Small Round Blue Cell Tumors

Ewing Sarcoma
Eosinophilic Granuloma
Myeloma and Lymphoma

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Small Round Blue Cell Tumors

- Composed entirely of cells
- Cells may have a hematopoietic appearance
- No Matrix Production

Small Round Blue Cell Lesions

- **Benign:**
  - Eosinophilic Granuloma (Langerhans Cell Histiocytosis; Histiocytosis X)
  - Osteomyelitis
- **Malignant:**
  - Ewing Sarcoma/PNET
  - Lymphoma
  - Metastatic Neuroblastoma
  - Multiple Myeloma (Plasmacytoma)
  - Metastatic Small Cell Carcinoma
  - Rhabdomyosarcoma (rare in bone)

Eosinophilic Granuloma
(Langerhans Cell Histiocytosis)

General Information

- Benign proliferation of Langerhans cells usually accompanied with **eosinophils**, lymphocytes, neutrophils and scattered plasma cells.
- Solitary or multiple lesions confined to bone
  - 70% of cases consist of a solitary lesion
- Seldom leads to disseminated systemic disease
- Viewed as disorder of immune regulation or reactive process rather than neoplasm
- All organ systems may be affected with disseminated forms

General Information

- Hand-Schuller-Christian Disease (age:1-5 years): chronic disseminated histiocytosis
- Letterer-Siwe disease (age:<1 year): acute or subacute disseminated histiocytosis
  - Uniformly fatal
- Solitary EG is twice as common as multifocal EG
  - May arise from any bone and any site within a bone (epiphyseal, metaphyseal, diaphyseal)
  - Radiographically variable appearance: may appear benign (geographic) or malignant (permeative or moth eaten)

Hand-Schuller-Christian Disease

- Triad:
- Destructive skeletal lesions
- Exophthalmos
- Diabetes Insipidus
- 10% of patients with unifocal EG develop multifocal and extraskeletal disease
- Usually <5 years old
- Hepatosplenomegaly, adenopathy, anemia, fever, neurological complaints
- Fatal in 15%
- Any bone but 90% have skull involvement

Letterer-Siwe Disease

- Develops in 1st year of life
- Disseminated disease and small bone lesions
- Fatal in 95% who develop before 1 year of life

Clinical Presentation

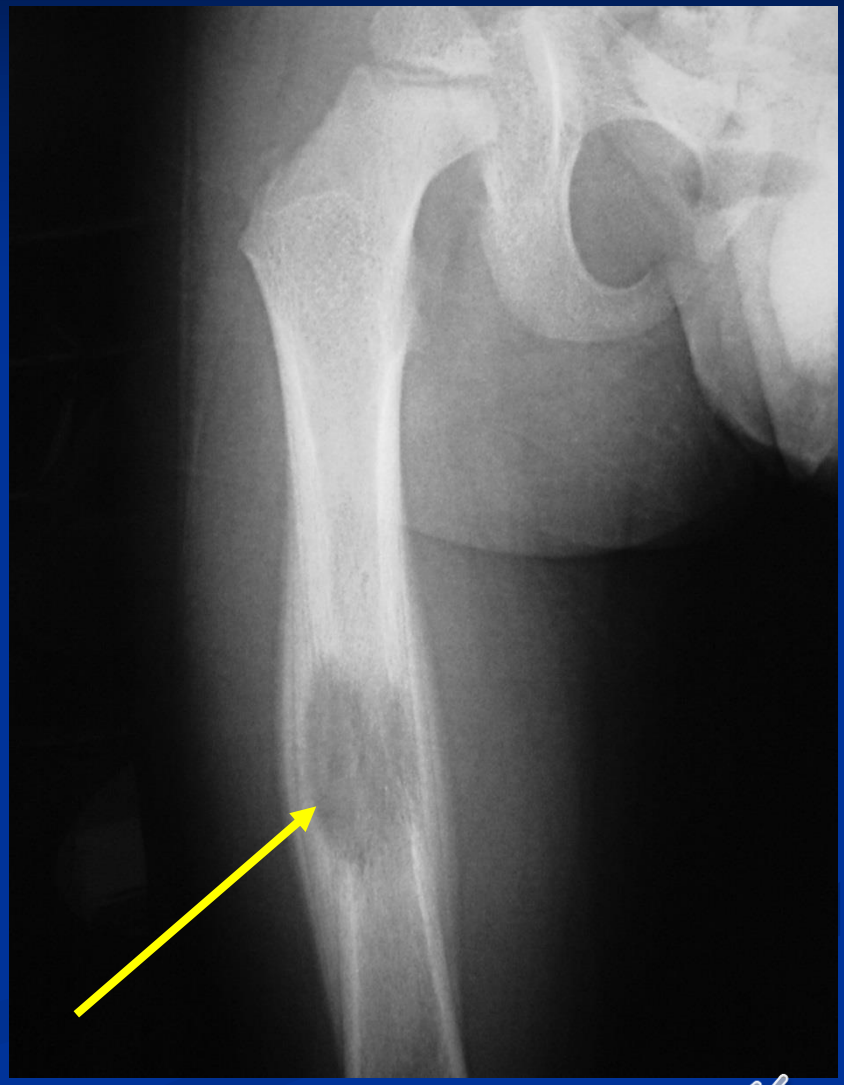
- **Signs/Symptoms:** Pain and soft tissue swelling
  - May have a fever
  - Mild peripheral eosinophilia (5%-10% of patients)
- **Prevalence:** Male predilection (2:1)

- **Age:** 1 month – 71 years
  - Most common age 5-15 years old

- **Sites:**
  - Flat Bones (most common—70%)
    - Skull
    - Pelvis
  - Femur
  - Humerus
  - Hands and Feet are rare in solitary disease

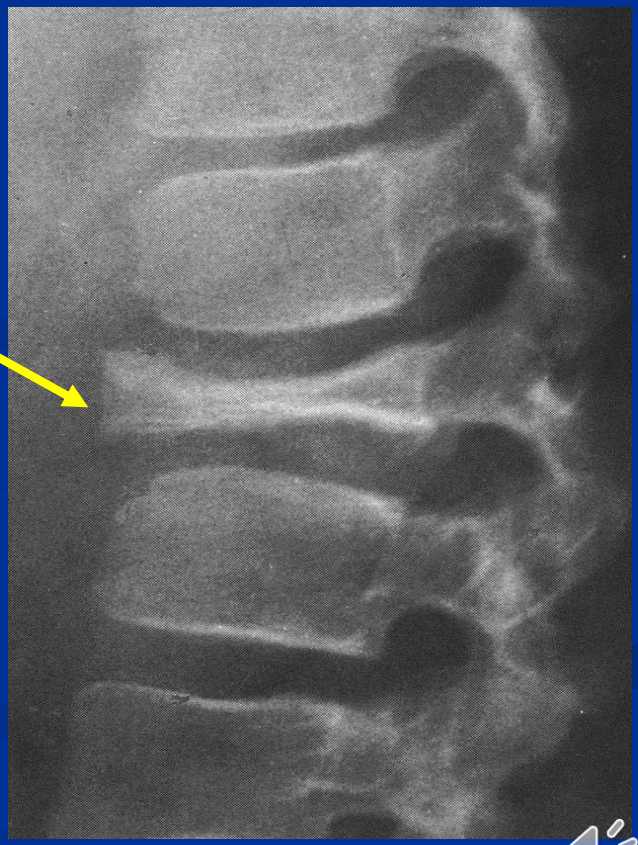
Radiographic Presentation

- **Radiology:**
- Variable appearance
- Permeative or Geographic
- Periosteal reaction (lamellated)
- Rind of sclerosis
- Soft tissue mass (5-10%)
- Sequestrum (button-like); Hole in a Hole

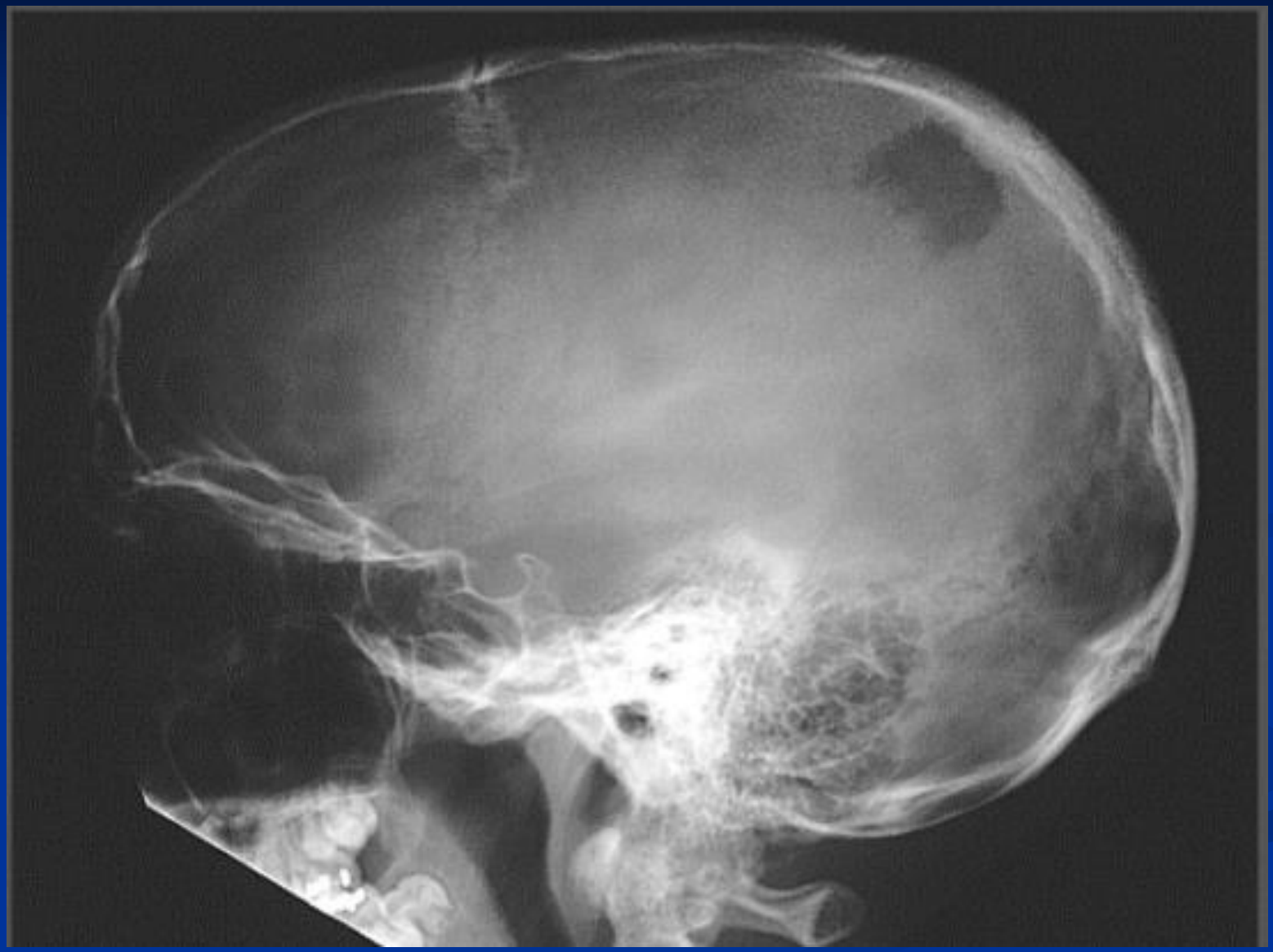


Radiographic Presentation

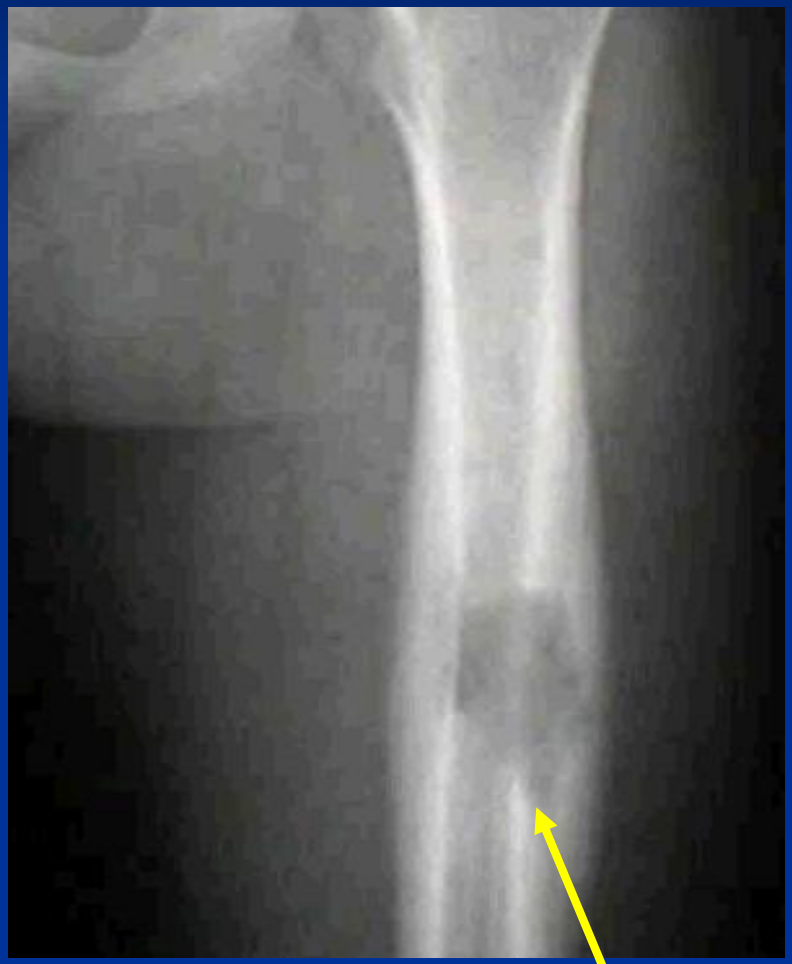
- Spine: vertebra plana
- Long bone:
  - Diaphysis: (58%)
  - Metadiaphysis (18%)
  - Metaphysis (28%)
  - Epiphysis (2%)



