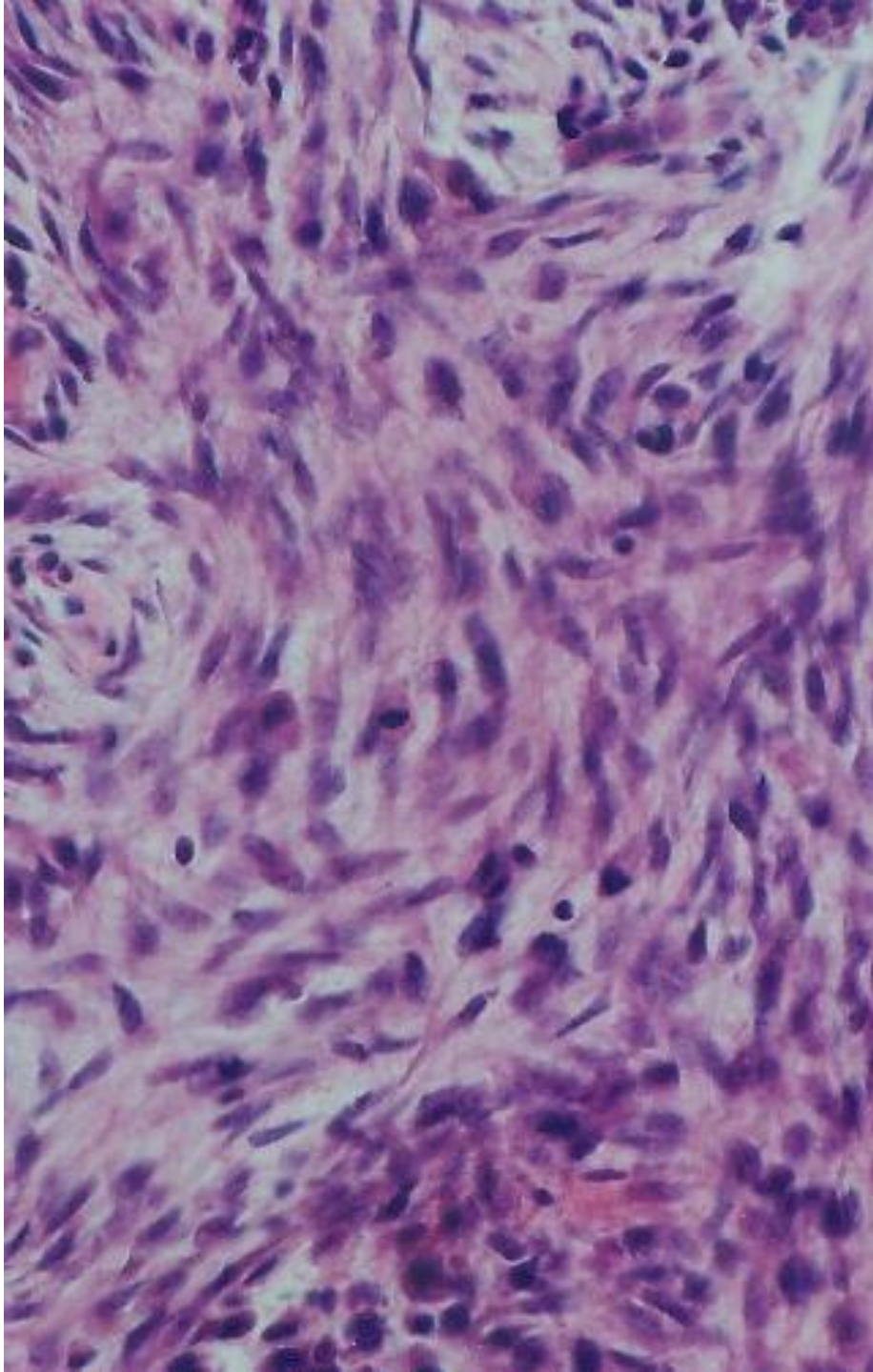










# Histopathology

- 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

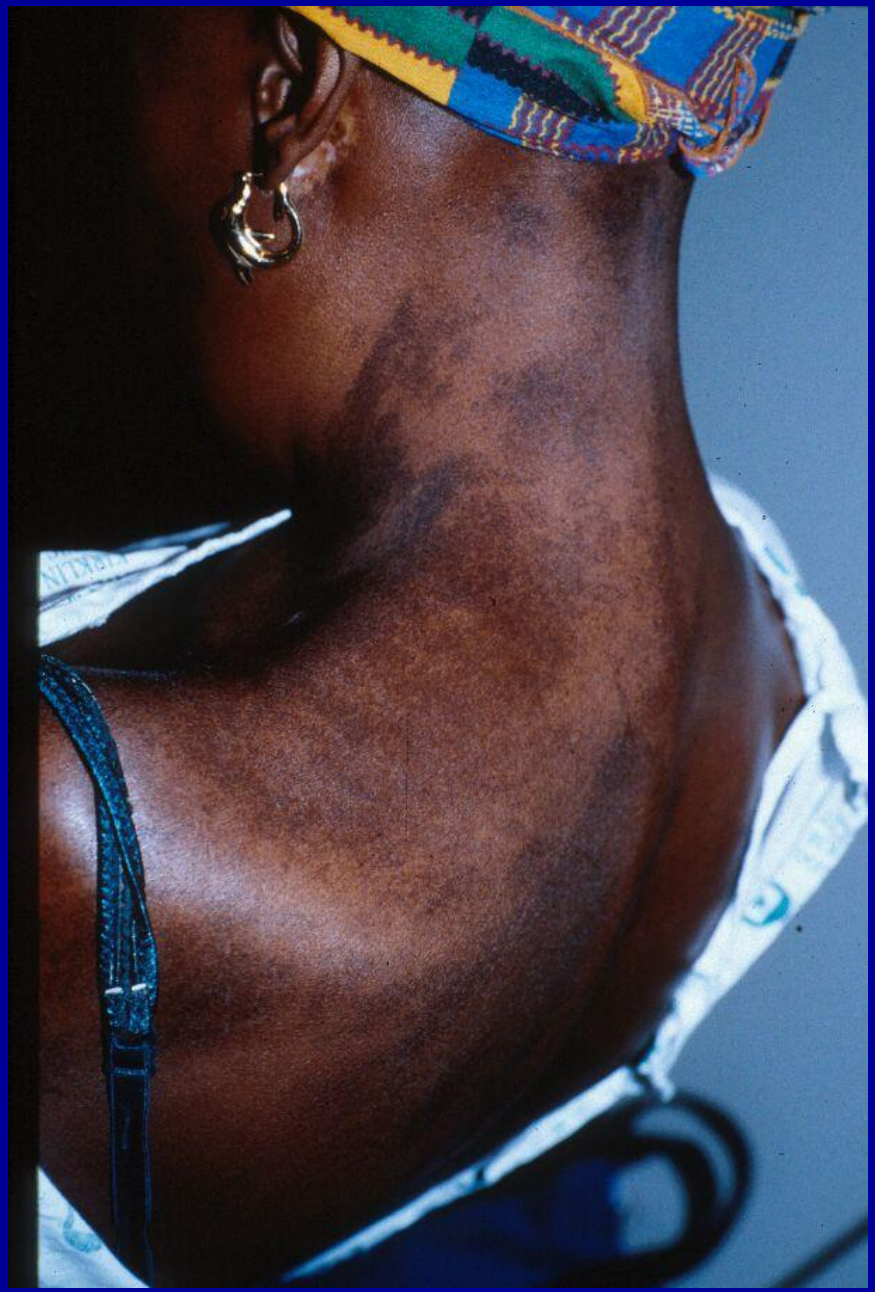
(involving the sphenoid bone, pterygoids and extending into the right nasal cavity)

# Representative Example of a Patient with Mazabraud's Syndrome

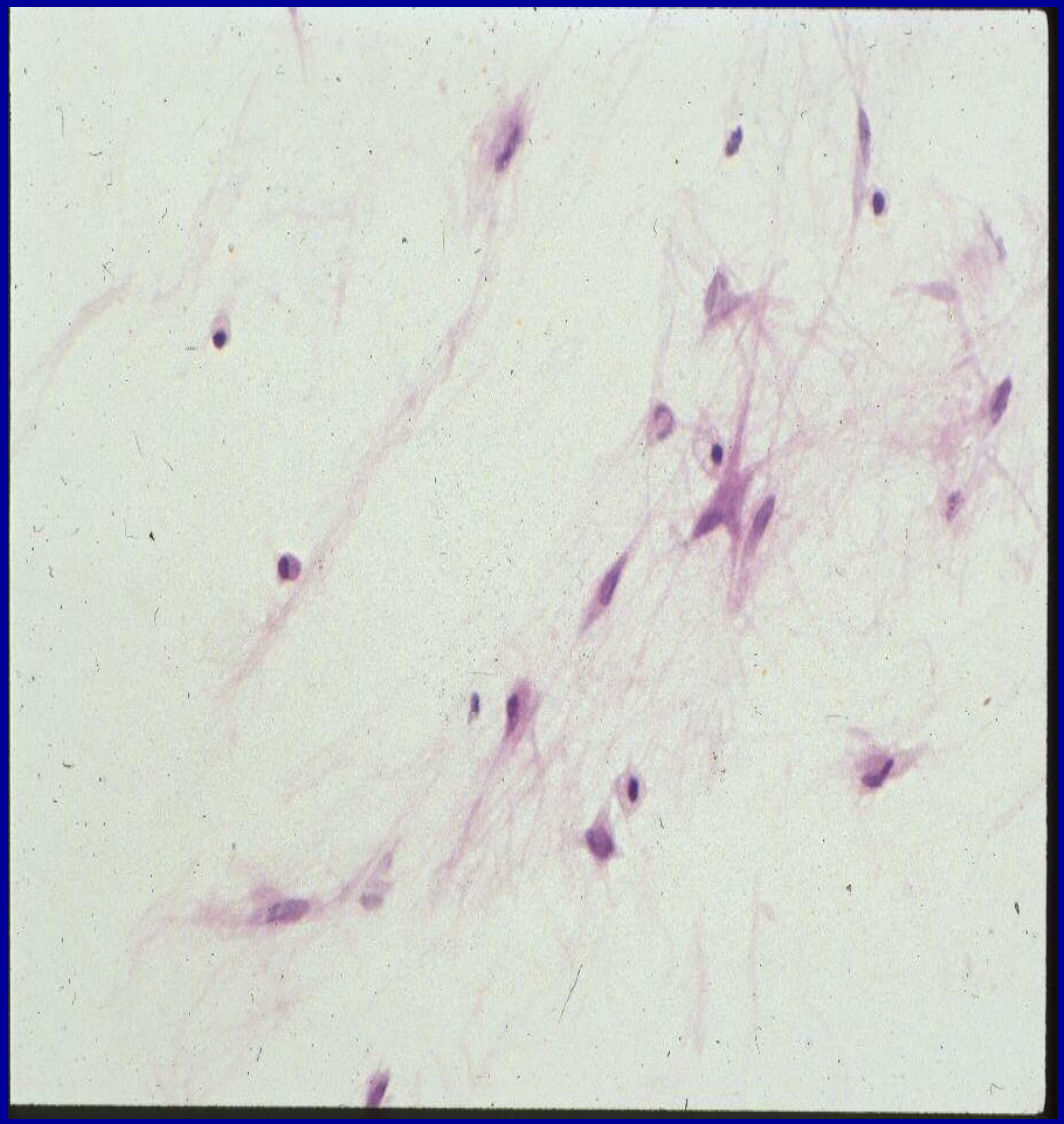
- **A 40-year-old woman presented with a 2-month history of an enlarging mass of her right proximal forearm.**

- **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 suggestion deformities of her maxilla and zygomas bilaterally