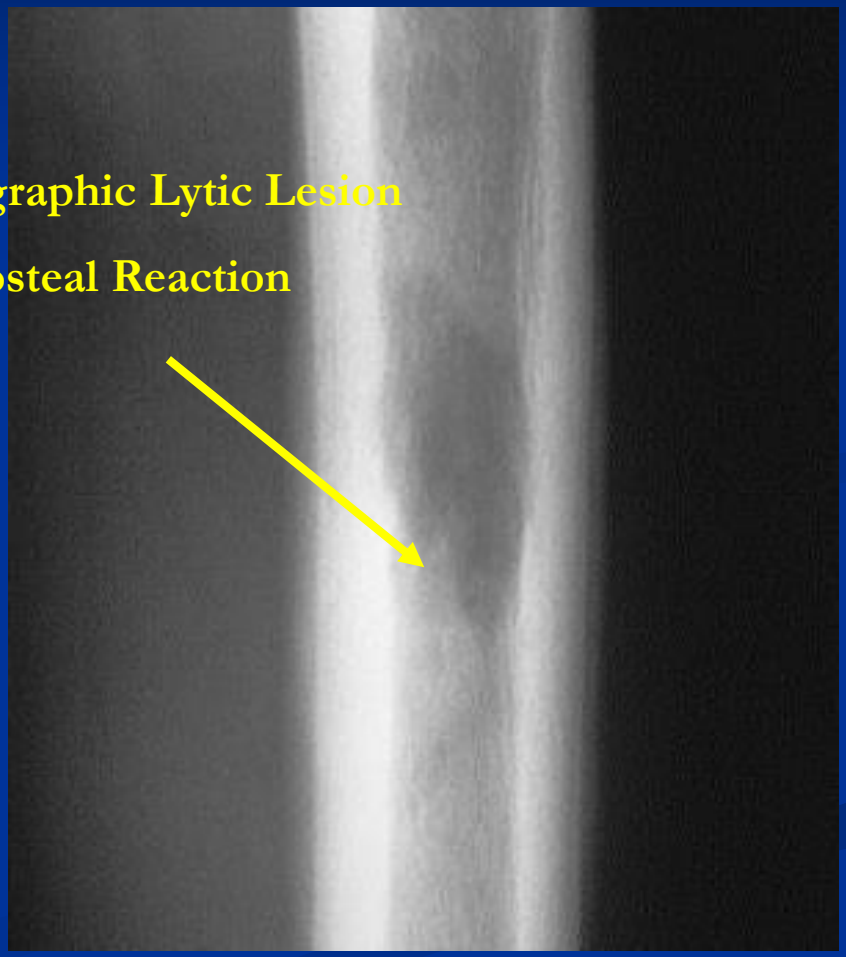
X-Ray: Eosinophilic Granuloma of Skull



X-ray: Eosinophilic Granuloma of Femur



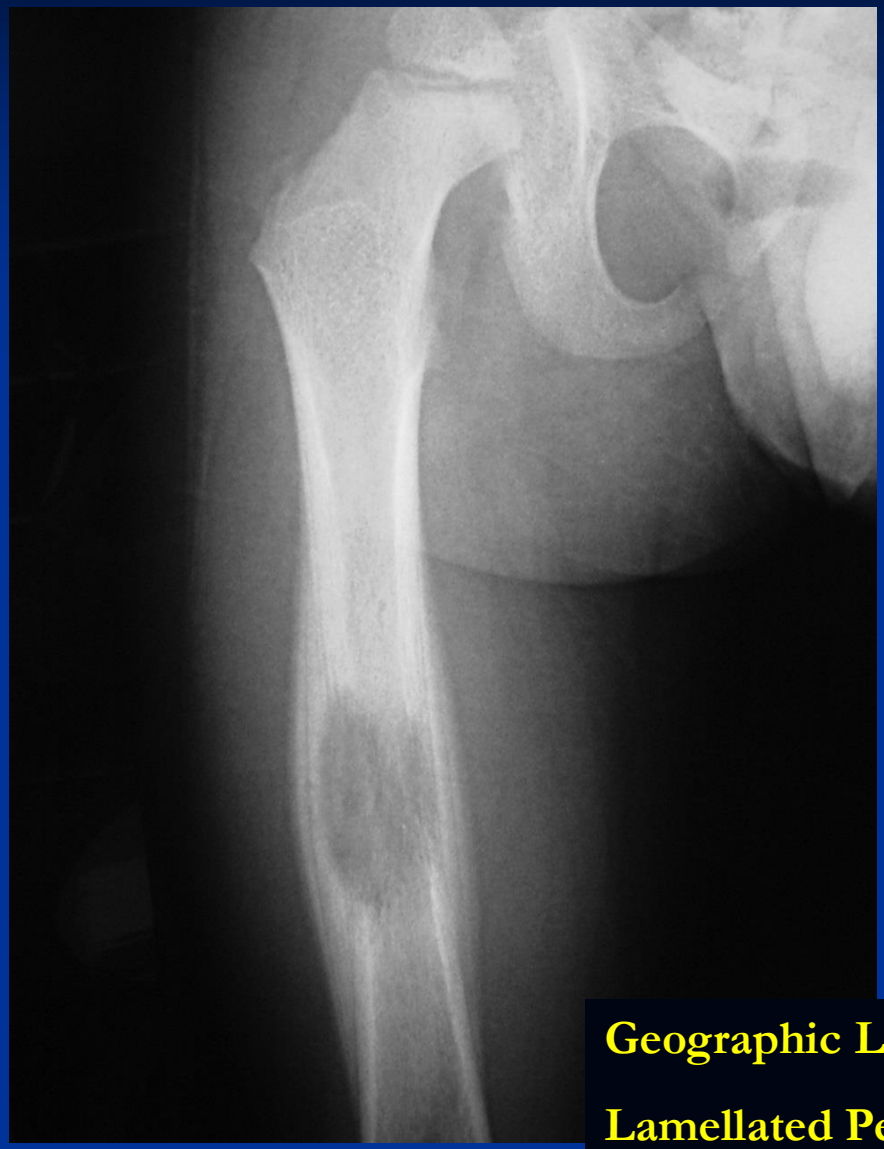
Geographic Lesion with
Periosteal Reaction

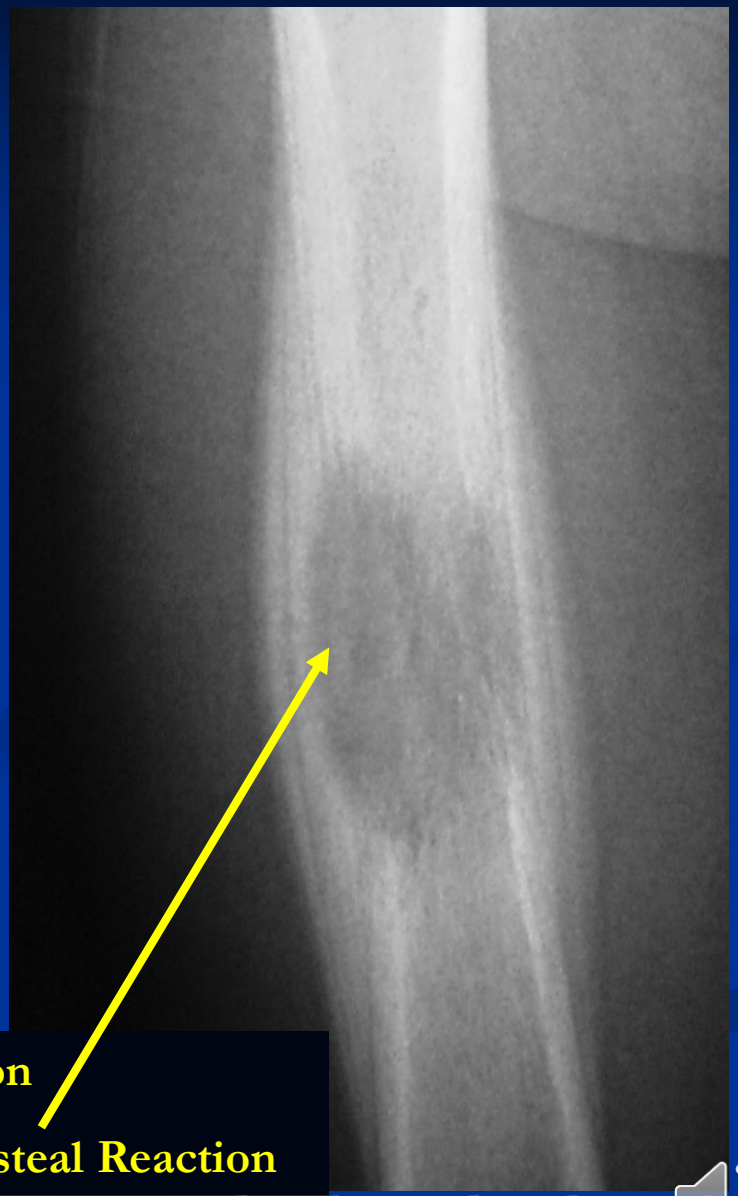


Geographic Lytic Lesion

Periosteal Reaction

X-ray: Eosinophilic Granuloma of Femur

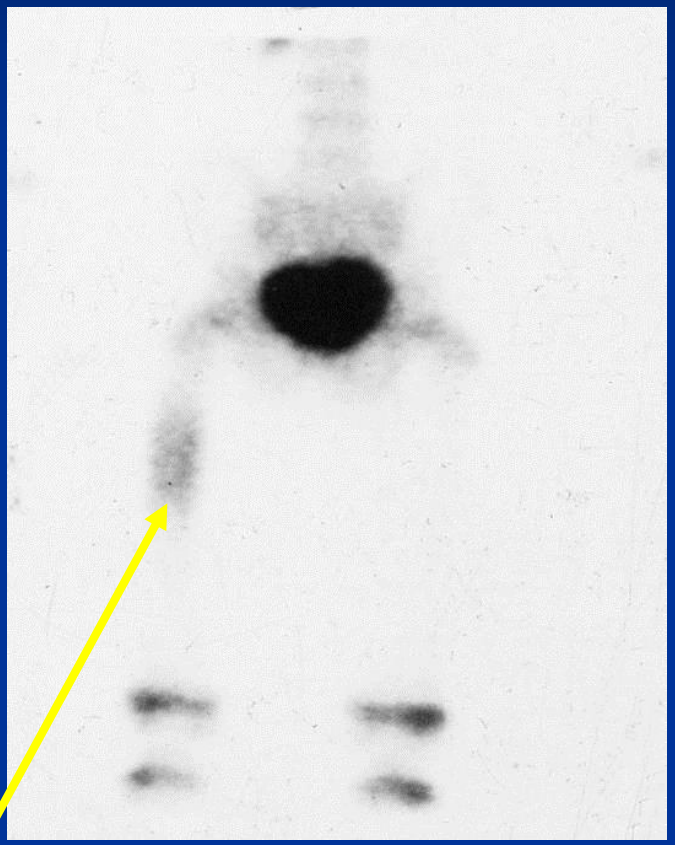




Geographic Lesion

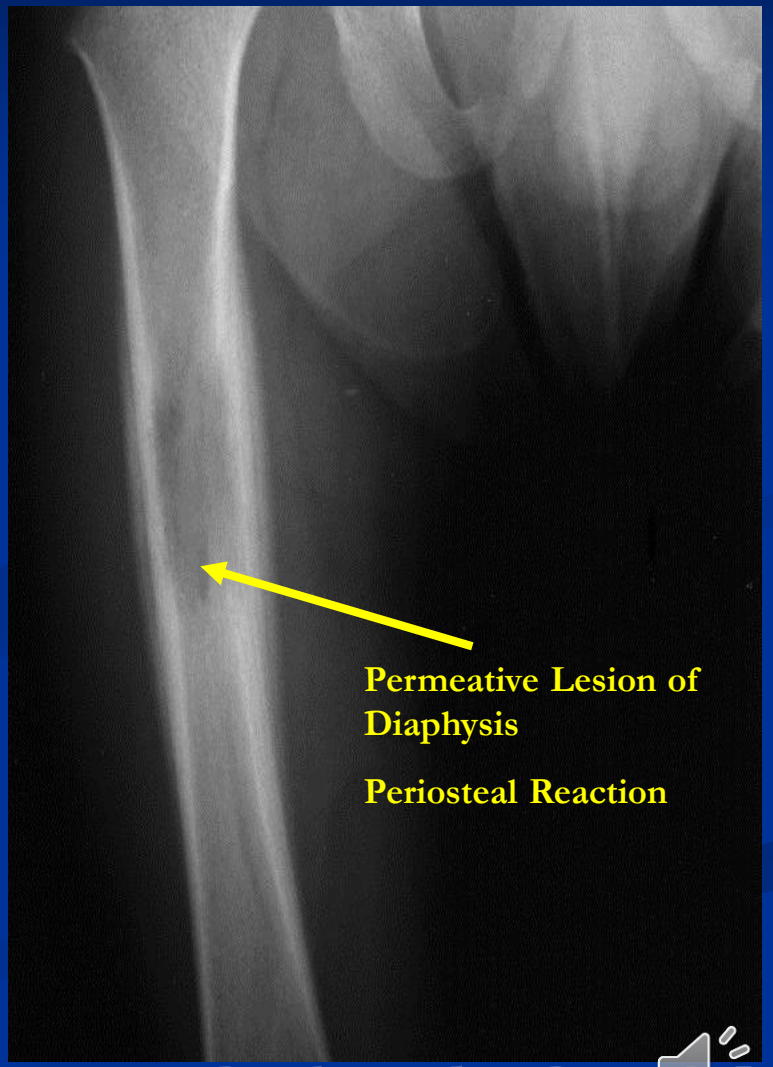
Lamellated Periosteal Reaction

X-ray/Bone Scan: Eosinophilic Granuloma of Femur



Bone Scan is Variable

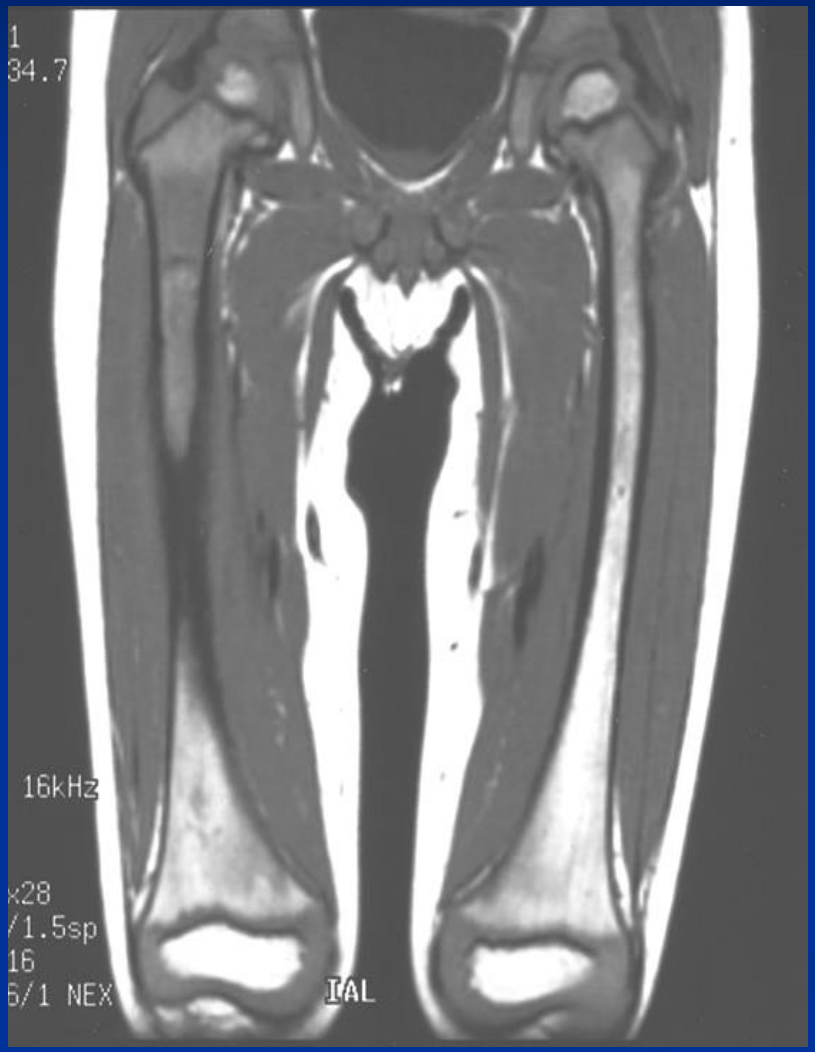
Uptake Intense, Mild or Cold

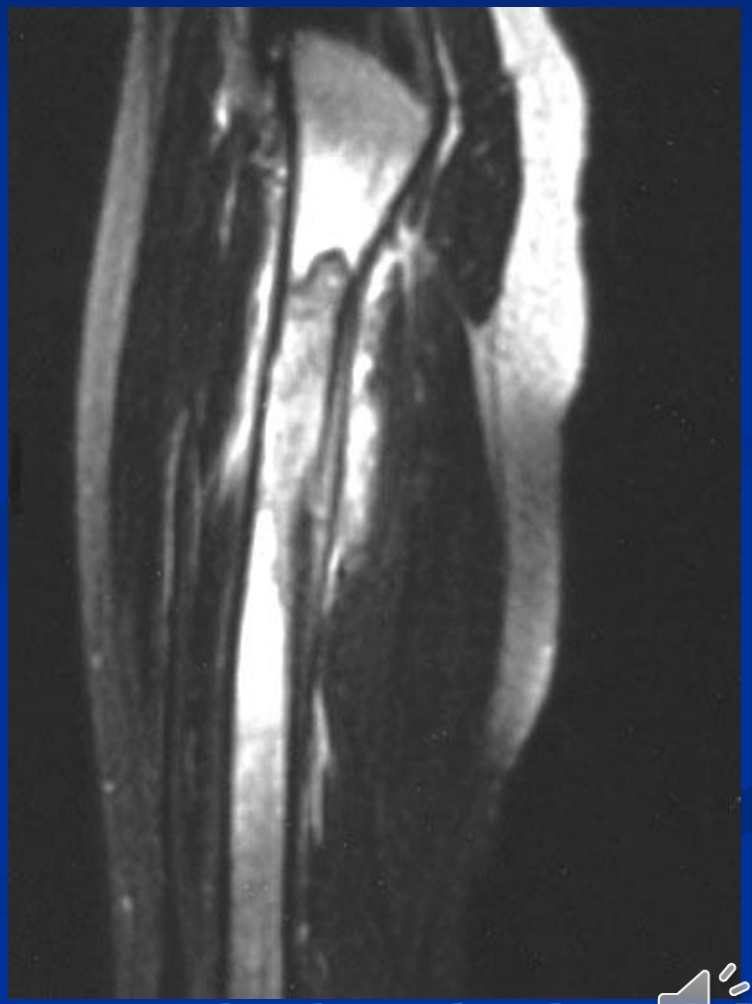


MRI: Eosinophilic Granuloma

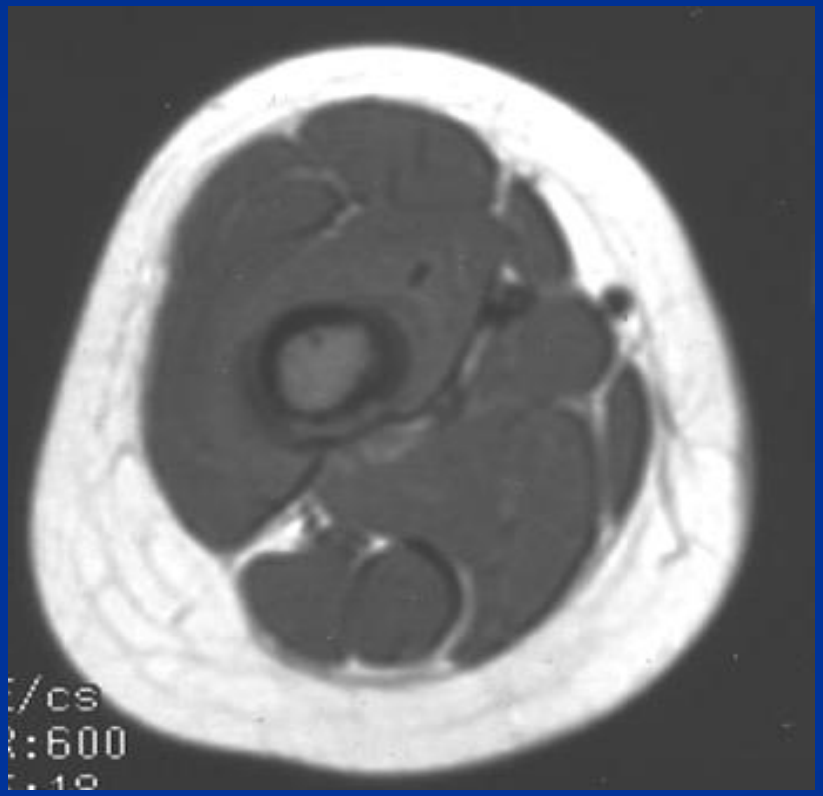
- Marrow replacement on T1
- High SI on T2
- ST mass possible

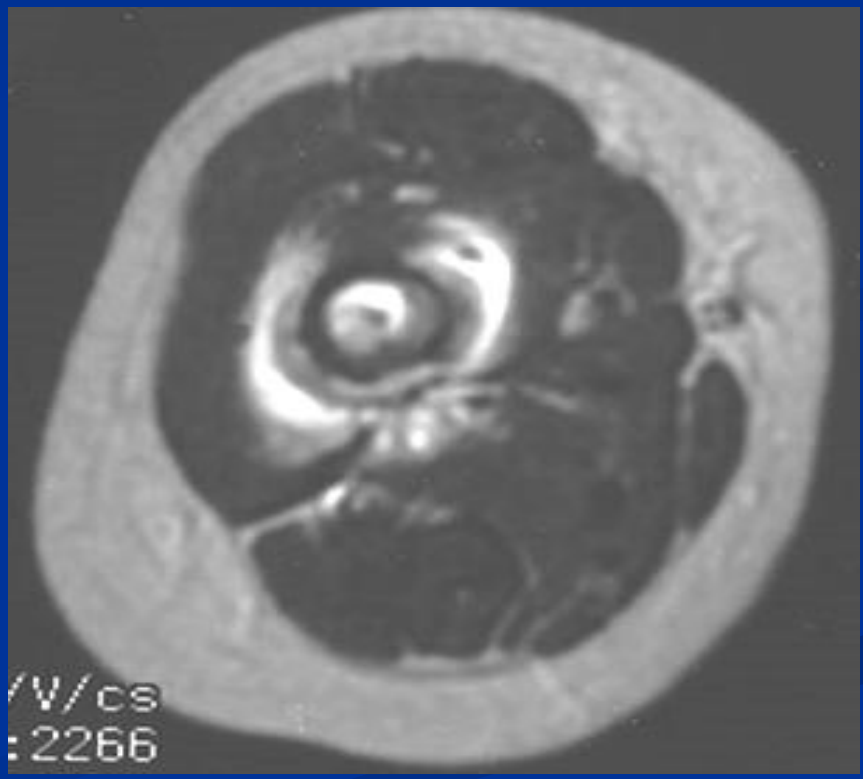
MRI: Eosinophilic Granuloma of Femur



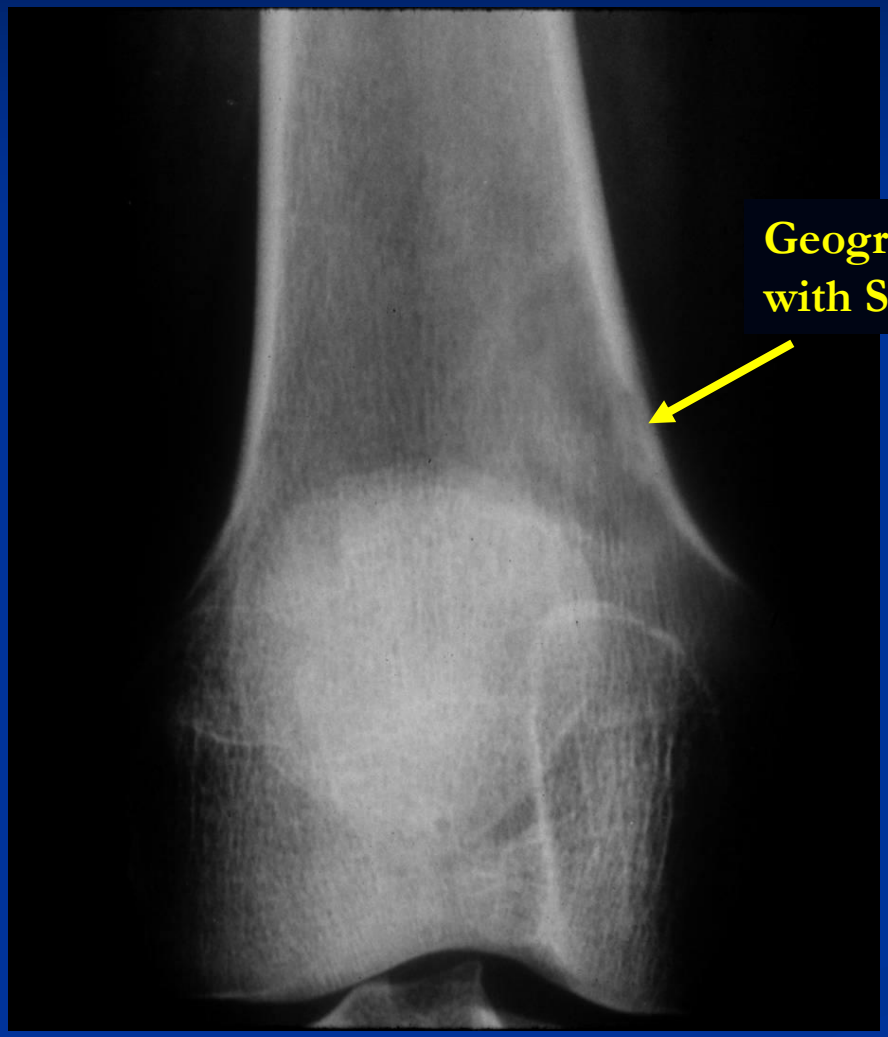


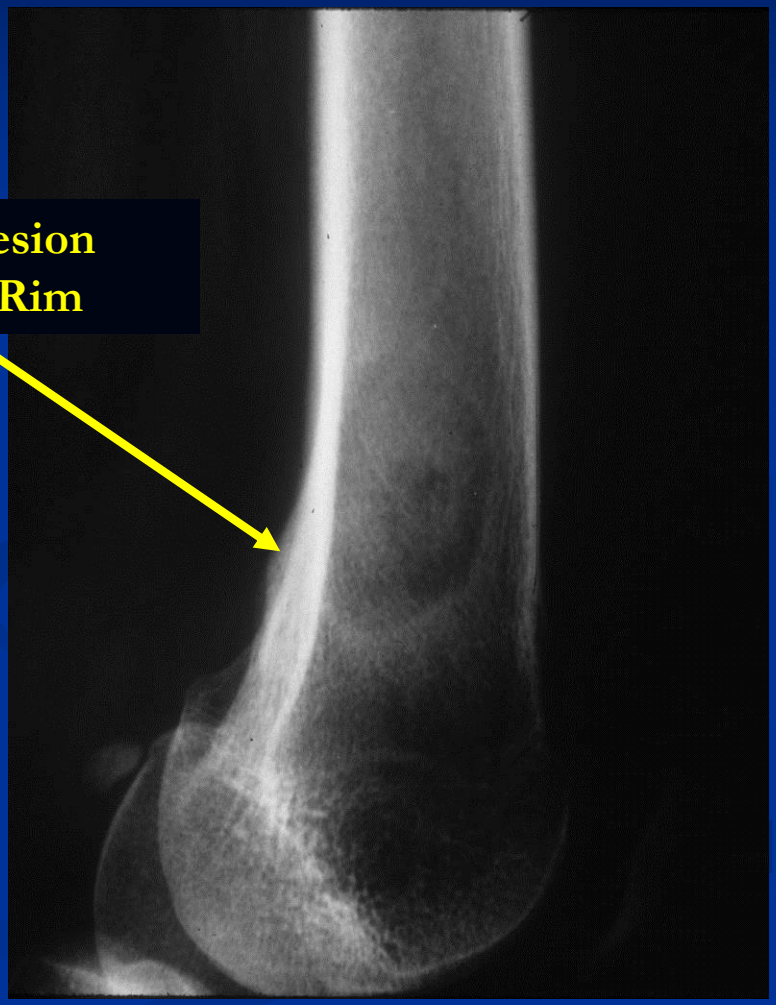
Langerhans Cell Histiocytosis





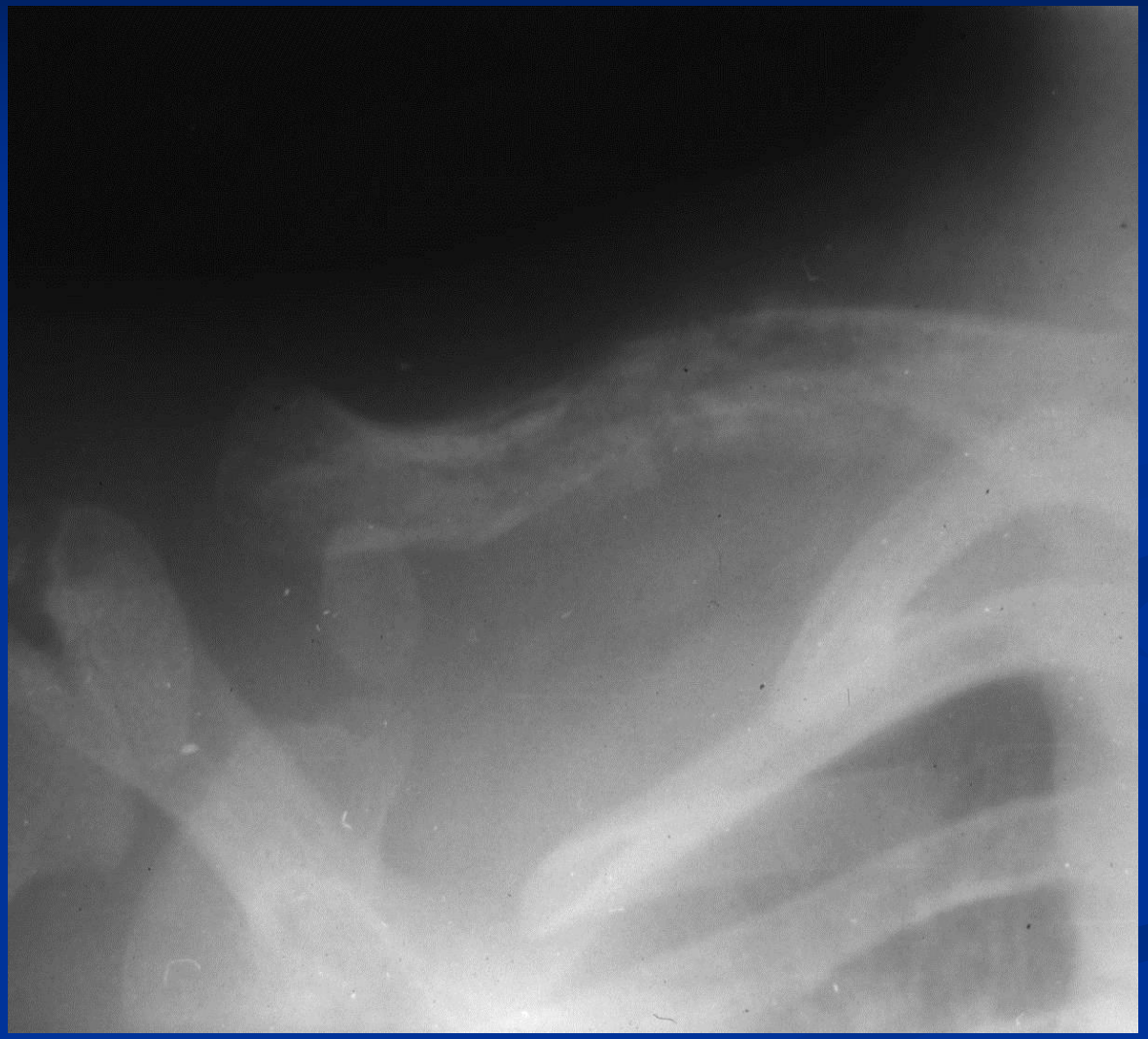
X-ray: Eosinophilic Granuloma of Femur



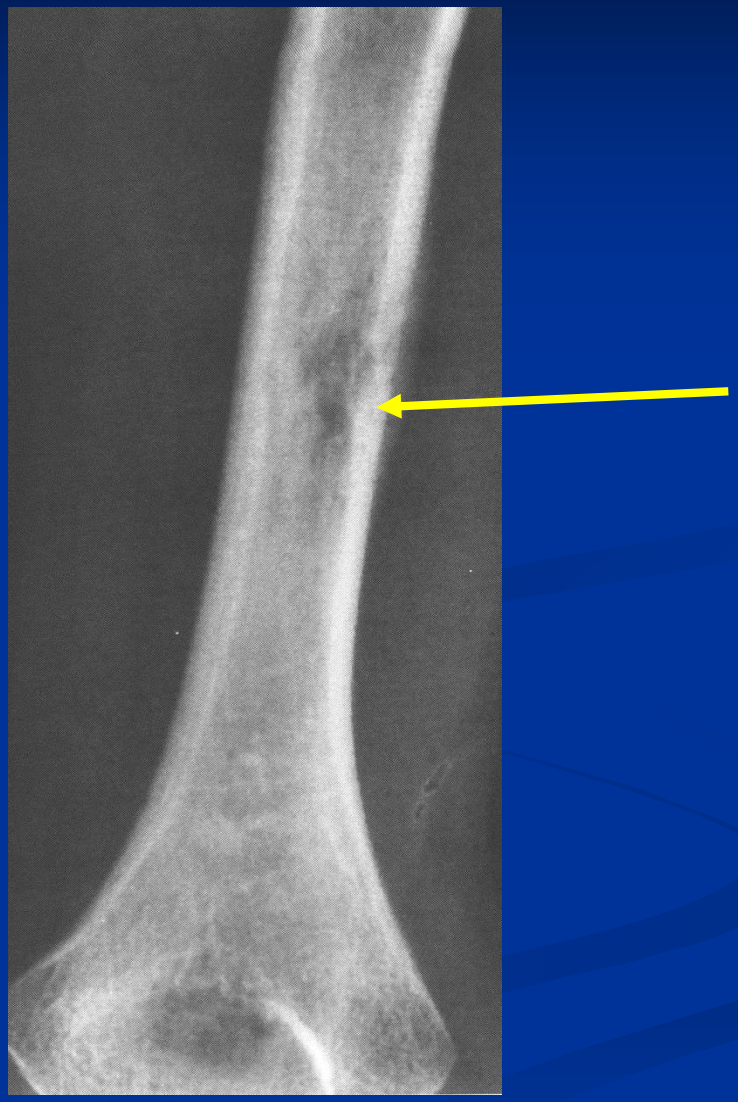


Geographic Lesion
with Sclerotic Rim

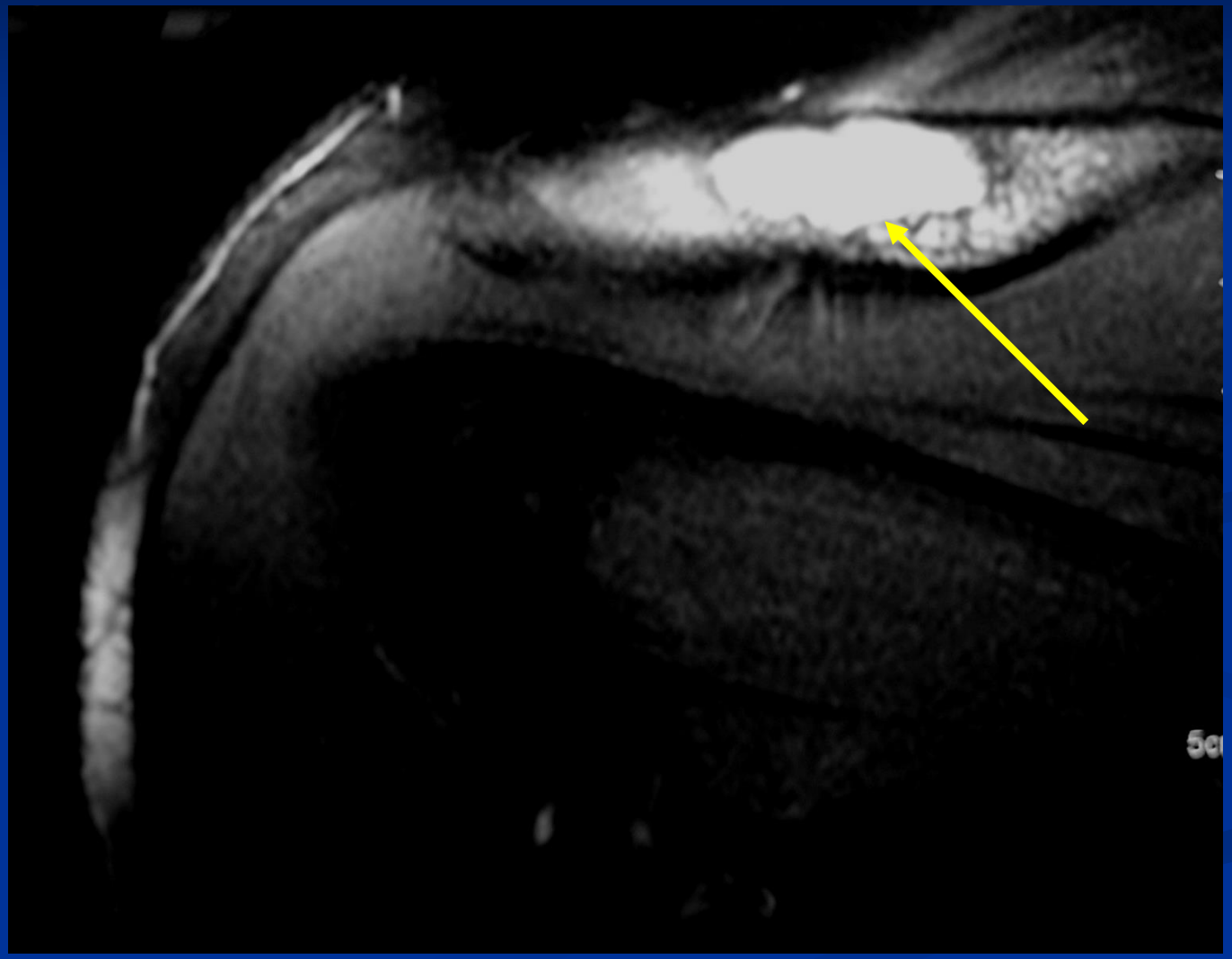
X-ray: Eosinophilic Granuloma of Clavicle
Permeative Lesion



Plain X-ray: Eosinophilic Granuloma of Humerus
Permeative Lesion



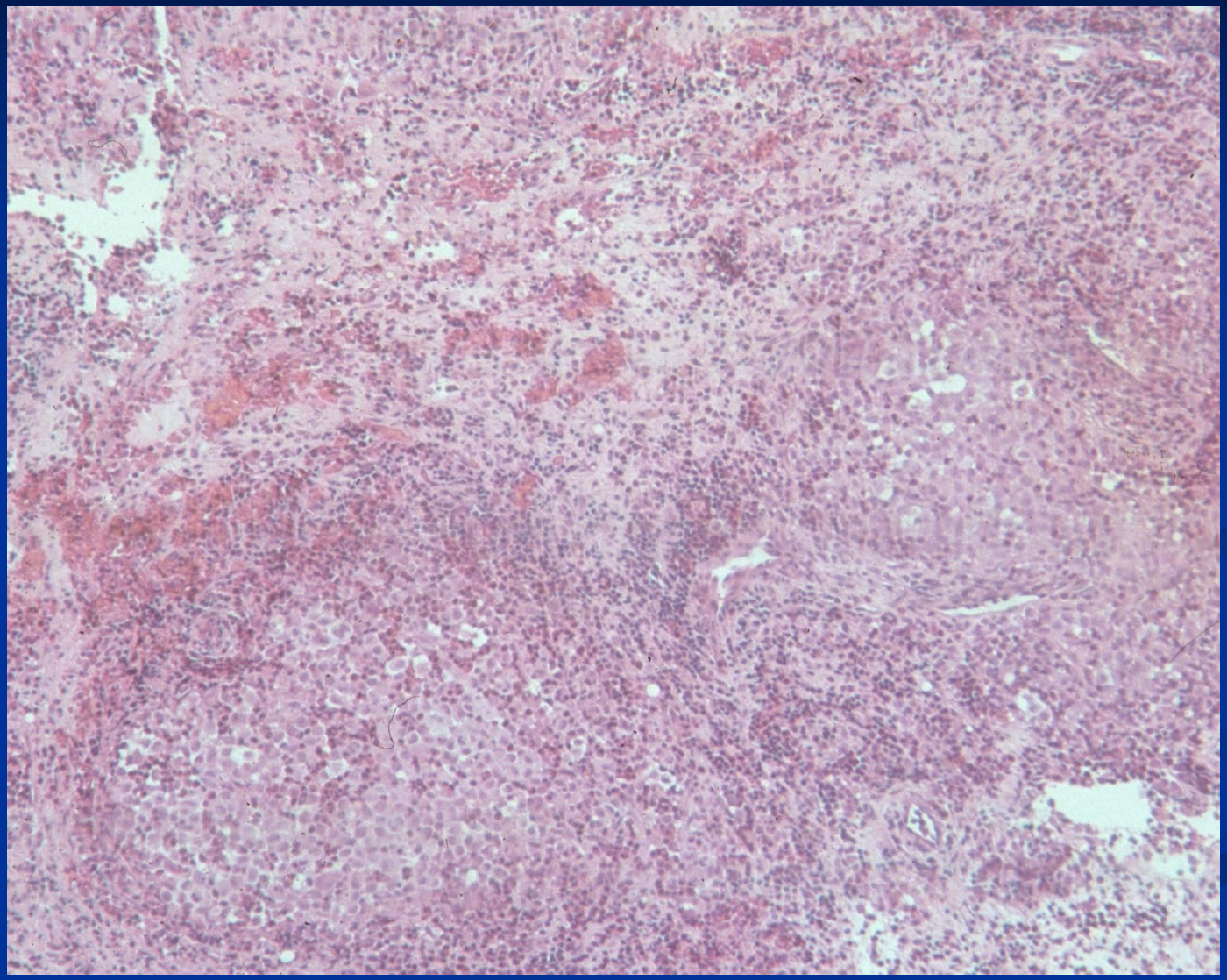