**Multiple café-au-lait pigmented macules were present on her neck and back, predominantly left sided**

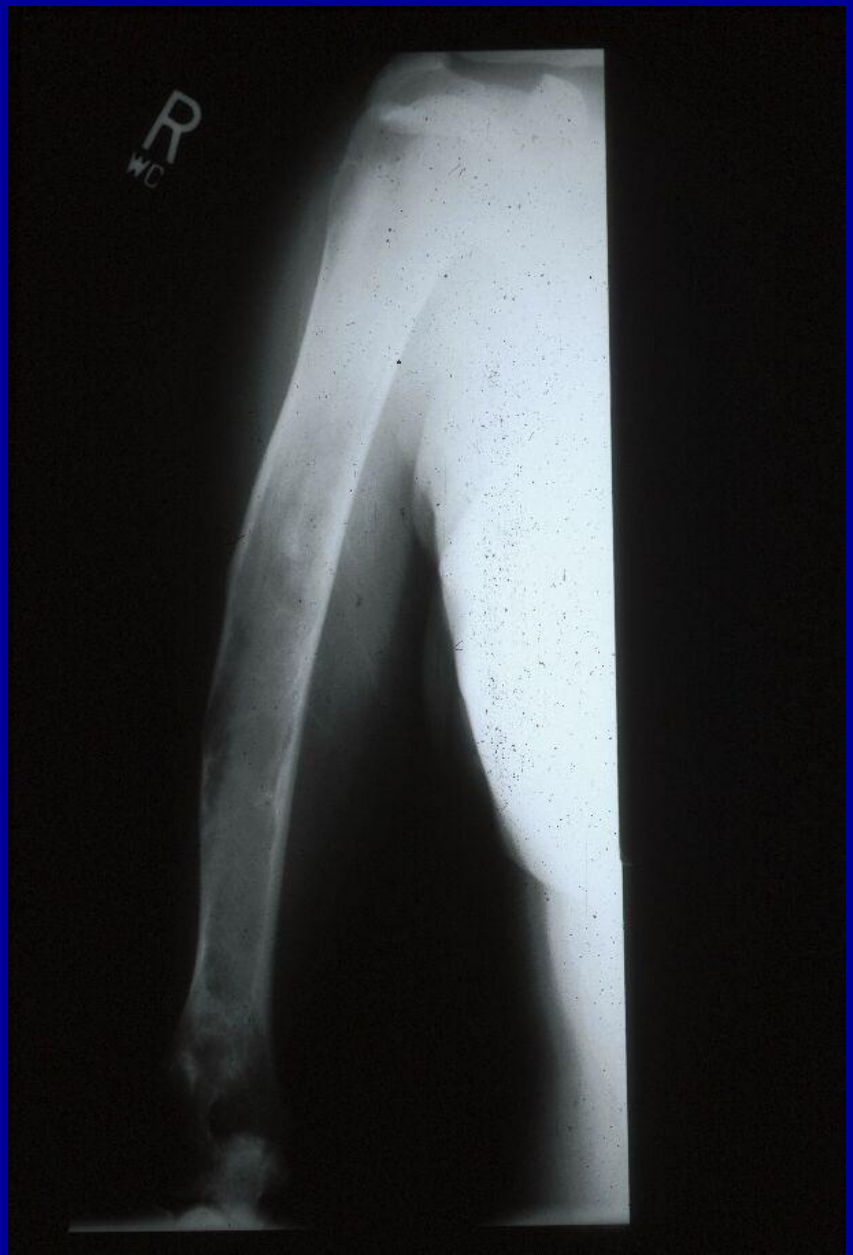


**A scar over her left buttock was secondary to an intra-muscular myxoma removed 10 years prior.**

- There was a tender mass palpated over her right proximal radius.
- No epitrochlear or axillary lymph nodes were clinically enlarged

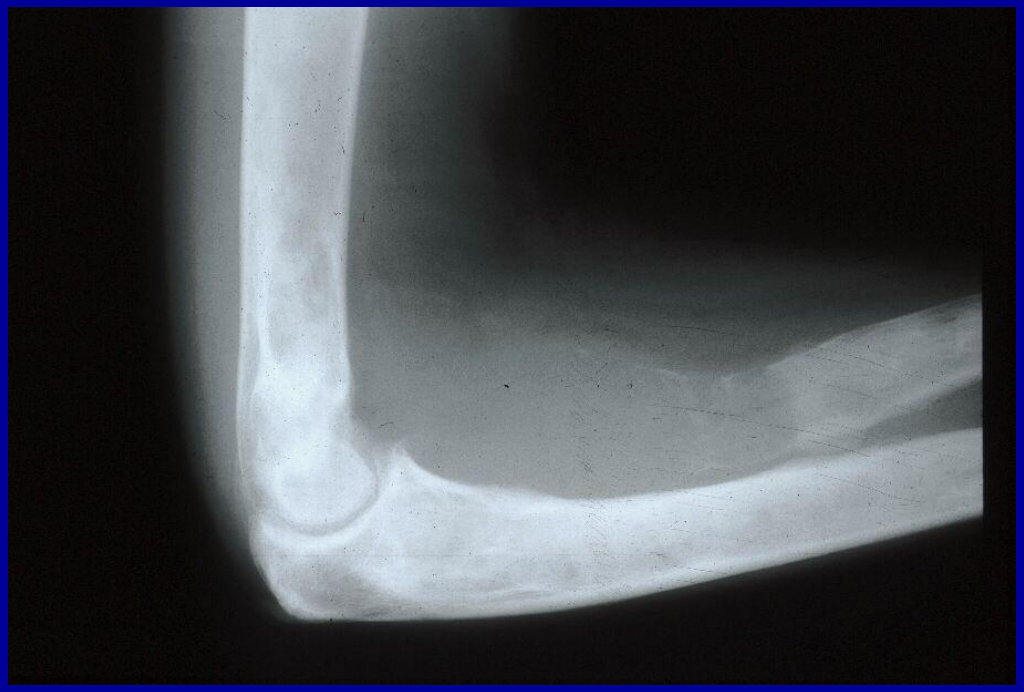
# Radiologic Findings

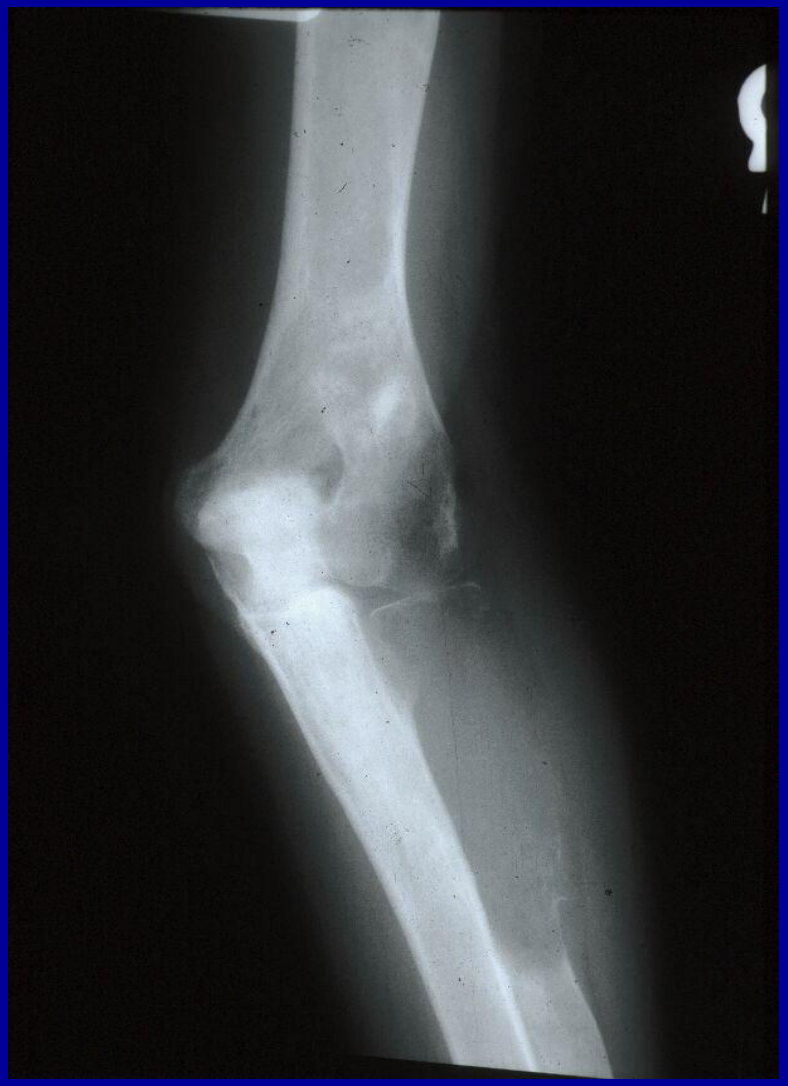
- Conventional radiographs demonstrated typical features of fibrous dysplasia in the pelvis, femurs, and humeri