MRI T2: Eosinophilic Granuloma of Scapula Spine



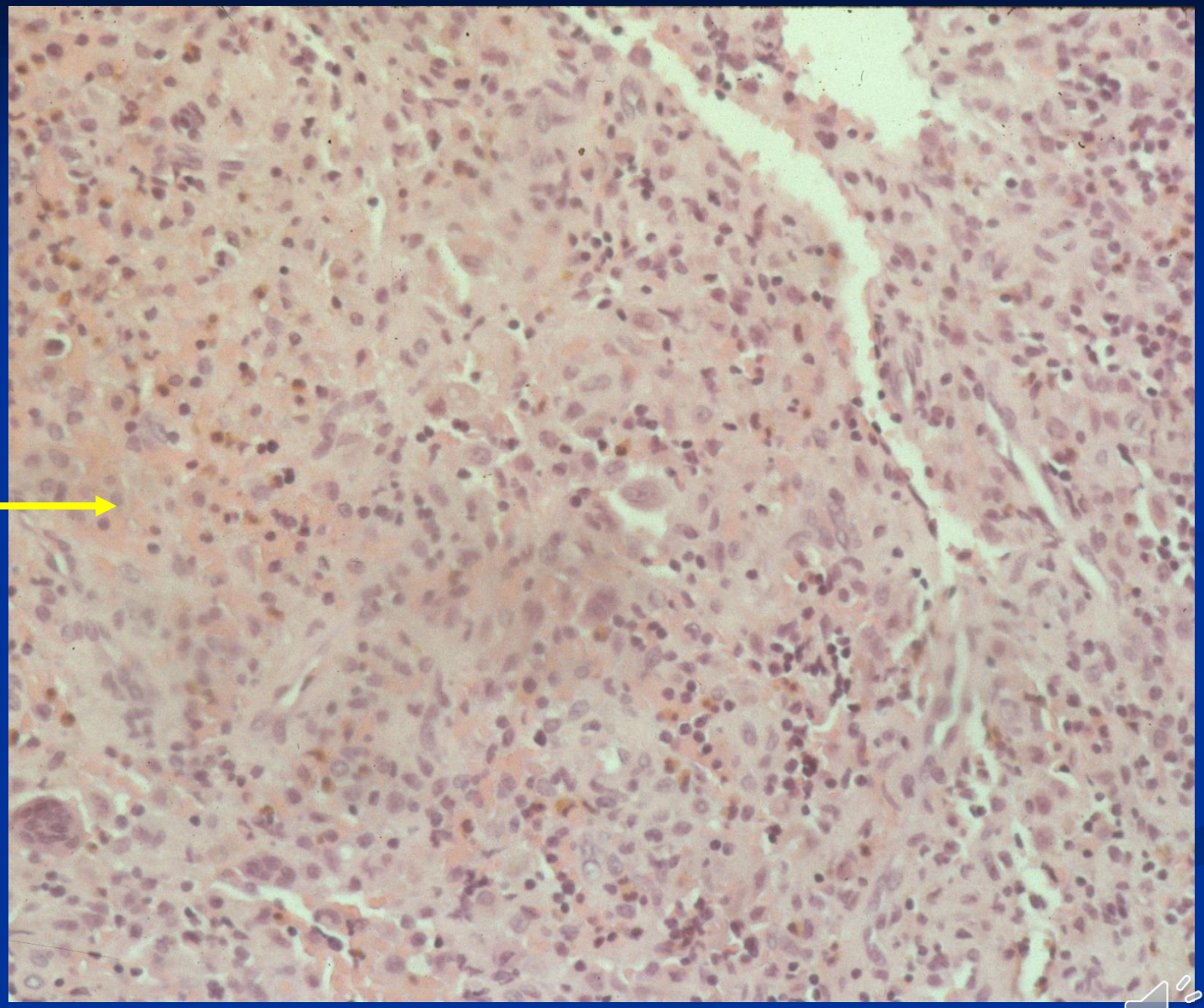
Microscopic Pathology

- Langerhans cell is diagnostic
  - Prominent nuclear groove (coffee-bean)
- Also composed of eosinophils and other inflammatory cells (non diagnostic component)
- **Birbeck Granules:** Electron Microscopy tennis raquet appearance from complex invaginations of the cell membrane
- Vimentin, CD1 and S-100 positivity

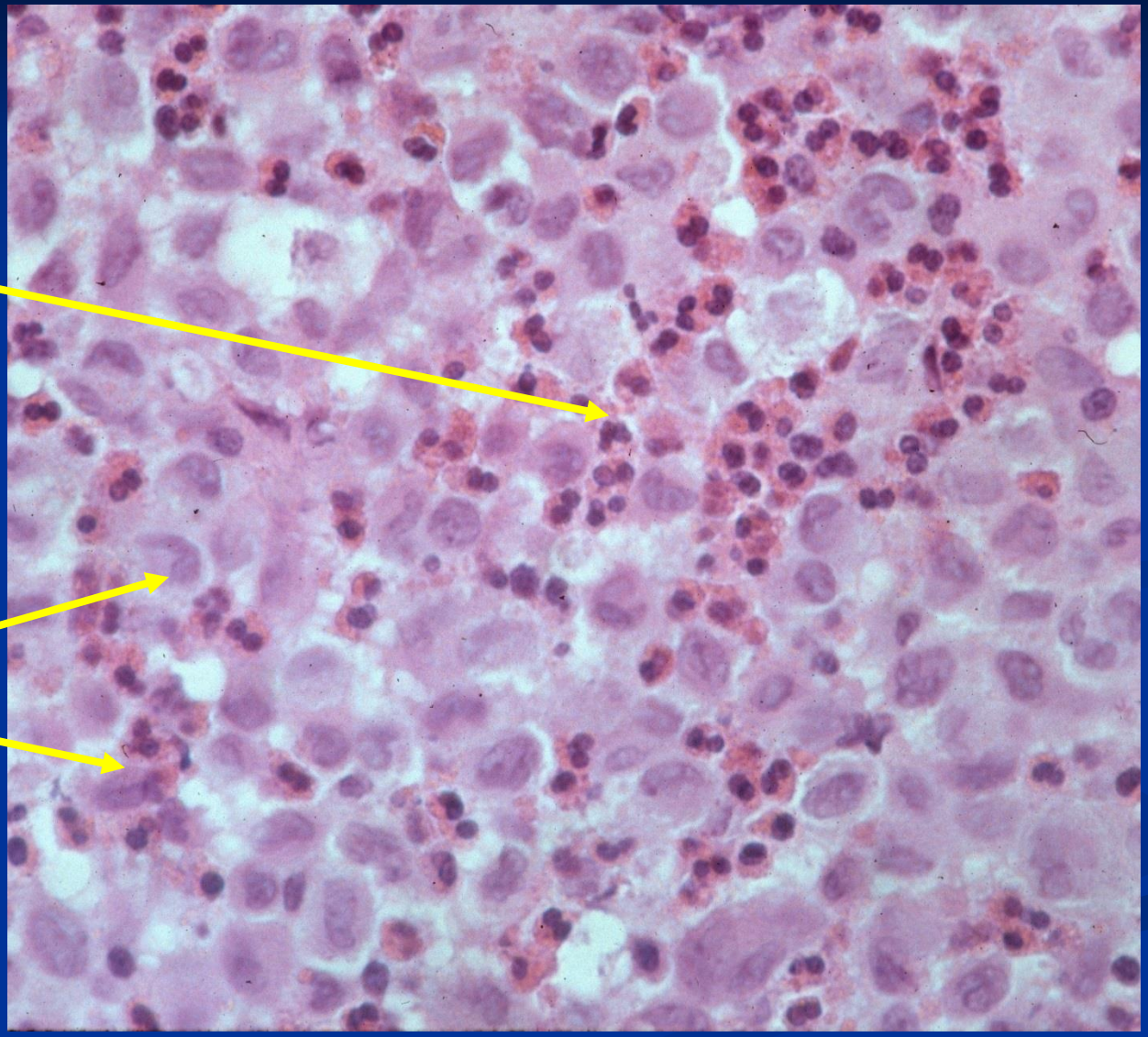
Microscopic Pathology: Eosinophilic Granuloma Cells and No Matrix



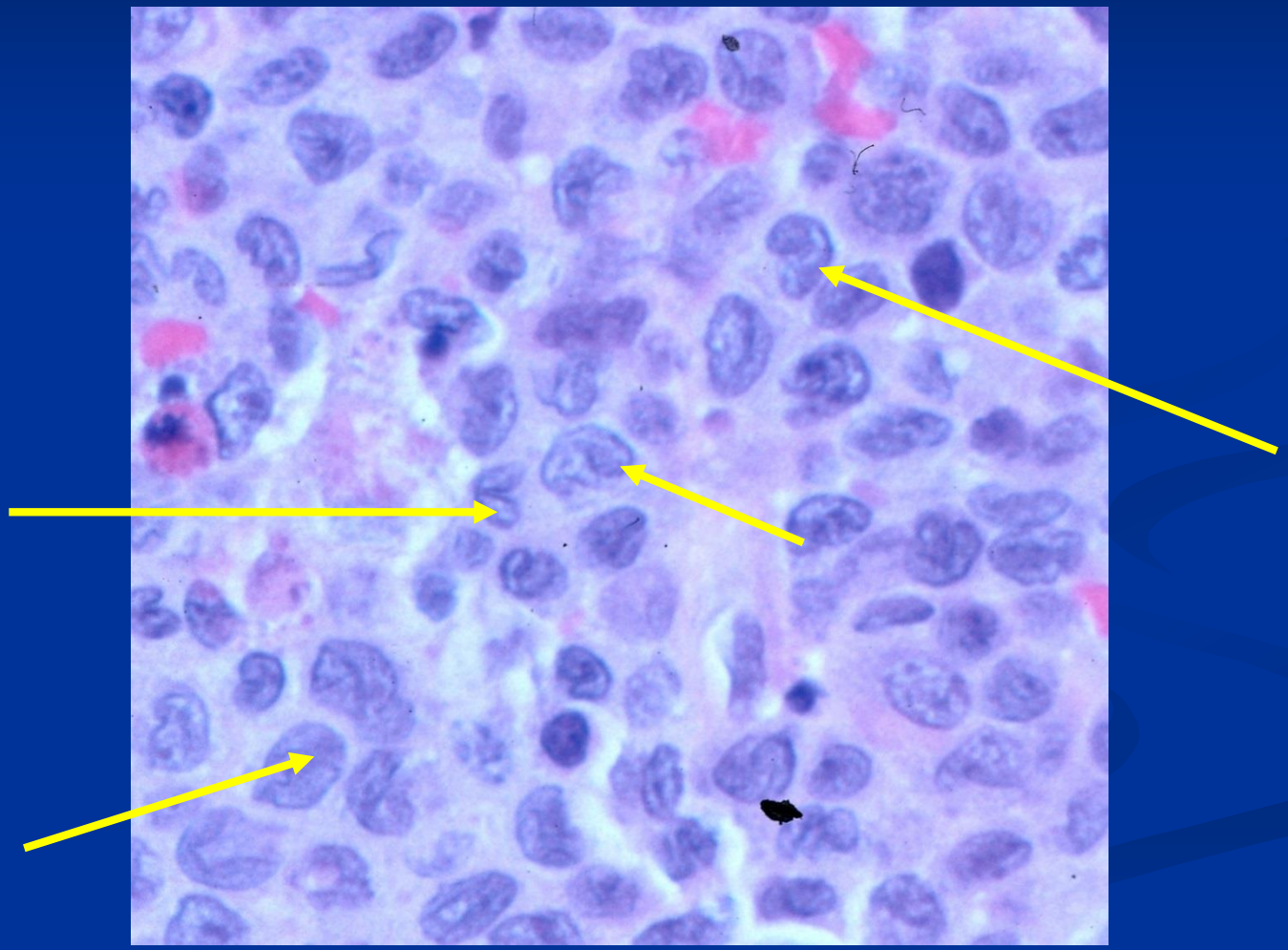
Microscopic Pathology: Eosinophilic Granuloma



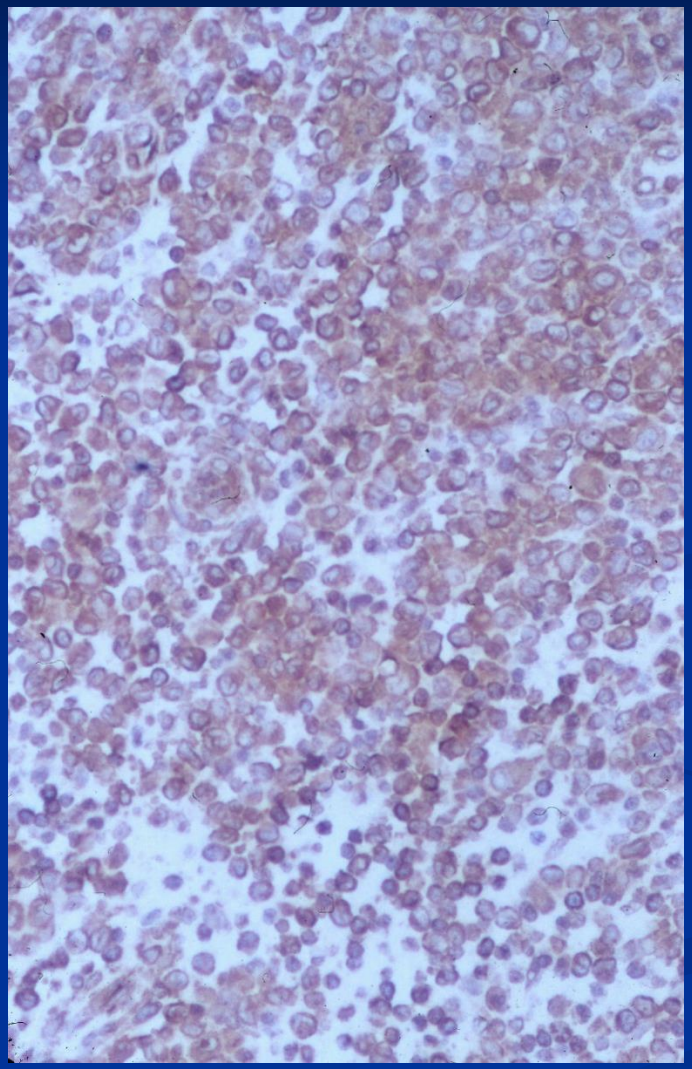
Microscopic Pathology: Eosinophilic Granuloma



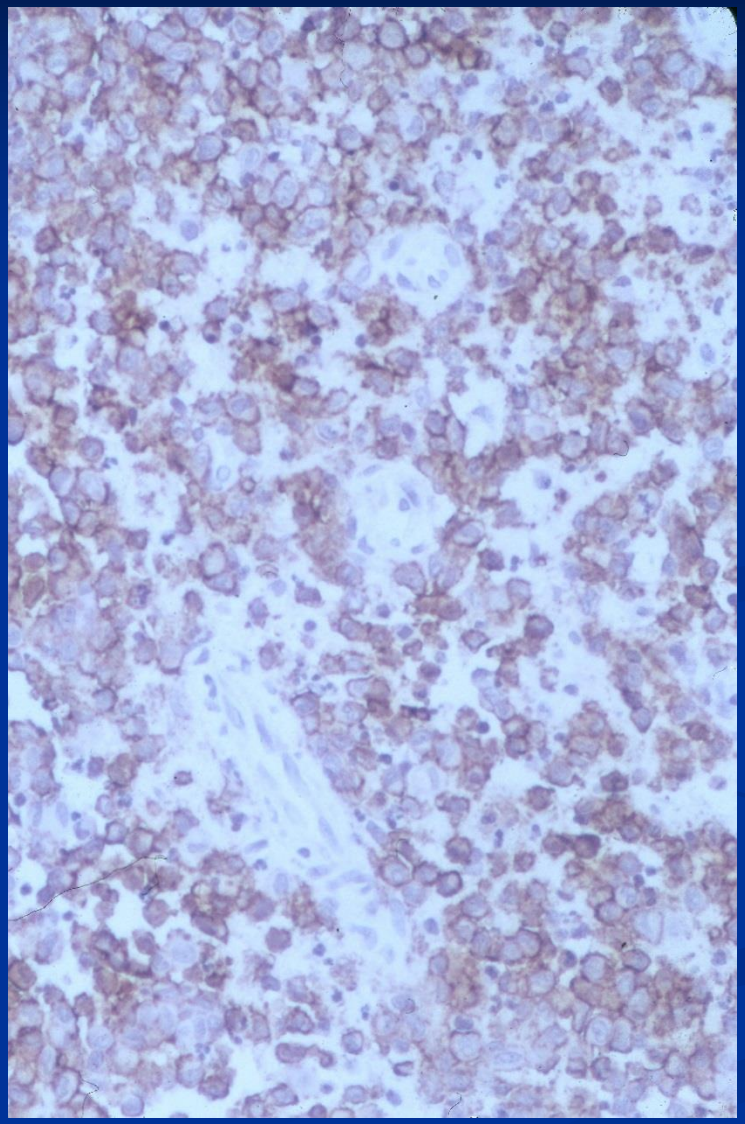
Microscopic Pathology: Eosinophilic Granuloma
High power
Coffee Bean/Indented Nuclei of Langerhans Cells