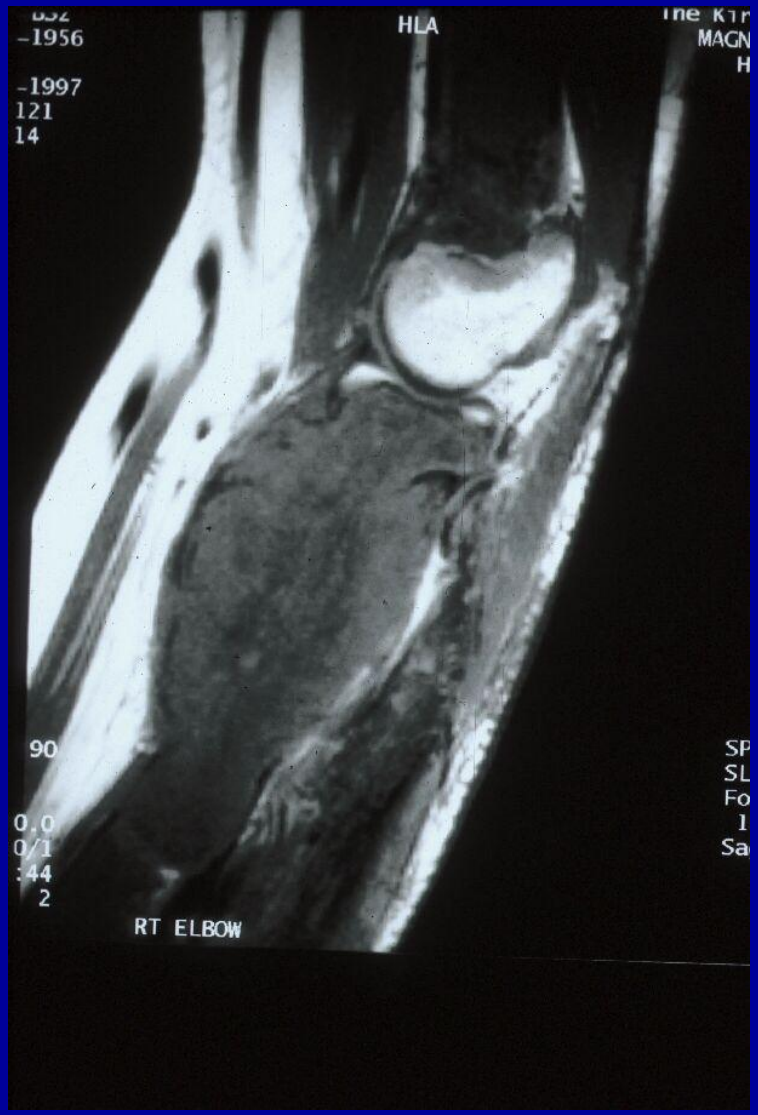
# Radiologic Findings

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

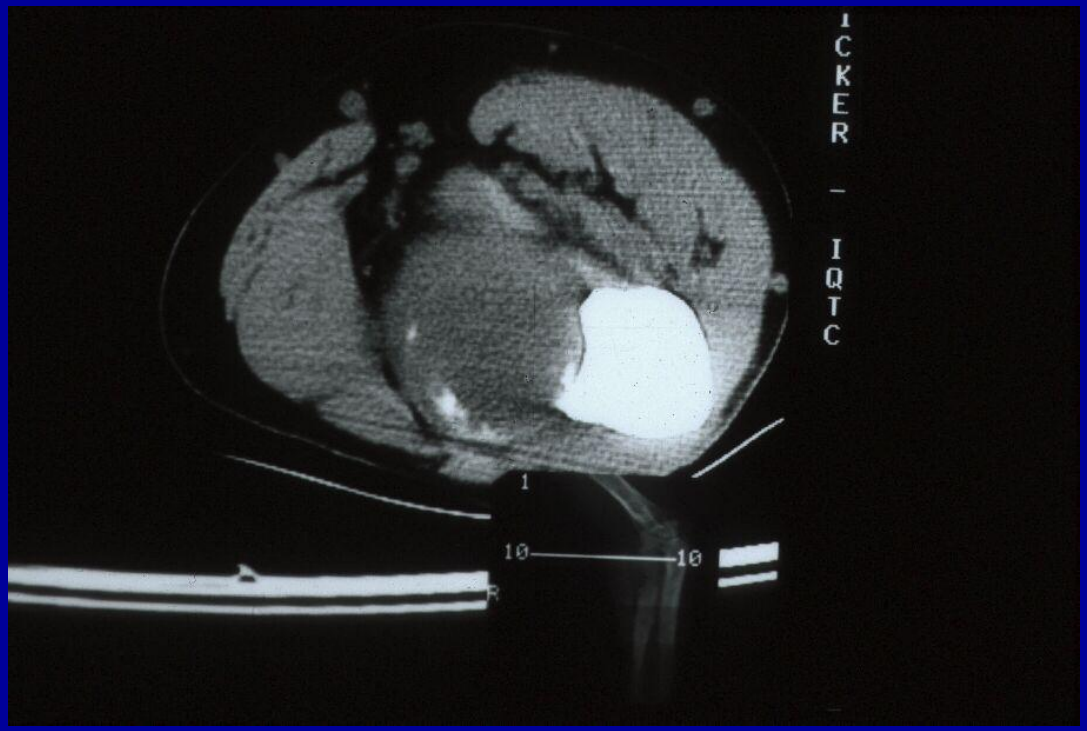


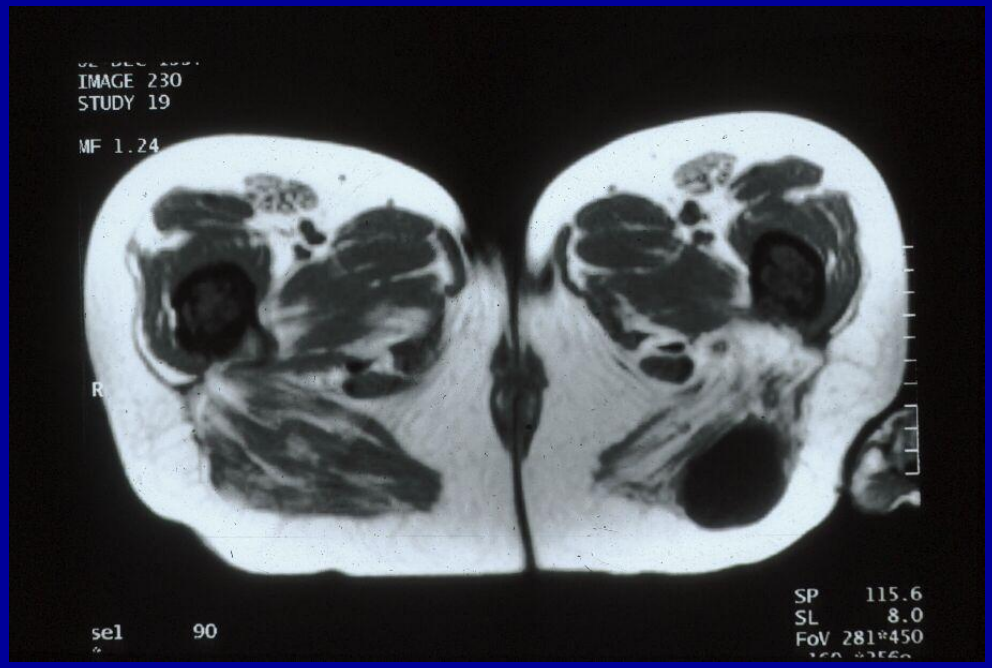


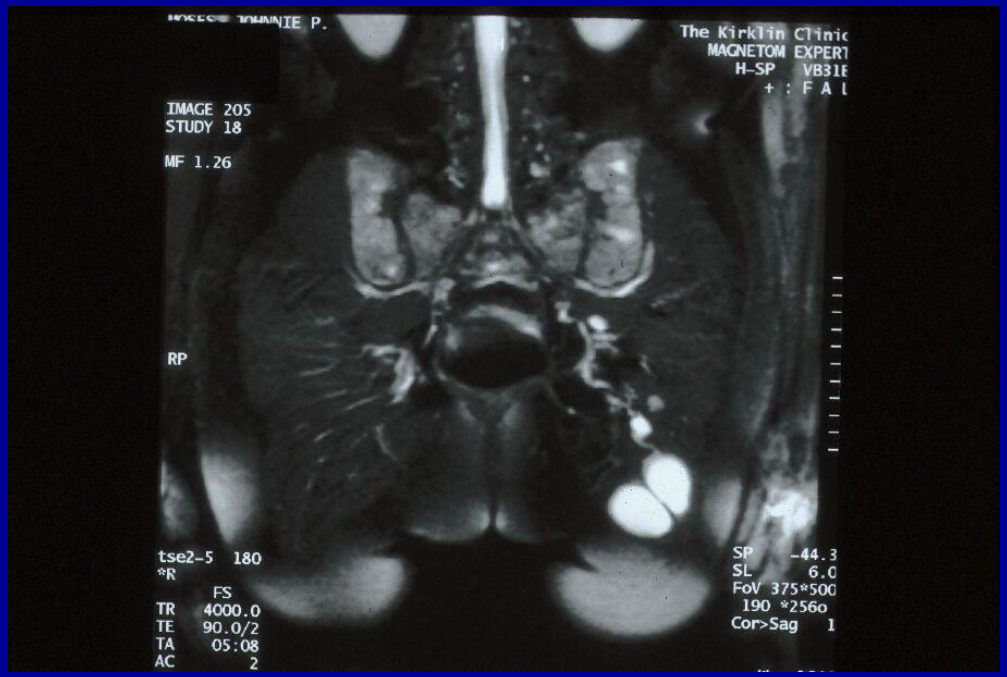
# Radiologic Findings




**MR of the elbow depicted the extent of the large proximal radial mass.**



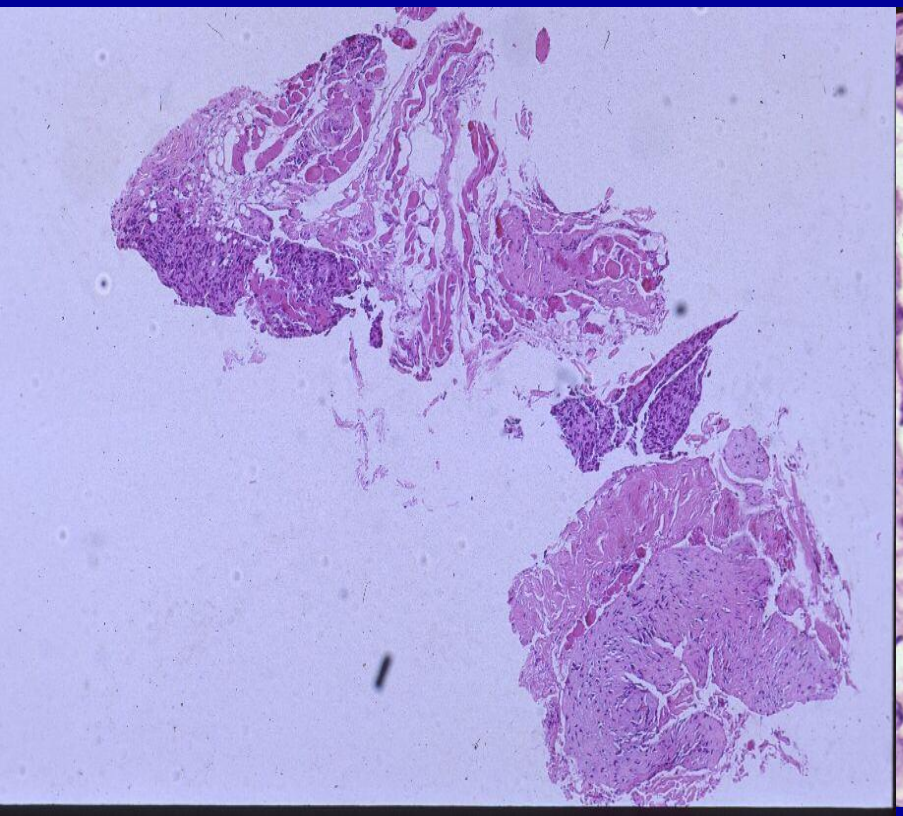


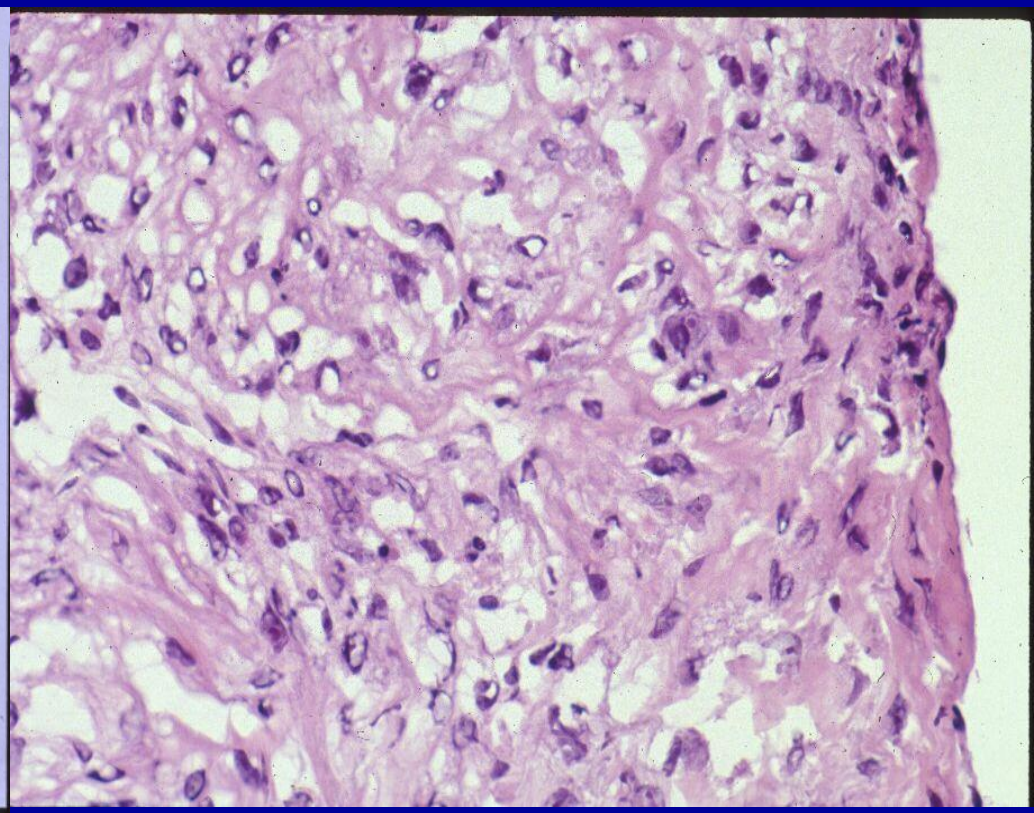




**Three well-marginated intra-muscular masses were identified by MR in the left gluteus maximus**

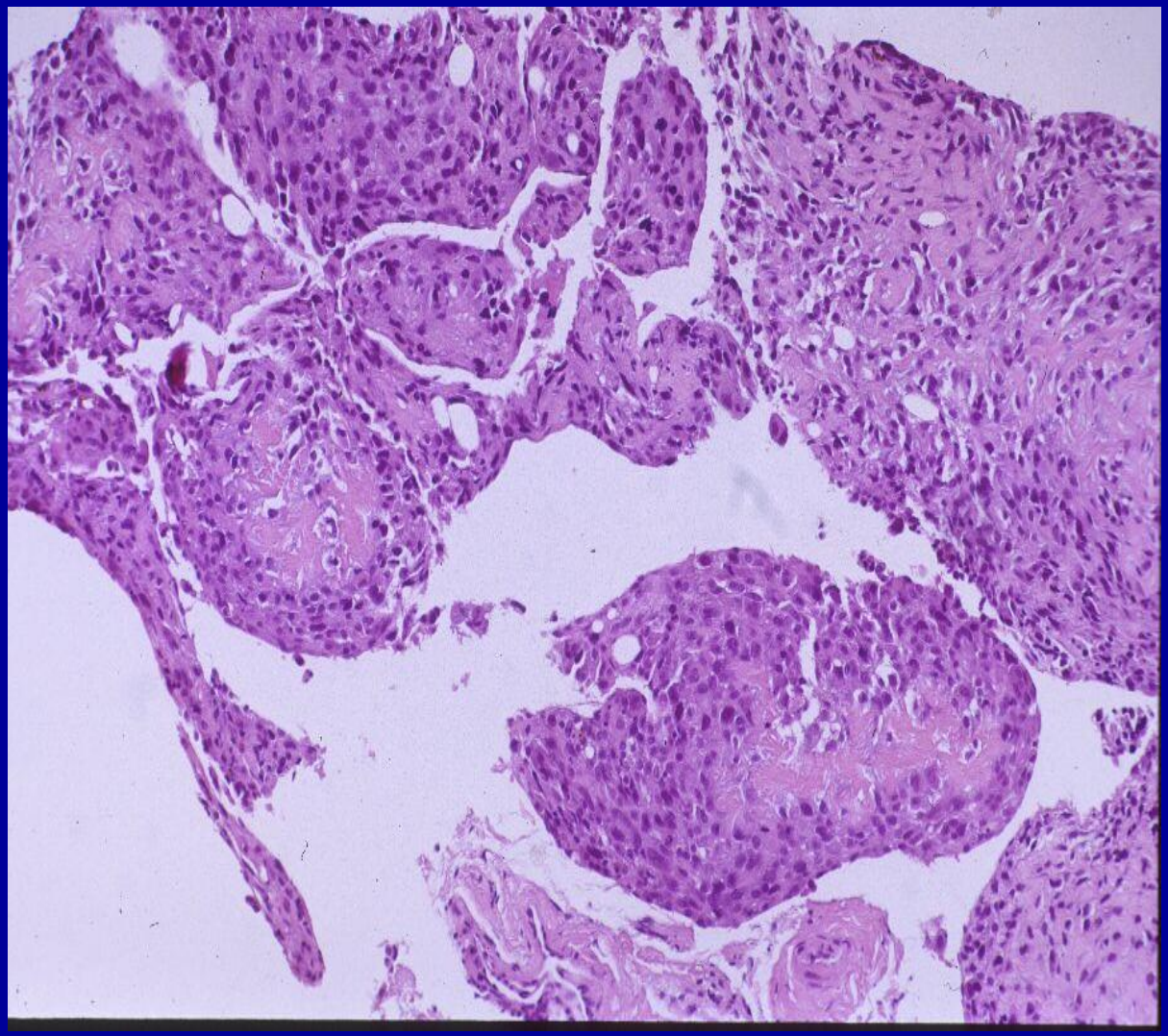
# Pathologic Findings

On initial biopsy, a cellular spindle cell lesion in a background of skeletal muscle was seen.