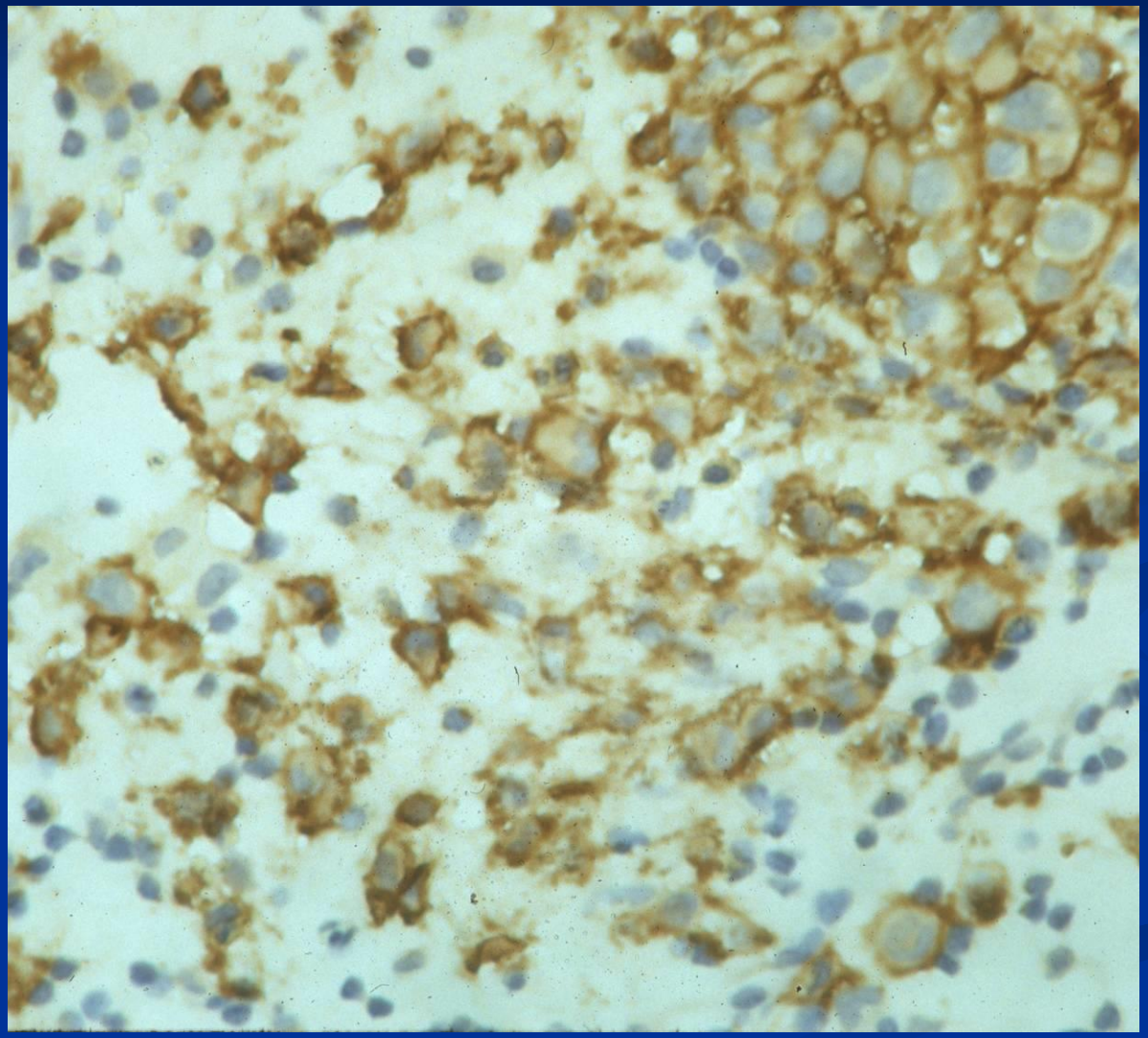
Eosinophilic Granuloma: Vimentin Stain



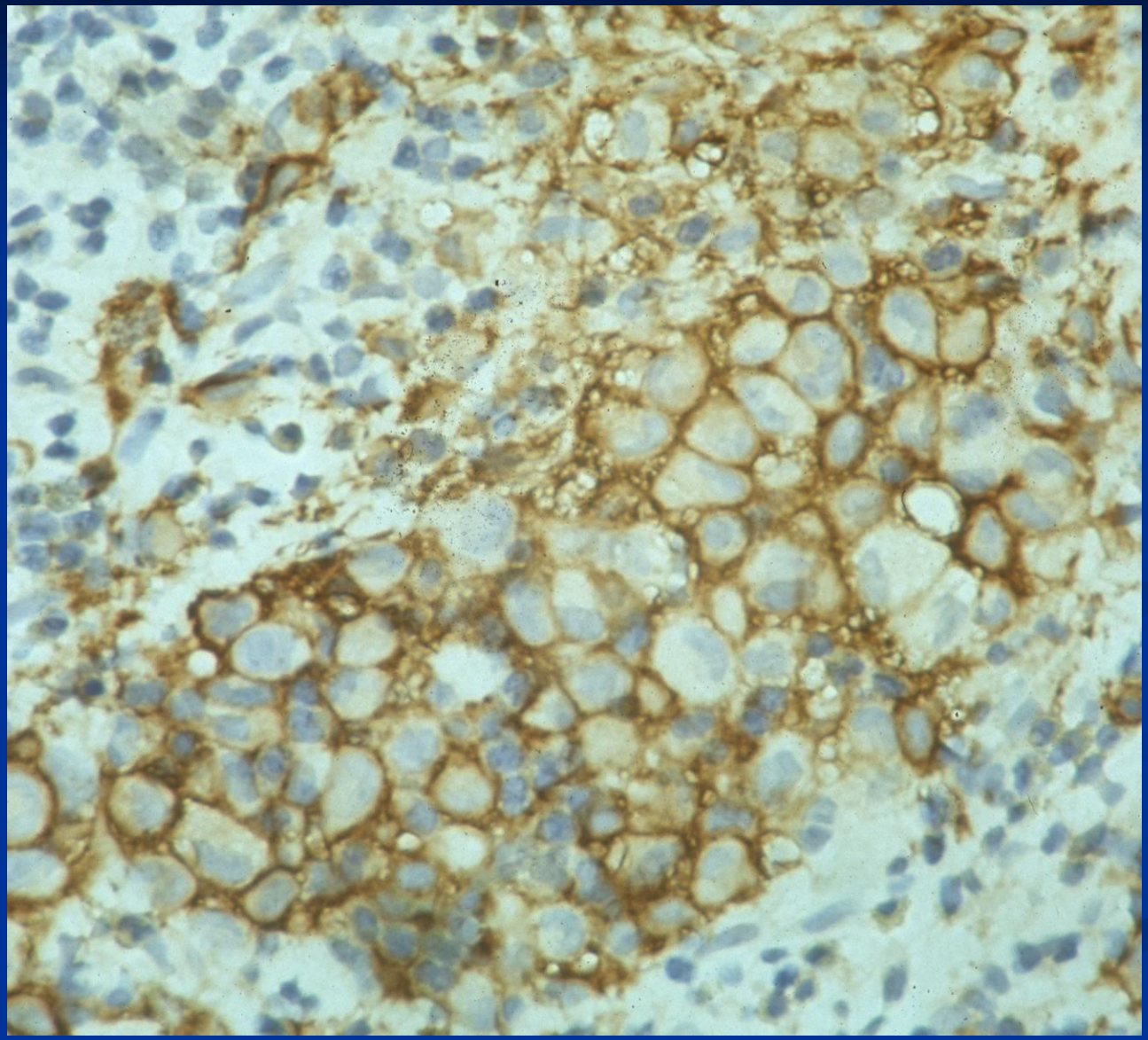
Eosinophilic Granuloma: CD1a Stain



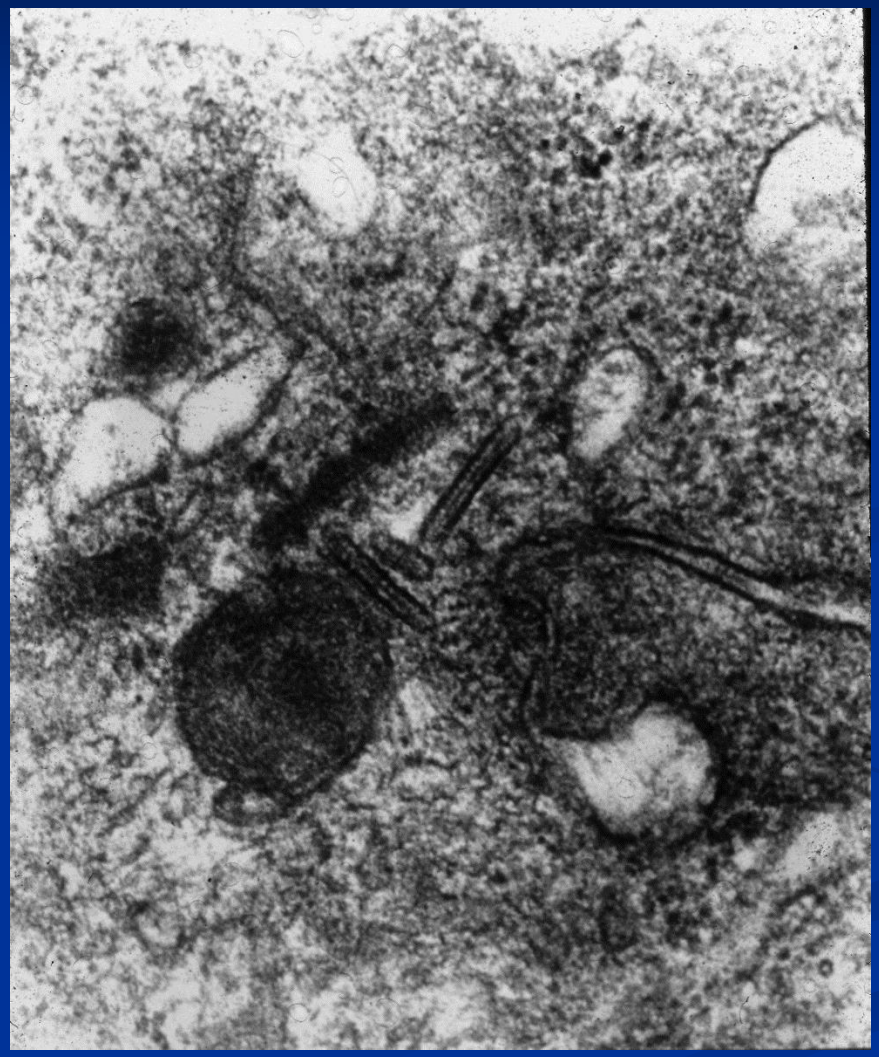
Eosinophilic Granuloma: S-100 Stain



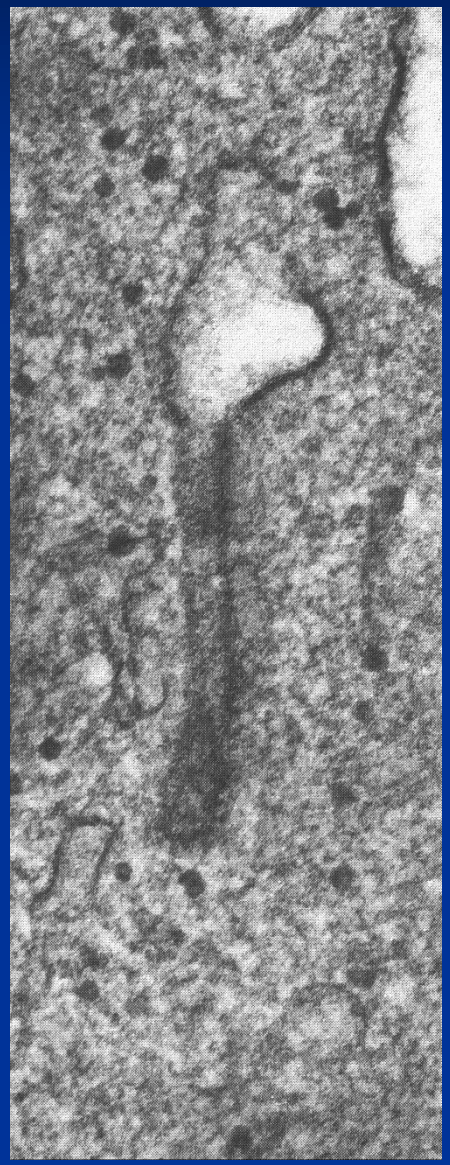
Eosinophilic Granuloma: CD-10 Stain

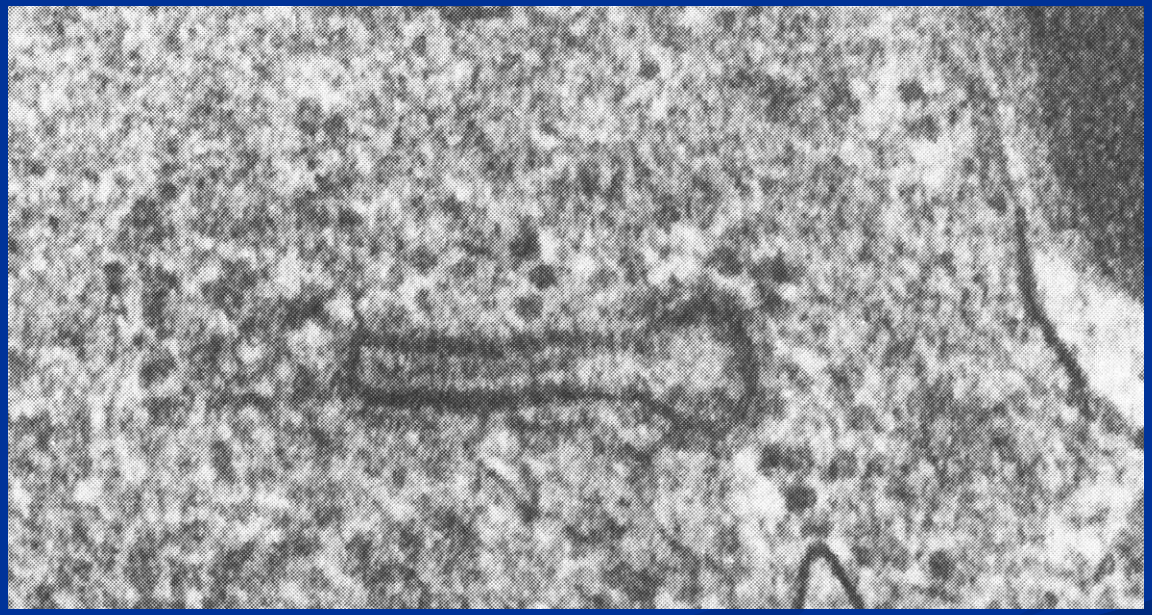


Eosinophilic Granuloma: Birbeck Granules



Birbeck Granules





Differential Diagnosis

- Osteomyelitis
- Granulomatous Inflammation
  - Tuberculosis
  - Fungus
- Hodgkin Disease

Biological Behavior

- Benign disorder
- May undergo partial or complete spontaneous resolution
- Patients with solitary lesions are at risk for developing additional bony lesions within 6 months to 2 years

Treatment

- Curettage or intralesional injection of a steroid
  - Curettage and bone grafting for long bones and weight bearing bones at risk for fracture
  - Intralesional steroids for non weightbearing bones
    - Complete healing may take a year
- Low dose radiation may be valuable for inaccessible lesions
- Vertebral plana is braced and observed

Ewing Sarcoma

General Information

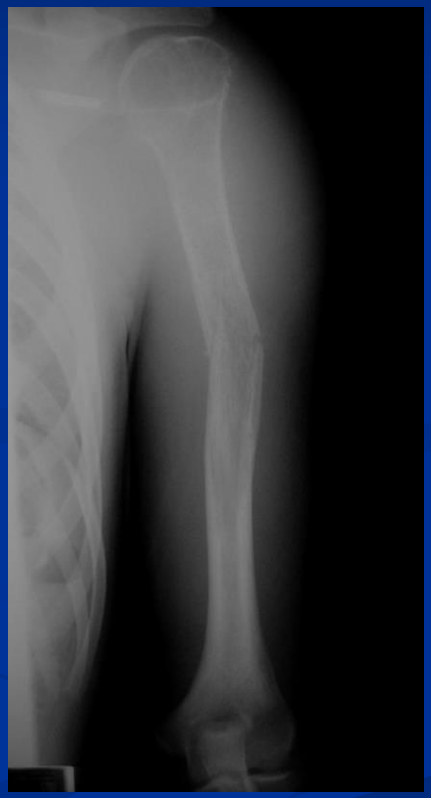
- Uniform, monotonous, small round blue cells without any matrix production
- Fourth most common primary malignancy of bone
- Rare
- Most Ewing sarcoma cases (85%) are associated with a characteristic chromosomal translocation **t(11;22)(q24;q12)** that results in **EWS/FLI-1** chimeric protein

Clinical Presentation

- **Signs/Symptoms:** Mass & localized pain.
  - Increased sedimentation rate, fever, anemia, malaise may occur and are usually indicative of metastatic disease
  - 10% of patients present with multiple bony lesions
  - May have elevated LDH
- **Prevalence:** Slight male predominance (1.5:1)
  - Uncommon in African Americans
- **Age:** 10-25 years of age most common
- **Sites:** **diaphysis** but can also arise from **metadiaphysis** and metaphysis; Very rare epiphyseal involvement
  - Femur: Single most common site
  - Humerus
  - Pelvis
  - Ribs

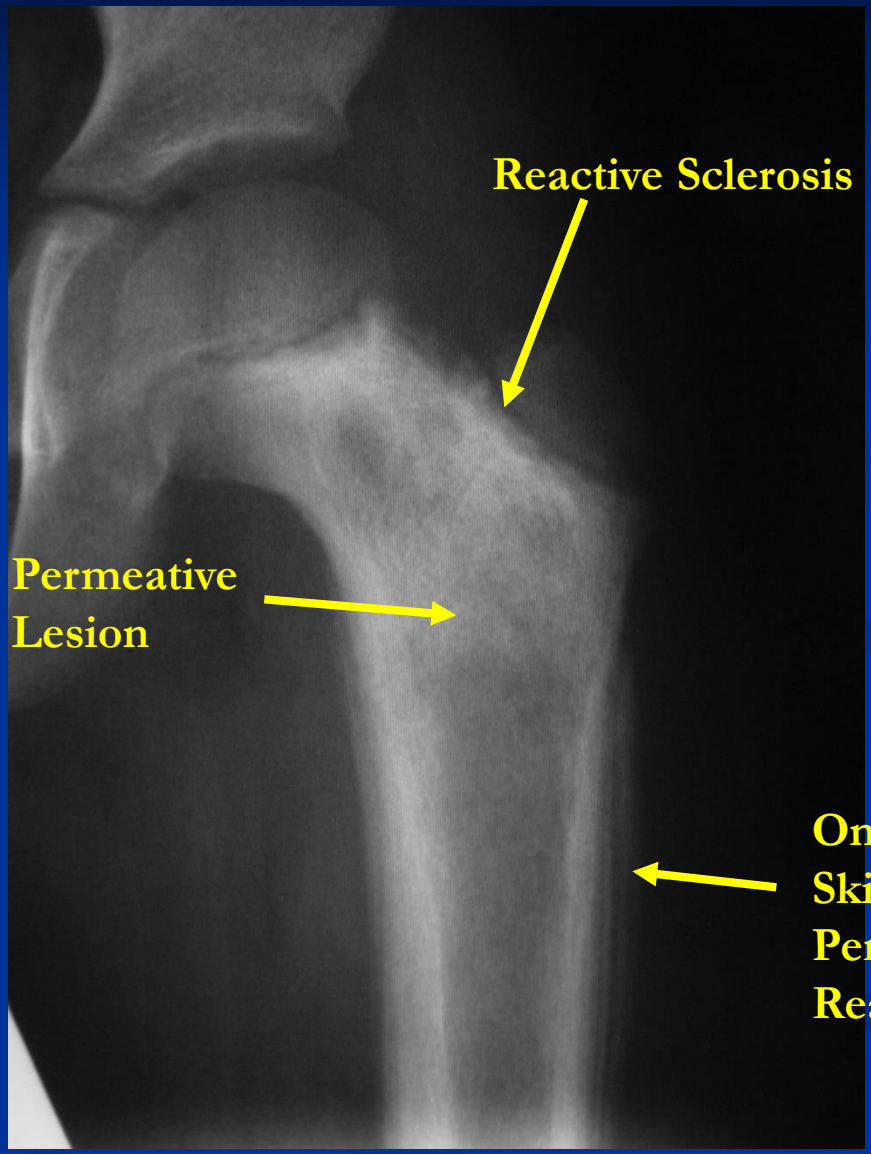
Radiographic Presentation

- Permeative or moth eaten bone destruction
- Soft Tissue Mass in 90% of of cases
- Periosteal Reaction in 50% of cases
  - **Onion Skin** (colic pattern of irritation)
  - **Hair on End** (rapid continuous lifting of periosteum)
- Reactive Bone Sclerosis is rare but occurs in 10% of cases
- No cartilage or bone production by tumor
- Pathologic fracture in 10-15%
- Rarely seen as a geographic, benign appearing tumor similar to a cyst or eosinophilic granuloma
- Rare cases of periosteal ewing sarcoma with no medullary involvement



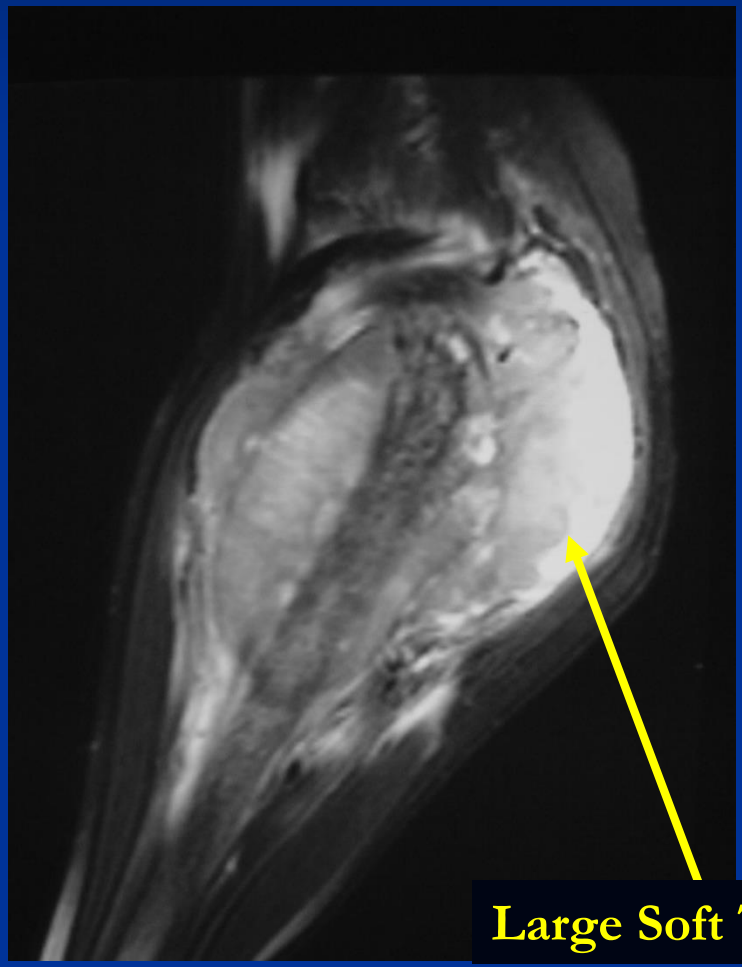
X-ray: Ewing Sarcoma of Proximal Femur

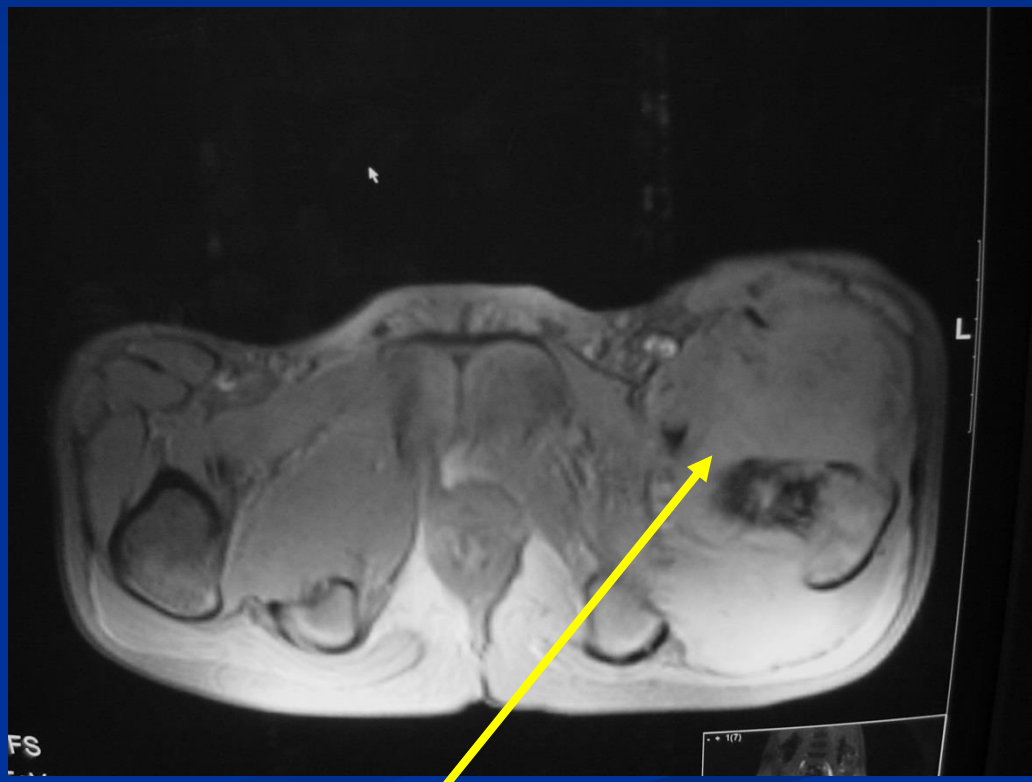
- Permeative Lesion
- Metadiaphysis
- Reactive Sclerosis
- Onion Skin Periosteal Reaction
- Skeletally Immature
- Soft Tissue Mass



MRI: Ewing Sarcoma of Proximal Femur

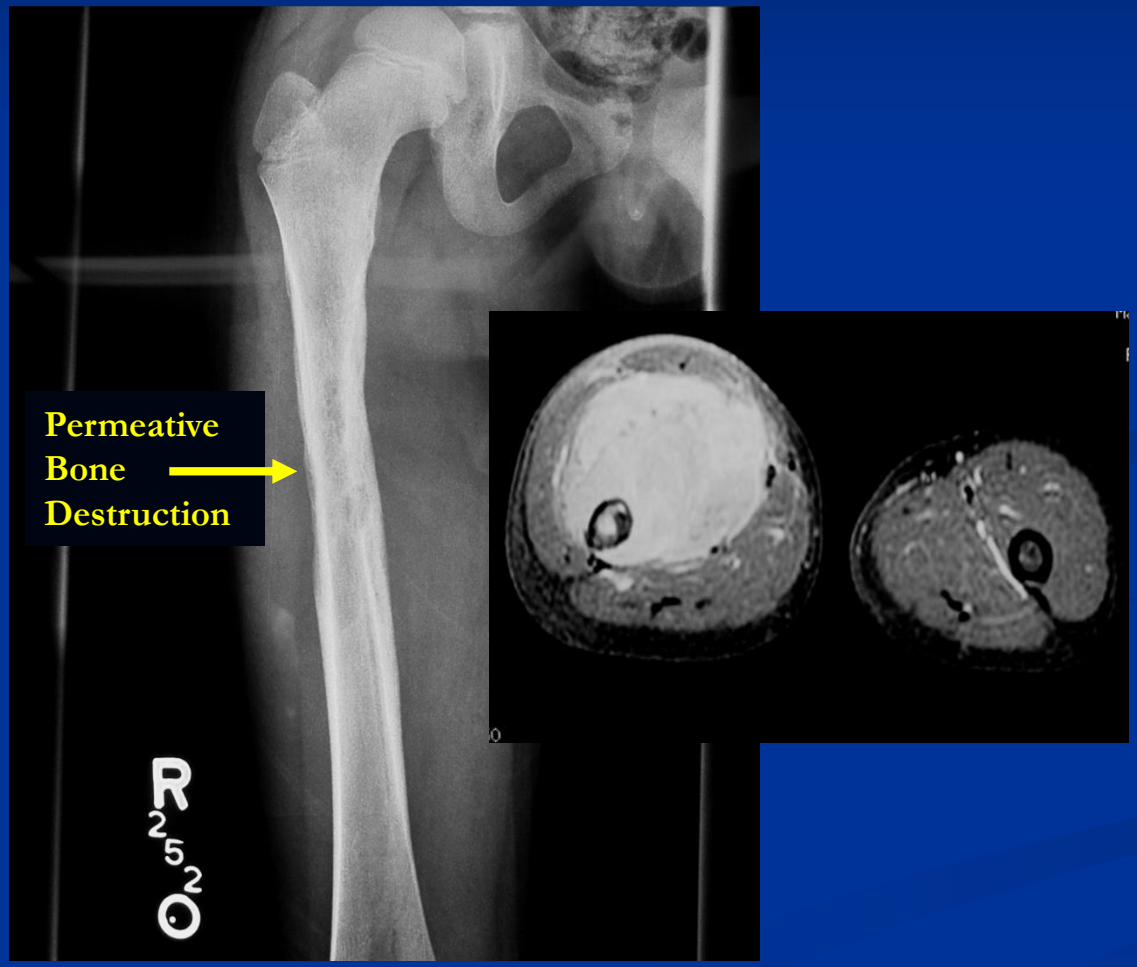
Large Soft Tissue Mass and Extensive Marrow Involvement

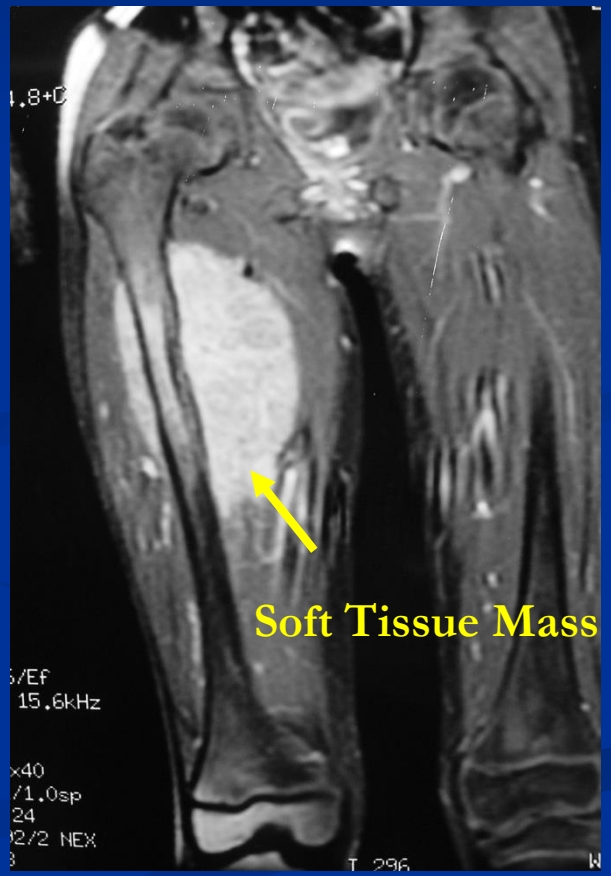




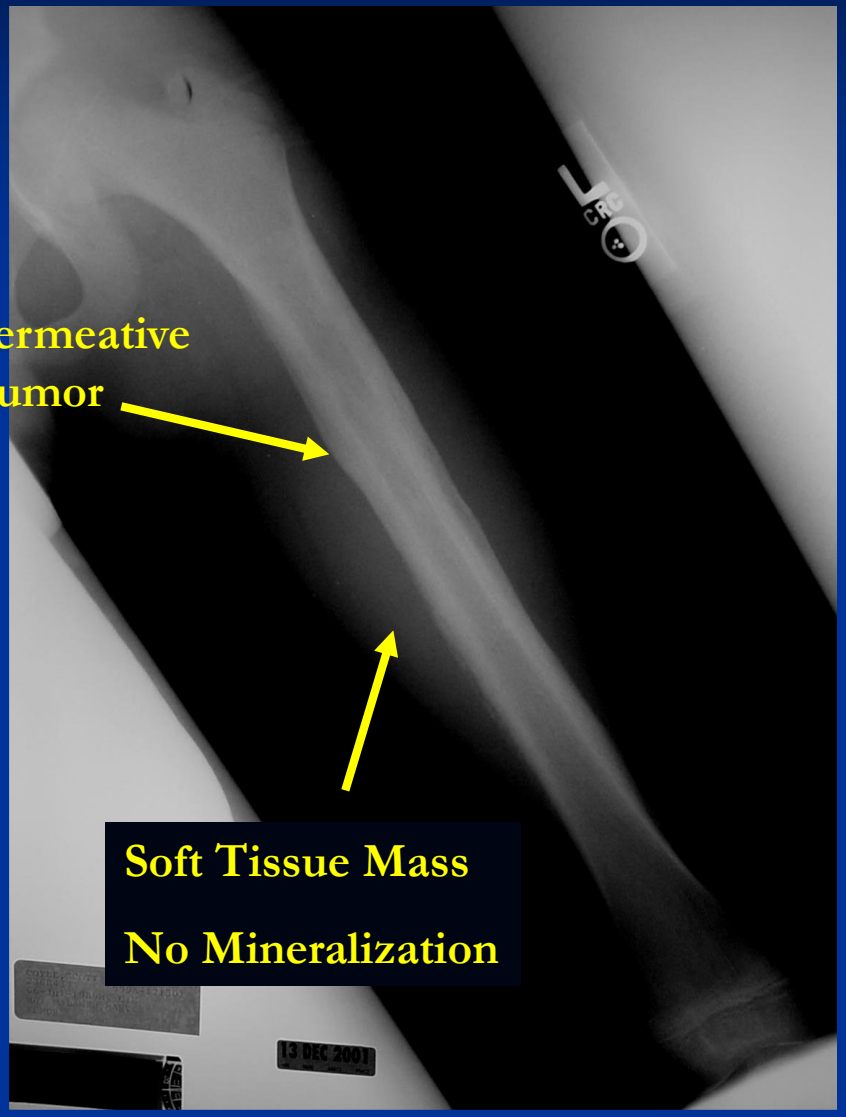
Large Soft Tissue Mass Best Visualized on MRI

X-ray/MRI: Ewing Sarcoma of Diaphysis of Femur
Tumor Barely Perceptible on X-Ray
MRI Demonstrates Marrow Involvement and Large Soft Tissue Mass

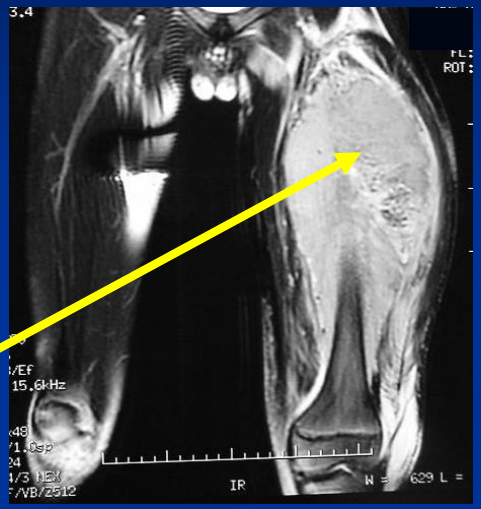


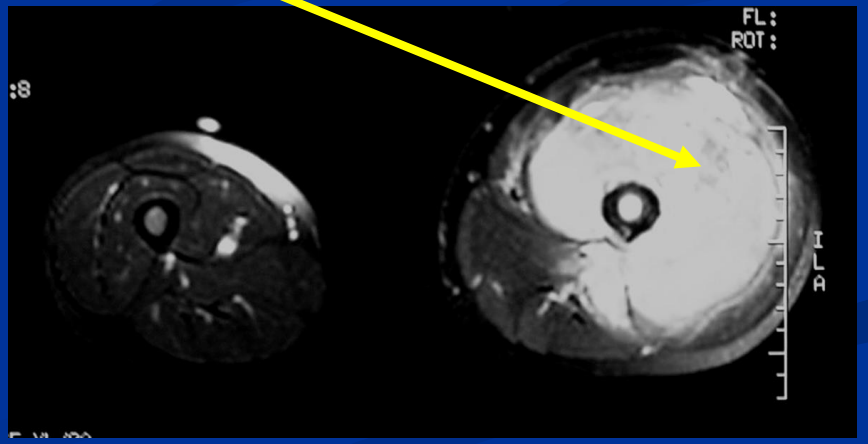


X-ray/MRI: Ewing Sarcoma of Diaphysis of Left Femur



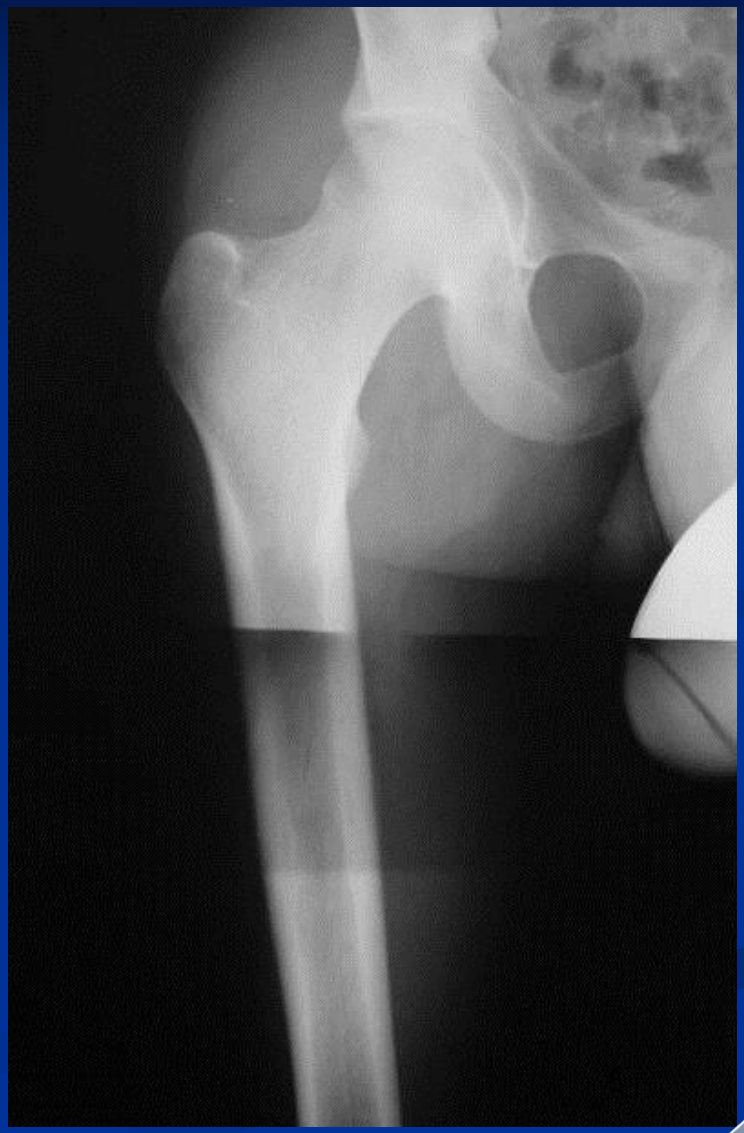
Large Soft
Tissue Mass





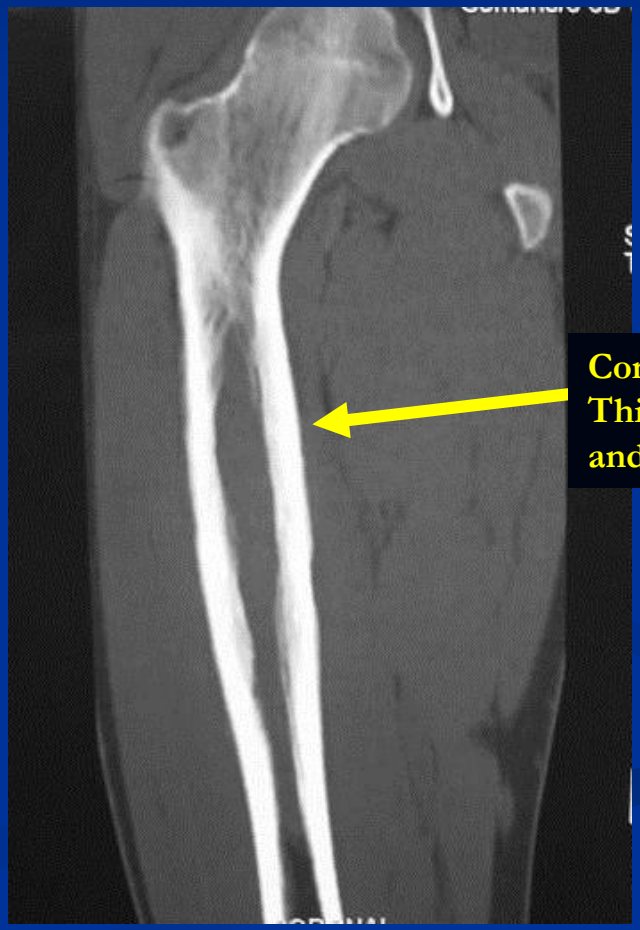
X-ray: Ewing Sarcoma of Right Femur

- X-rays demonstrate a **permeative lesion** of the right proximal femur with slight sclerosis
- The lesion is barely perceptible on the Xray
- There is no periosteal reaction in this case