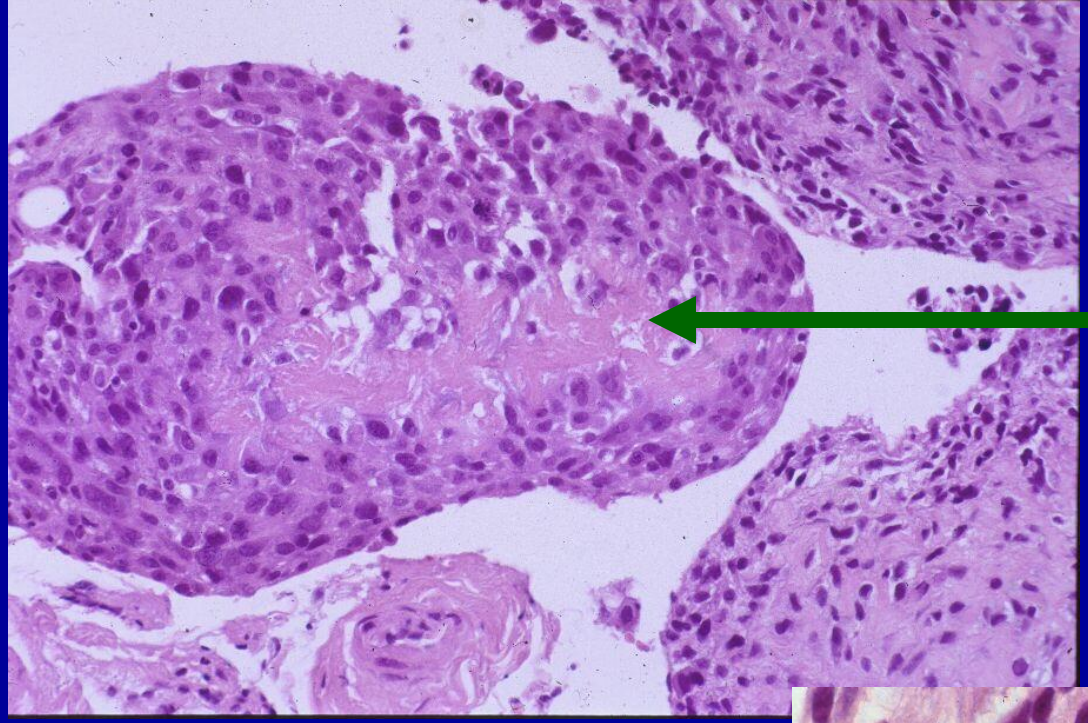




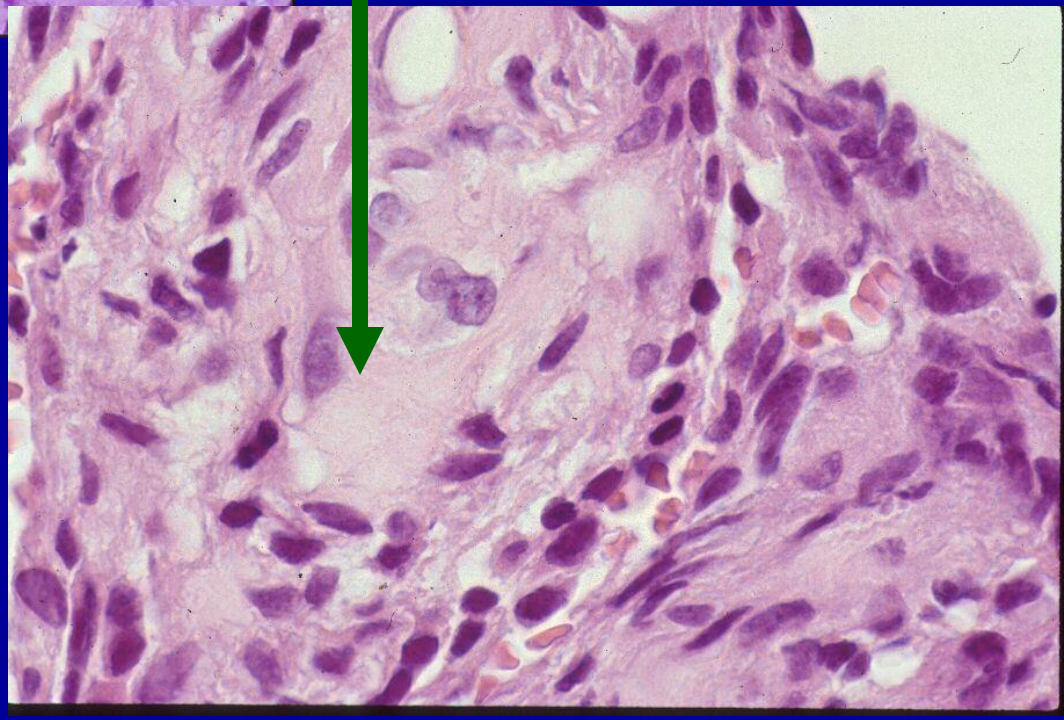
# Histopathologic Findings



A second biopy 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



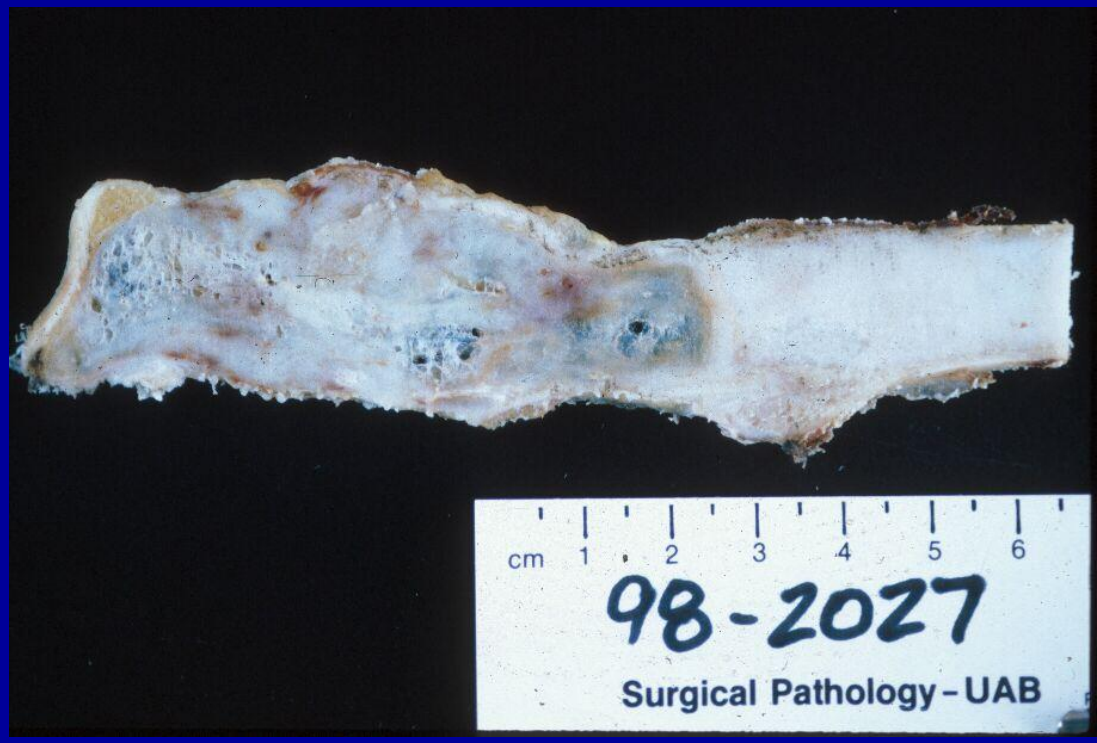
# Additional History

The patient underwent pre-operative radiation therapy, ifosfamide containing four-drug chemotherapy and subsequent surgical resection

# Gross Features

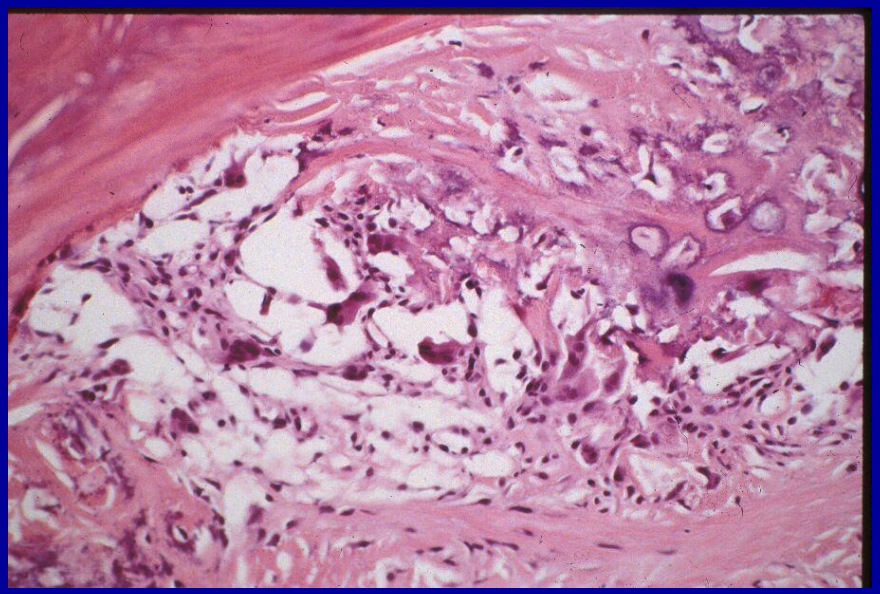
The patient had a surgical resection of her proximal radius and ulna, distal capitulum of the humerus and surrounding soft tissues and skin.

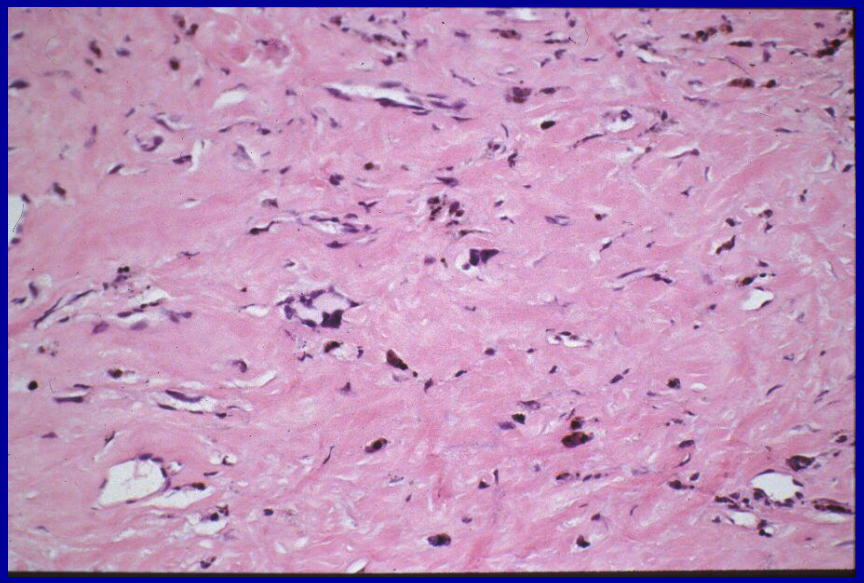
A 5 x 2.5 x 2.5 cm lobular tan tumor mass was identified within the proximal radius. The consistency varied from soft to “bone hard.”



# Microscopic Features

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



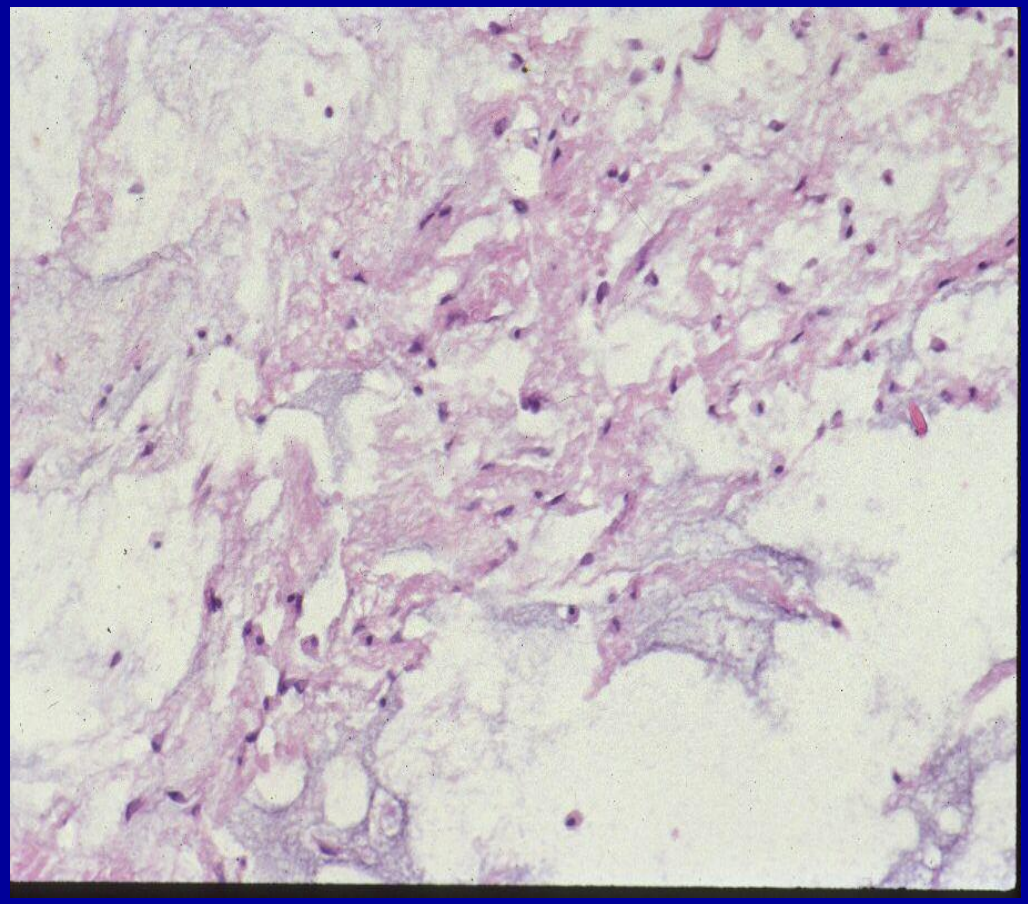


# Microscopic Features

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

# Follow-Up

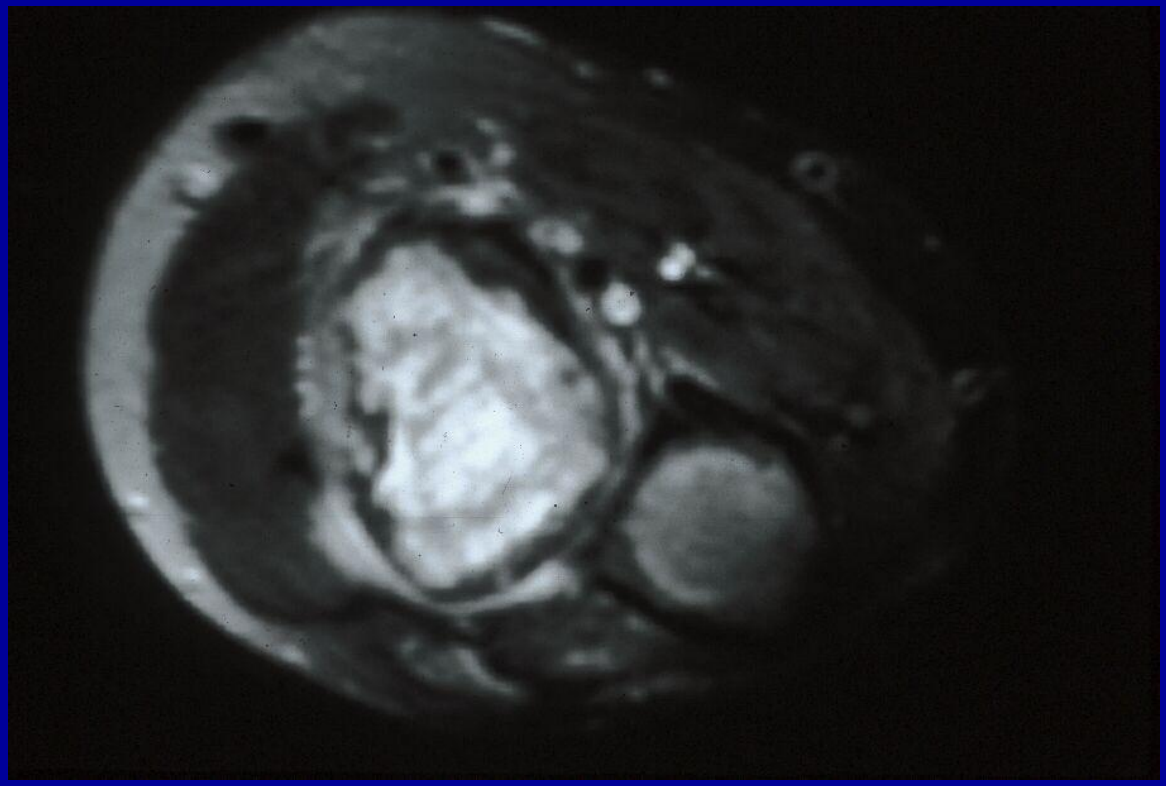
The patient subsequently underwent resection of 2 of the larger gluteal masses. Gross and histologic evaluation revealed intramuscular myxomas



**Karyotyping showed a normal 46,XX**

## Additional History

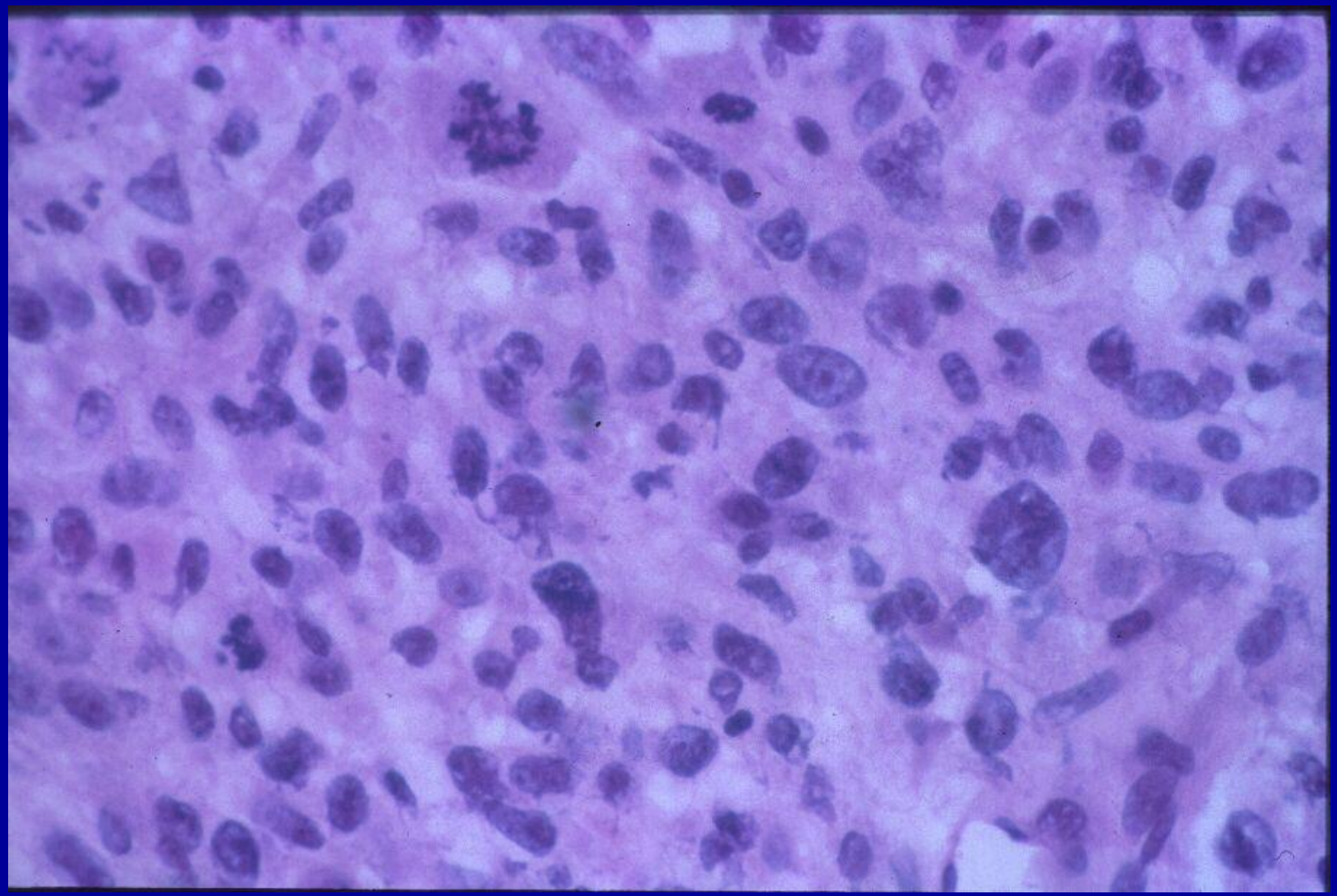
**2 years later, the patient re-presented with an enlarged mass on the lateral aspect of her elbow**



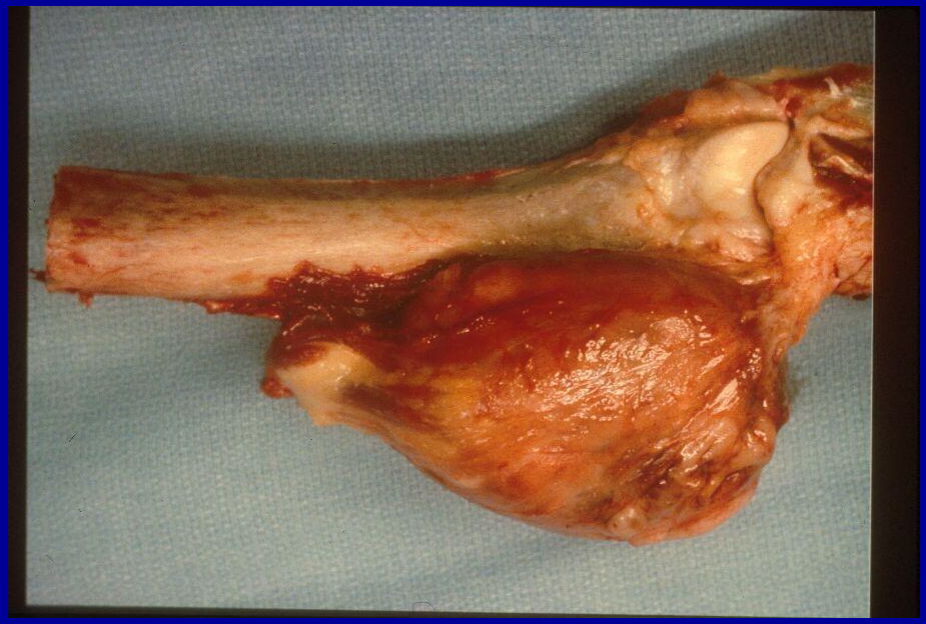
## Radiology

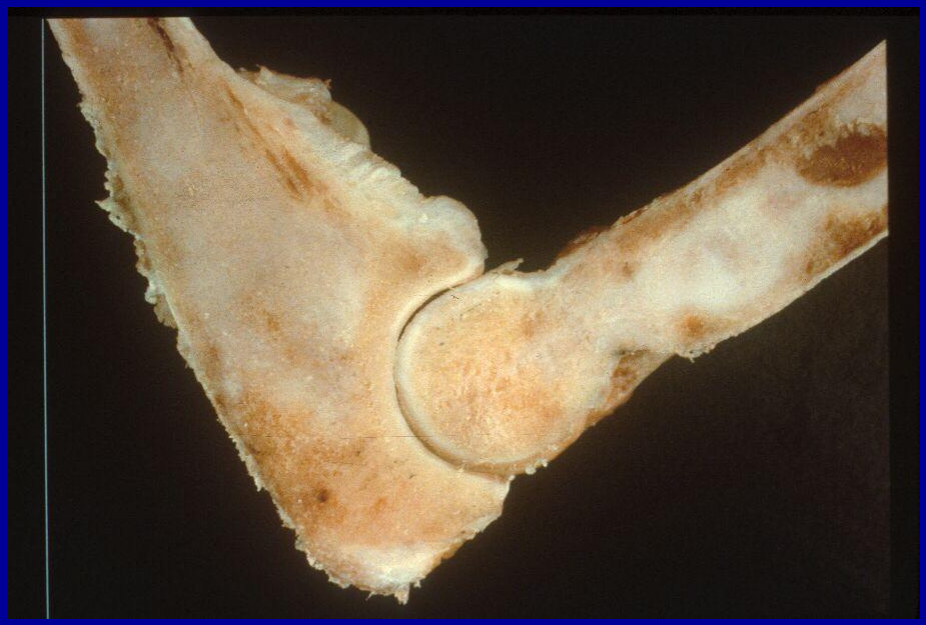
**Conventional radiographs of the humerus, radius & ulna showed changes typical of FD**
**MRI of the distal right humerus demonstrated a heterogenous mass with ↑ T2 –weighted signal**

**A cell block showed markedly atypical cells with high pleomorphism was noted as were bizarre mitosis**

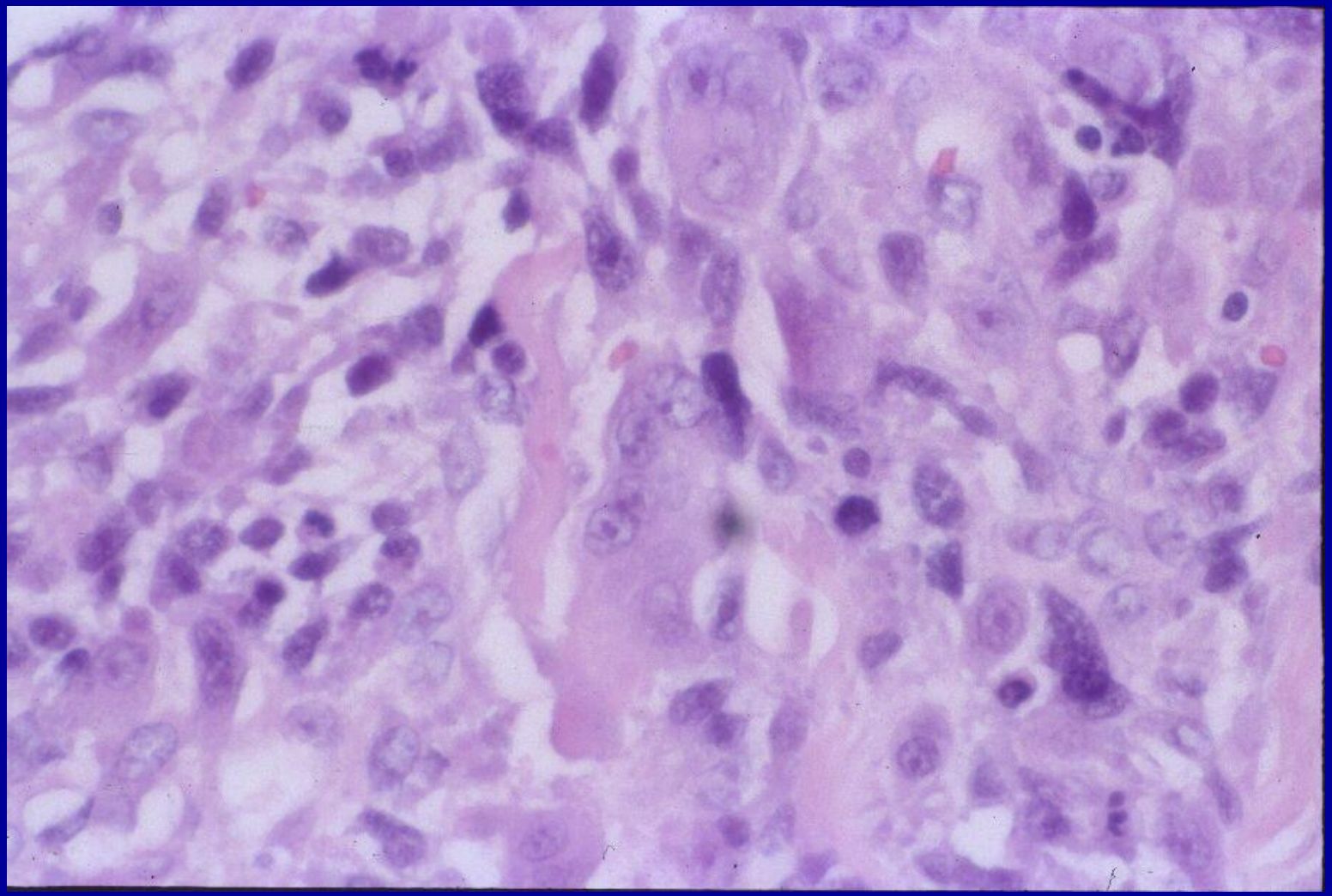


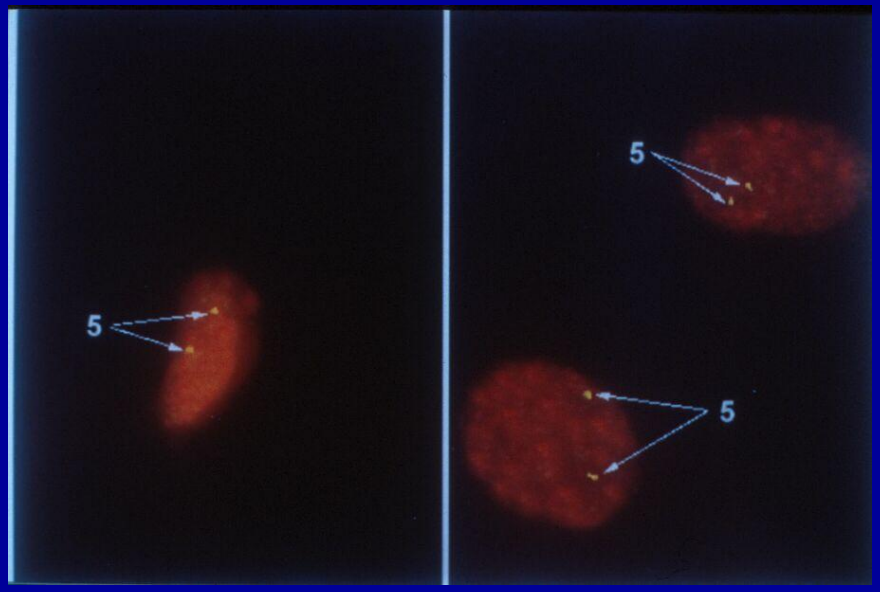
**The patient underwent a right above-elbow amputation and a 10 x 6.5 x 3.7 cm soft tissue, cystic, red-brown mass was removed**

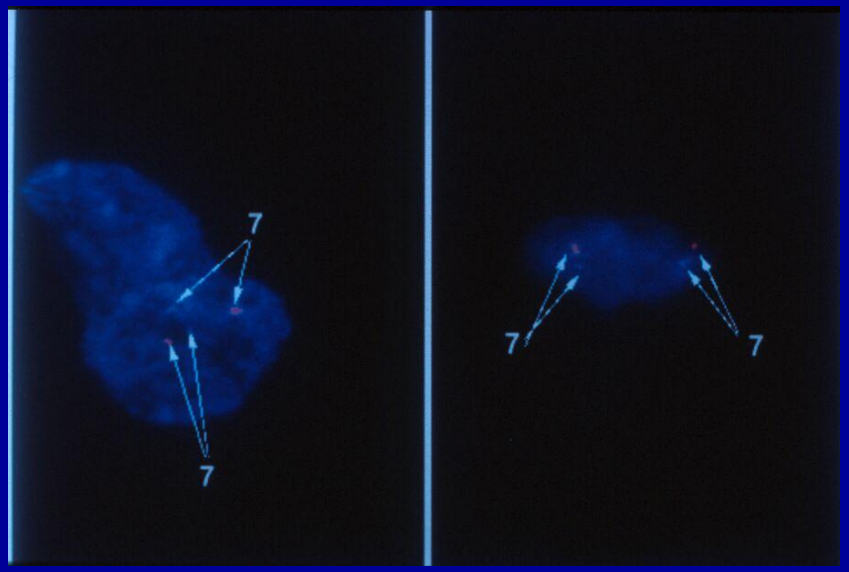




# Histologic evaluation verified recurrent osteosarcoma

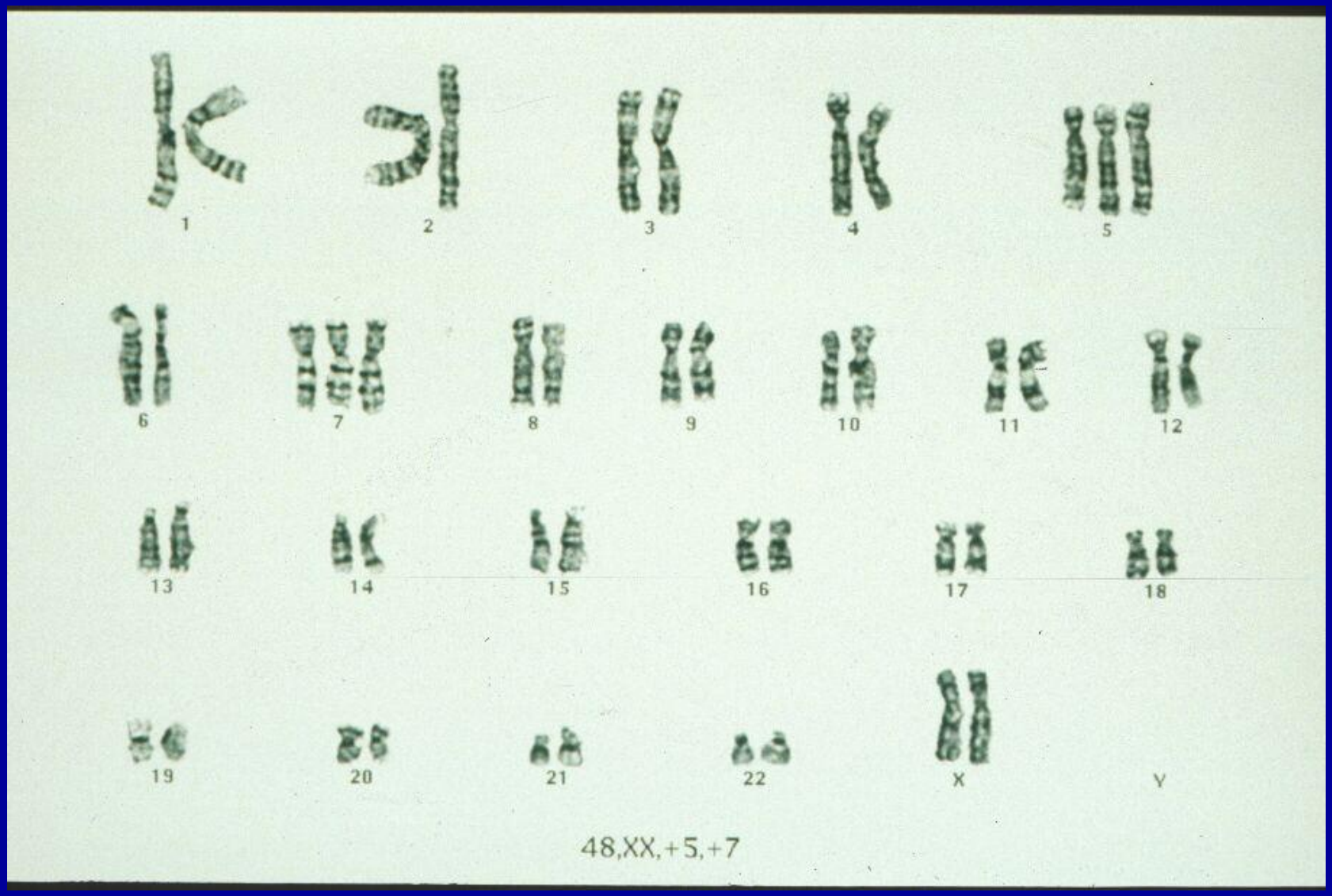




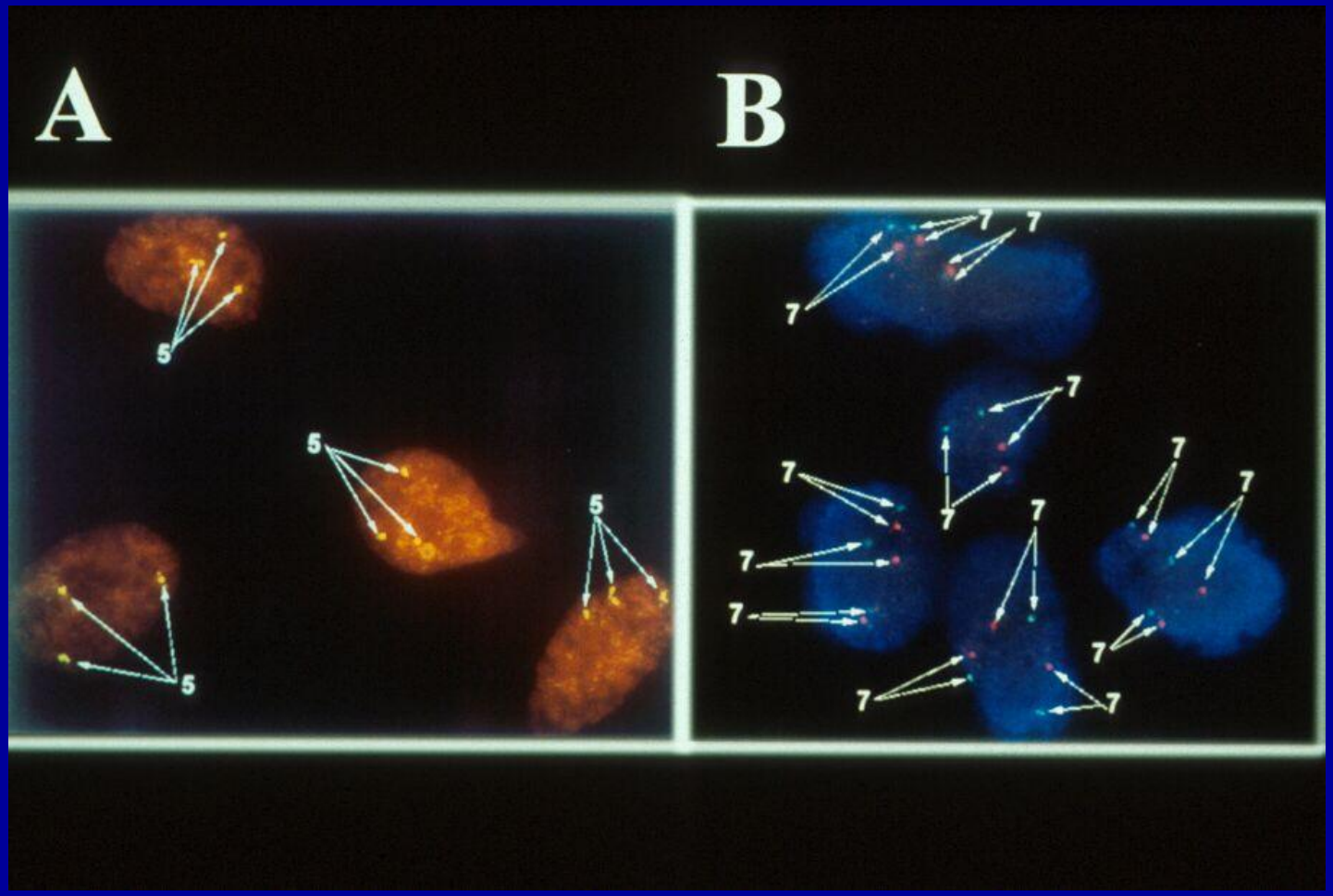




**Cytogenetic studies using GTG banding techniques showed a normal female karyotype (46,XX) in the FD portion of the spectrum which was confirmed by FISH in 98% of the cells.**

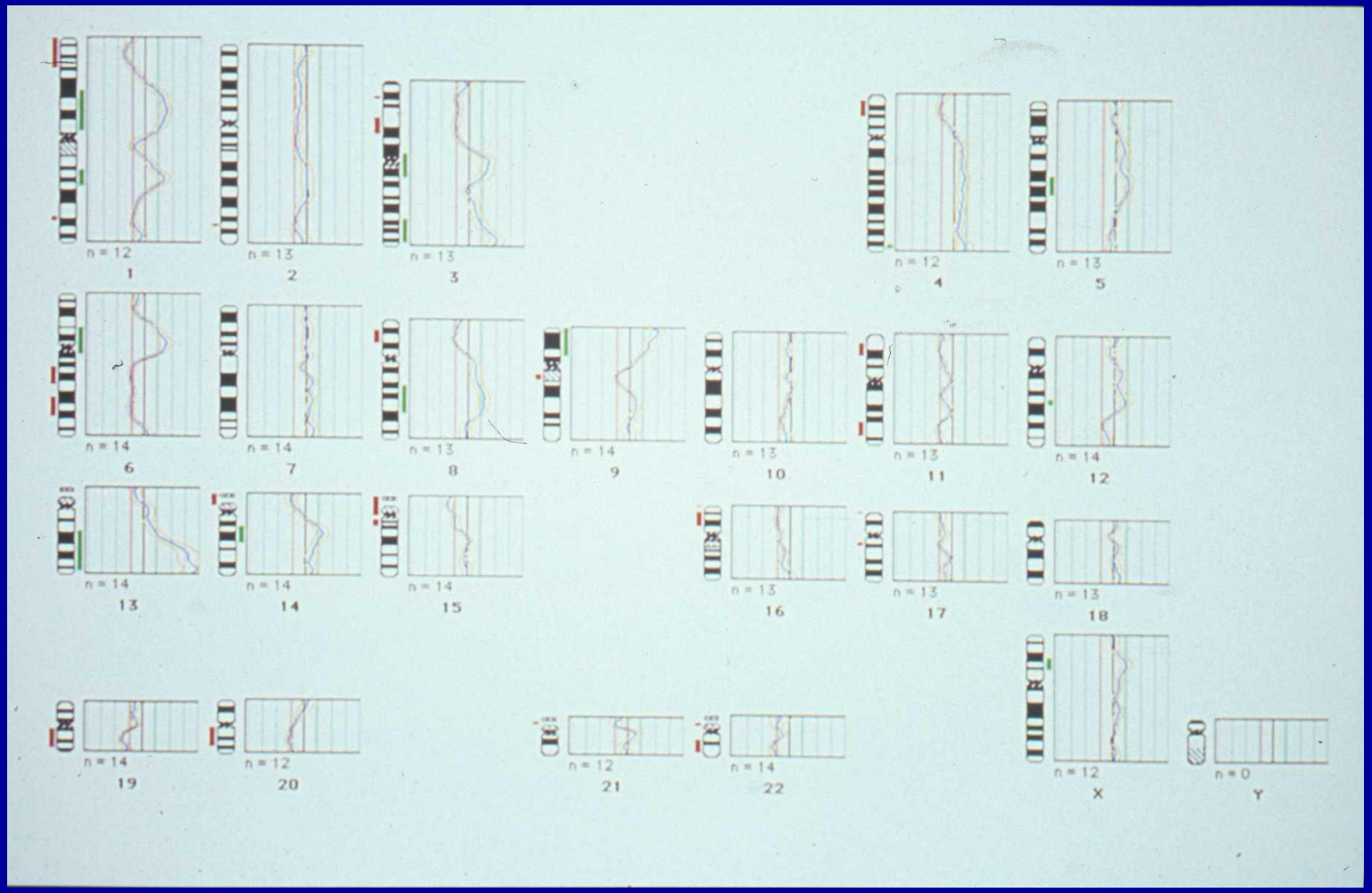
# The 0GS demonstrated a 48,XX,+5,+7 karyotype



**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

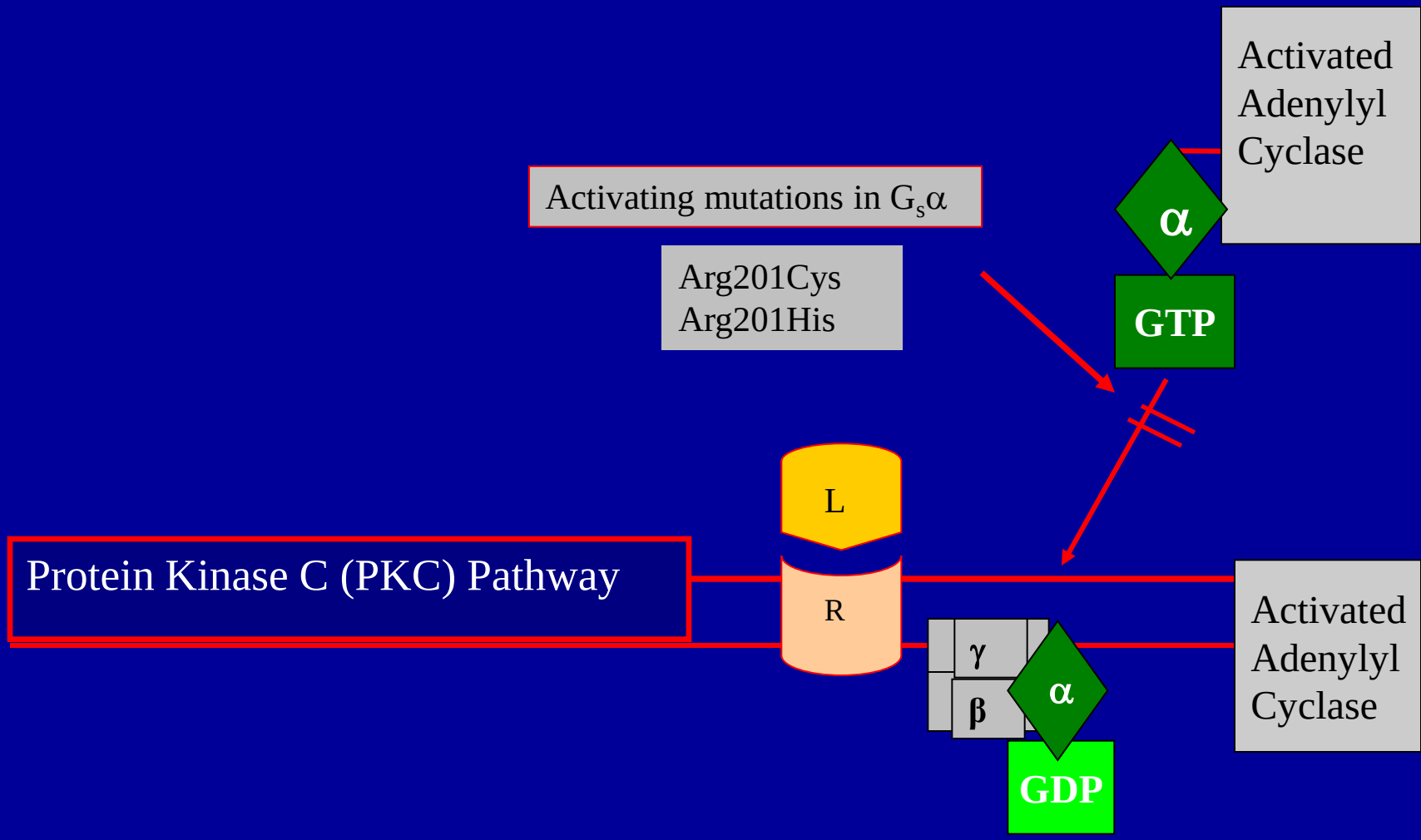
- Clonal structural aberrations
  CH 3, 8, 10, 12, 15
- Trisomy 2

- McCune-Albright Syndrome
- Polyostotic FD
- Monostotic FD
- Pituitary adenoma
- Intra-Muscular Myxomas

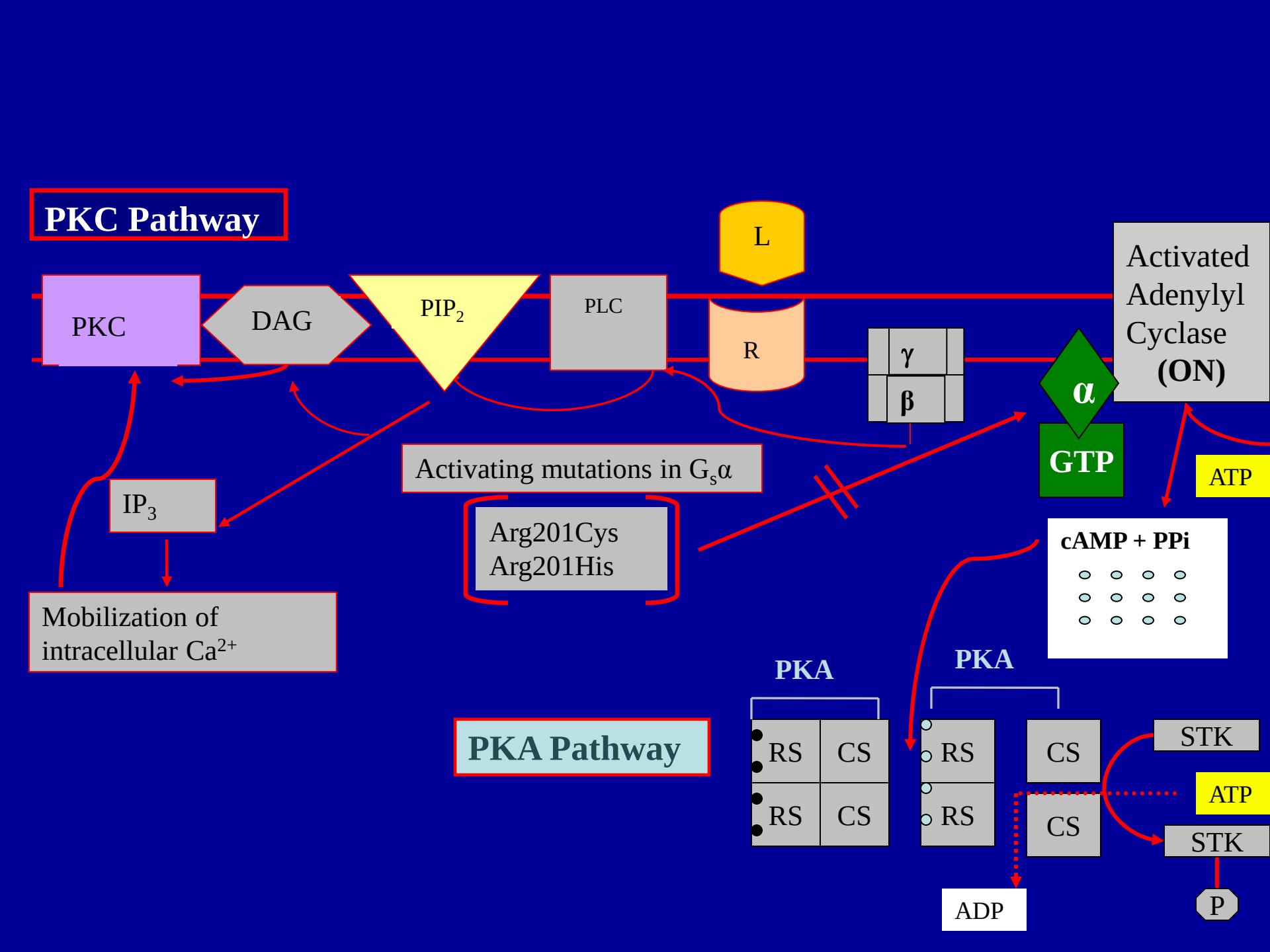
**All have the same genetic abnormality**
**GNAS 1 mutation in the alpha subunit of stimulatory G protein (CH 20 {20q13})**

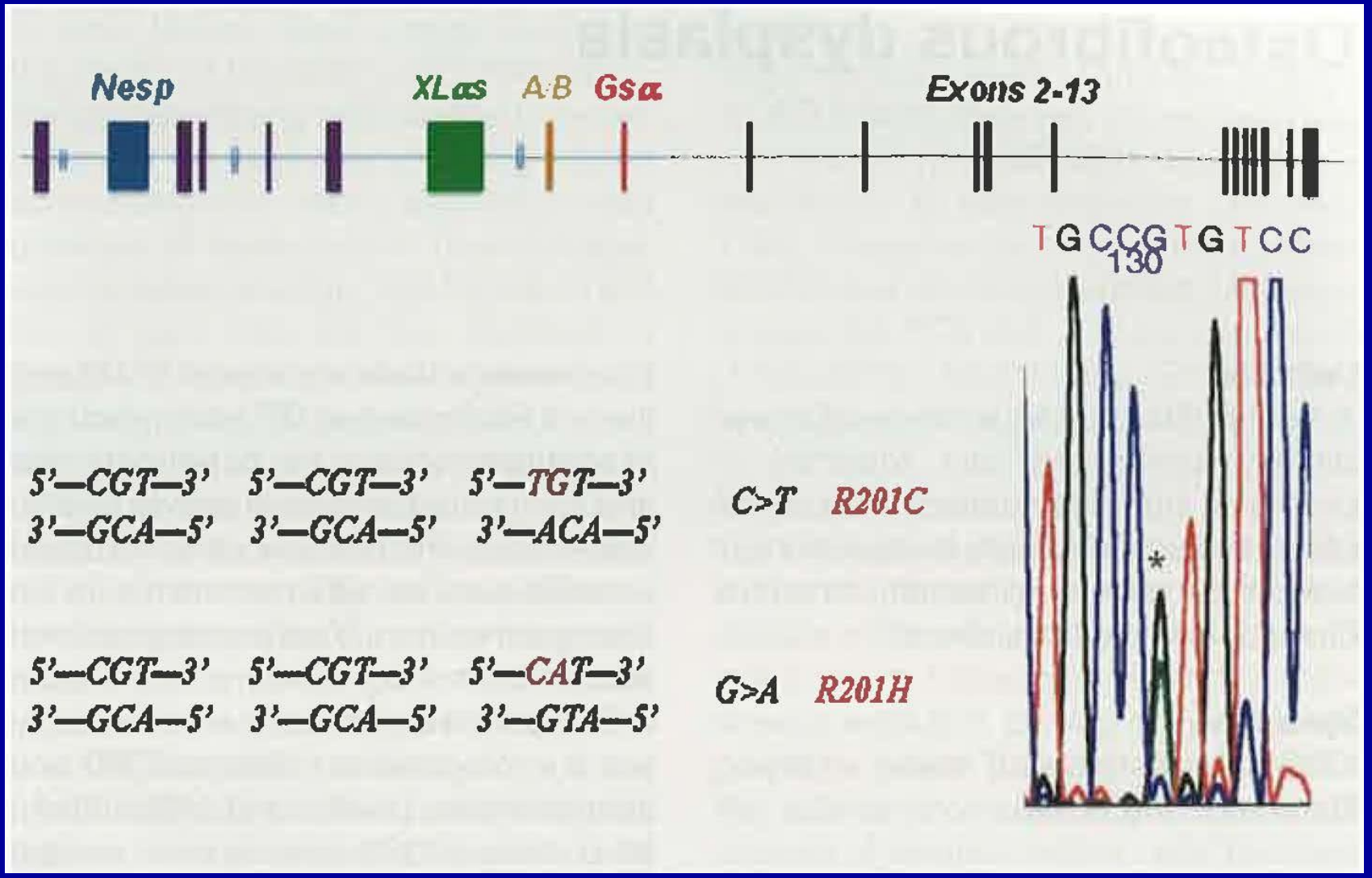
**Mertens, et al.:** ***Genes Chromos Cancer*** **11:271-2,1994**

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




Modified from Cohen, M.: Am J Med Gen 98:290-3, 2001


PKC Pathway
PKC
DAG
PIP2
PLC
L
R
γ
β
α
GTP
Activated Adenylyl Cyclase (ON)
ATP
cAMP + PPi
Activating mutations in Gsα
Arg201Cys
Arg201His
IP3
Mobilization of intracellular Ca2+
PKA Pathway
PKA
PKA
RS
CS
RS
CS
RS
CS
RS
CS
STK
ATP
STK
P
ADP




Siegal, G. et al., WHO Classification of Tumours of Soft Tissue and Bone, 2012

# Activating Missense Mutations in the GNAS gene

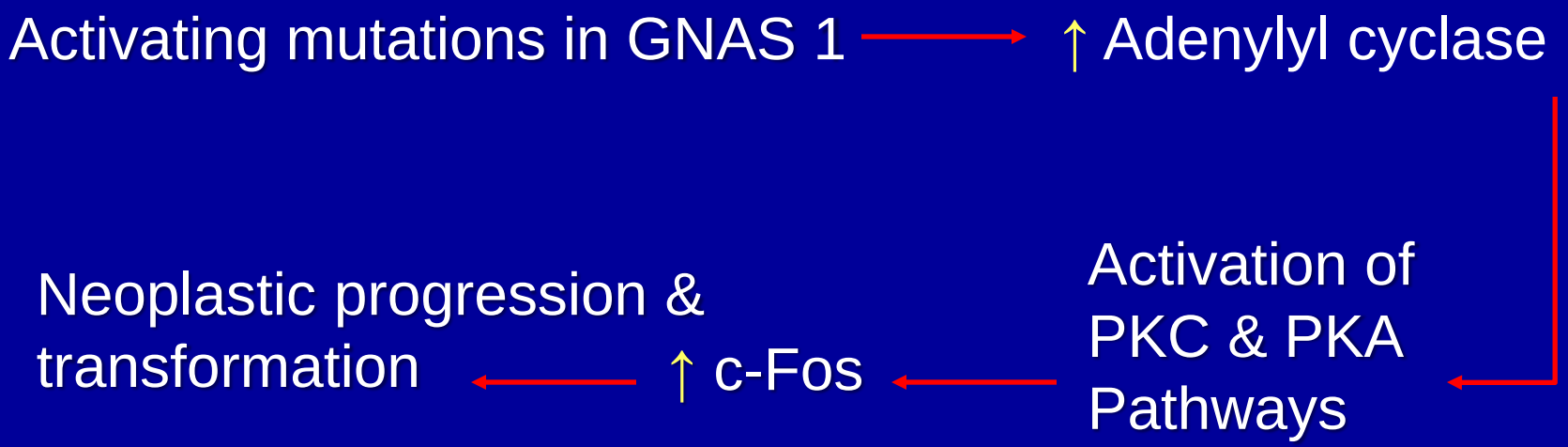
- R201H 57%
- R201C 38%
- Q227L 05%

R = Arginine
H = Histidine
C = Cysteine

Q = Glutamine
L = Leucine

# Etiology

c-Fos is also overexpressed in FD thereby:



# 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

**Cohen, M. & Howell, R.: *J Oral Maxillofac Surg* 28:336-71, 1999**

# 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%)

Schwartz et al., *Am J Med Sci* 274:1, 1964; Lopez-Ben, et al.: Osteosarcoma in a patient with McCune-Albright Syndrome and Mazabraud's syndrome *Skeletal Radiol* 28:522-26, 1999.

# 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

**Yanagawa, T. et al.:** ***Clin Radiol*** **56:877-86, 2001**
**Inoue, Y., et al.:** ***J. Surg Oncol*** **75:42-50, 2000**

# 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


# Special Thanks To:

**Michael J. Klein, M.D.**