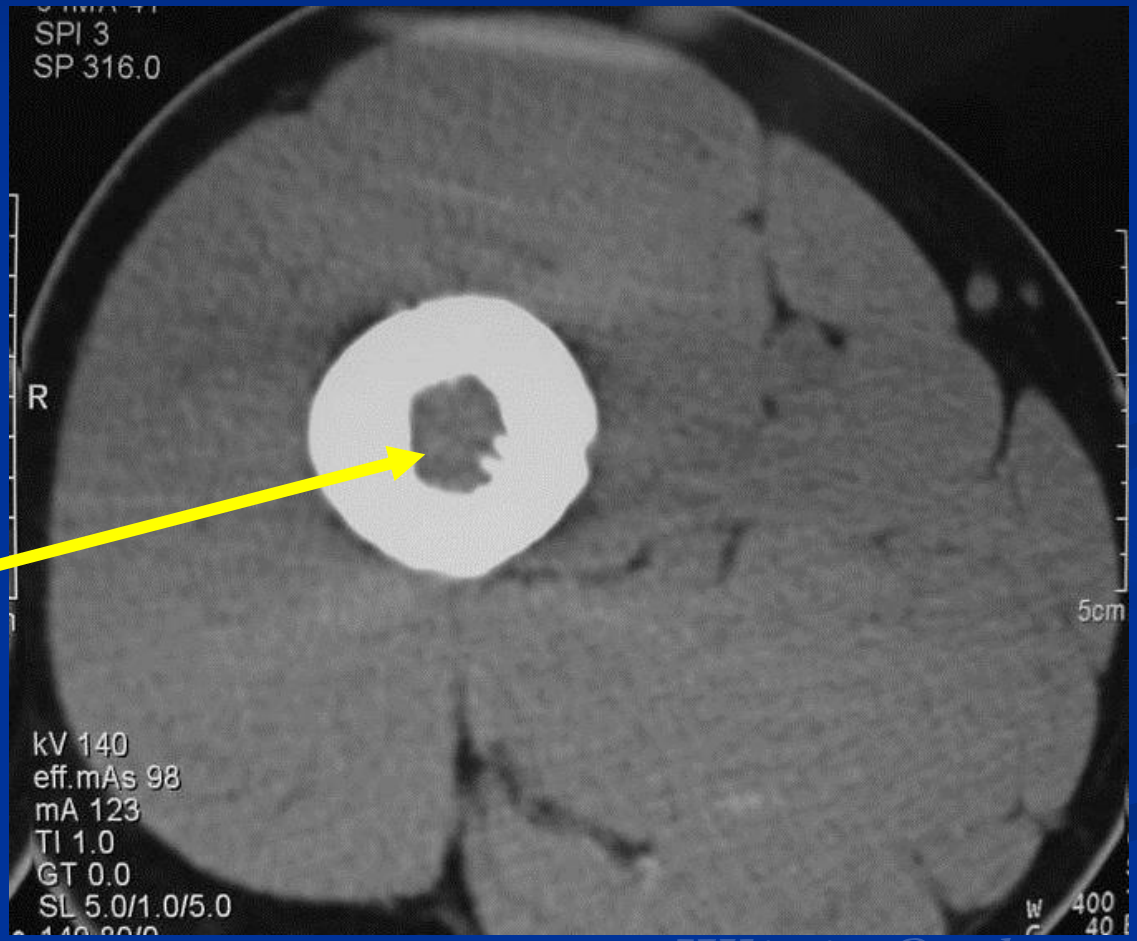
CT Scan: Ewing Sarcoma of Right Femur *This is a rare case where there is no soft tissue component*

- The CT scan demonstrates a permeative lesion through the proximal ½ of the femur
- The cortex was mildly thickened and expanded (arrow)
- There is no soft tissue component
- There is no mineralization
- 10% of Ewing sarcomas do not have a soft tissue mass



CT Scan: Ewing Sarcoma of Right Femur

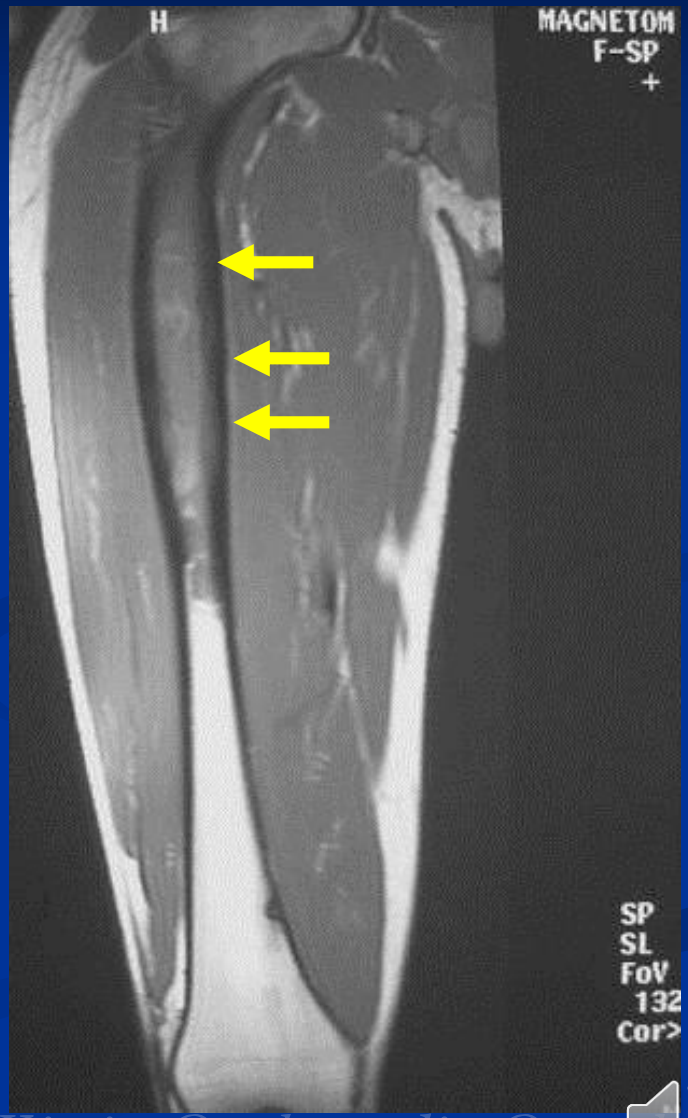
This is a rare case where there is no soft tissue component



Marrow Replacing Lesion

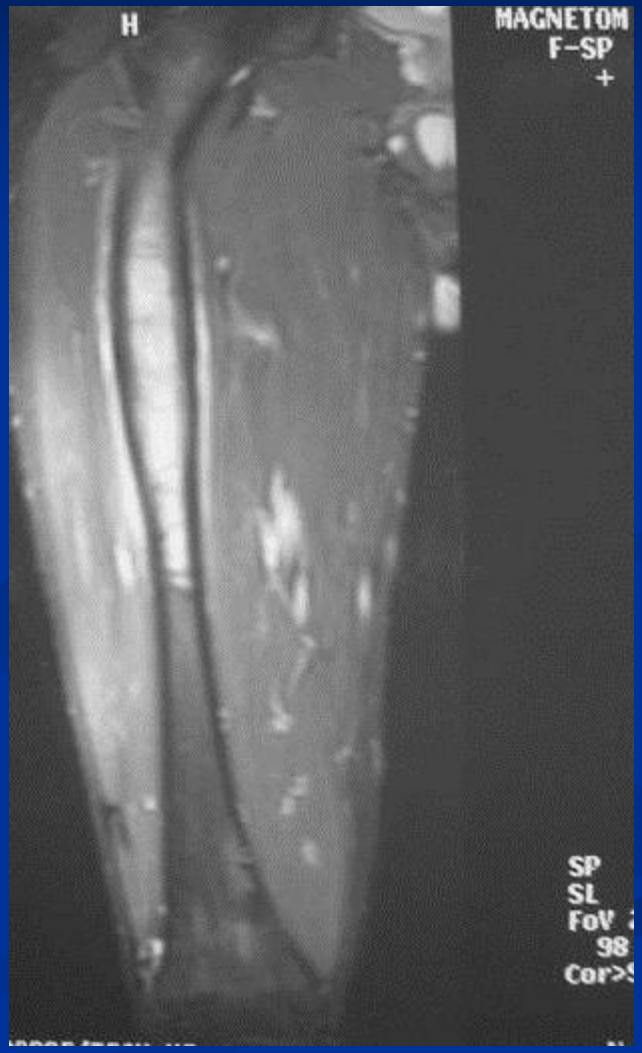
MRI T1 Weighted Image: Ewing Sarcoma of Right Proximal Femur

- The T1 weighted MRI demonstrated a permeative lesion involving the upper ½ of the femur (arrows).
- The bone was mildly expanded and the cortex slightly thickened
- There was no Codman's triangle, hair on end or sunburst periosteal reaction
- The MRI demonstrates fatty marrow replacement



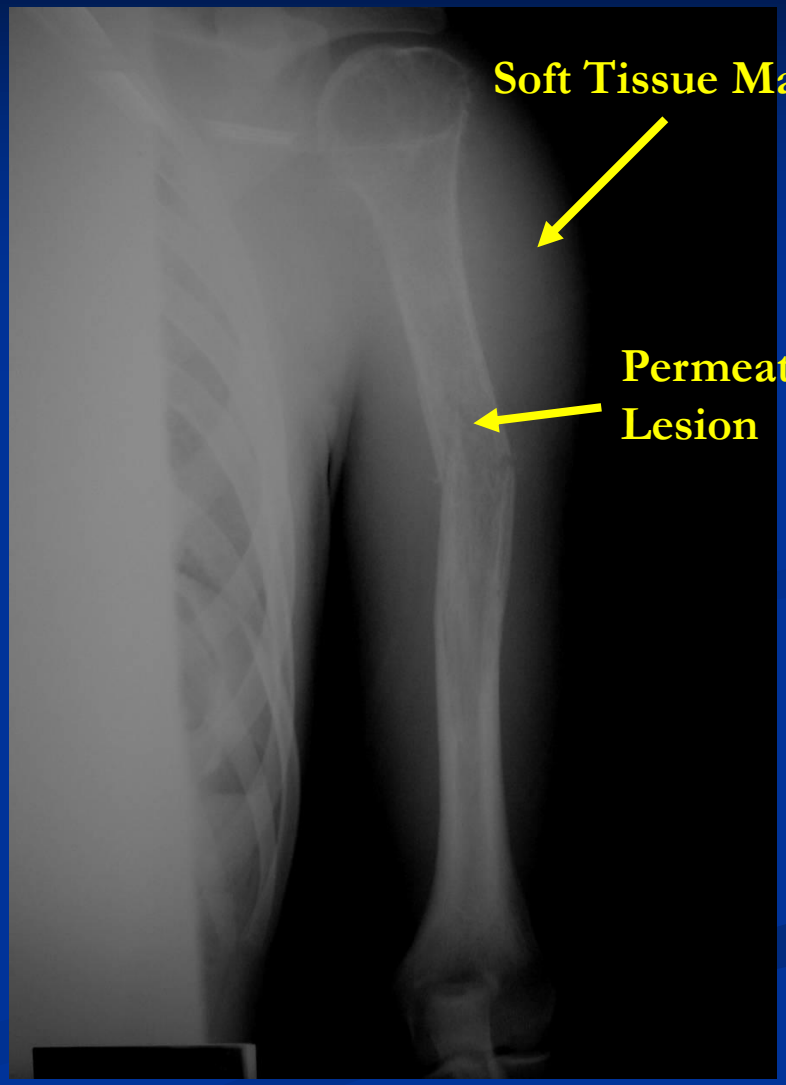
MRI T2 Weighted Image: Ewing Sarcoma of Right Proximal Femur

- The T2 weighted image demonstrates significant edema around the bone and lesion (bright signal)
- There was no soft tissue component associated with the tumor

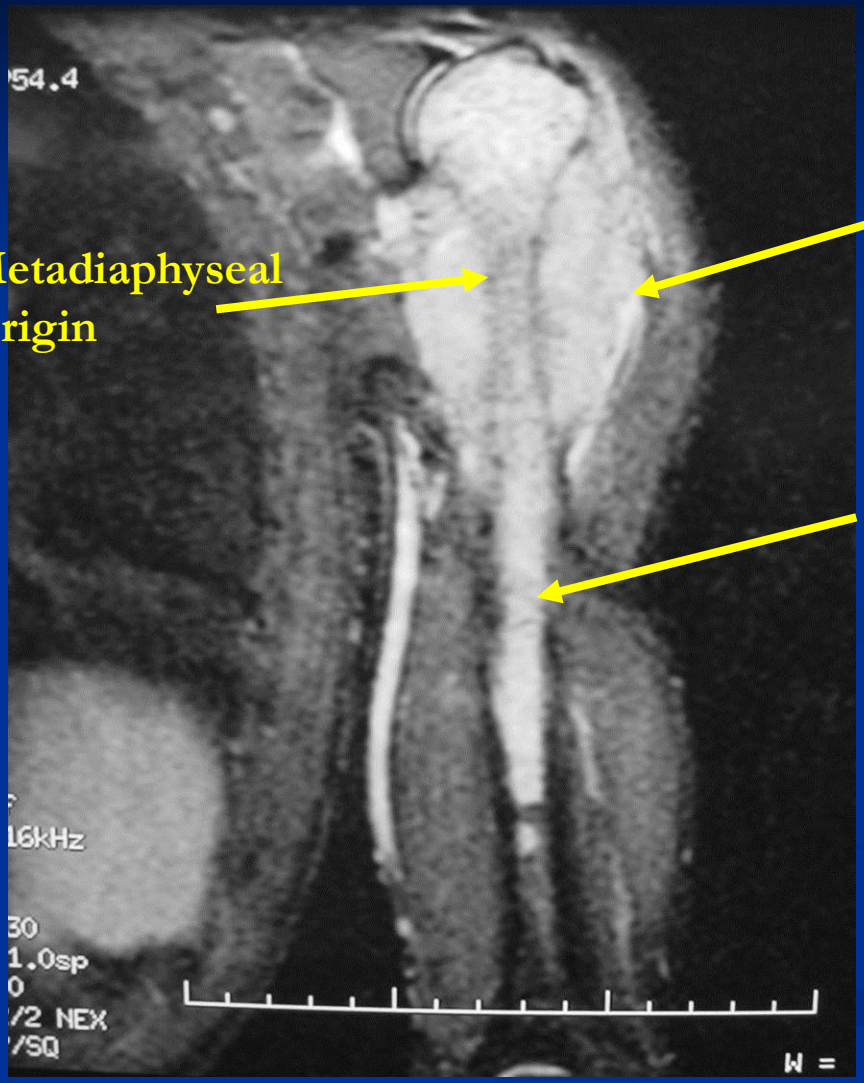


X-ray: Ewing Sarcoma of Left Humerus Metadiaphysis

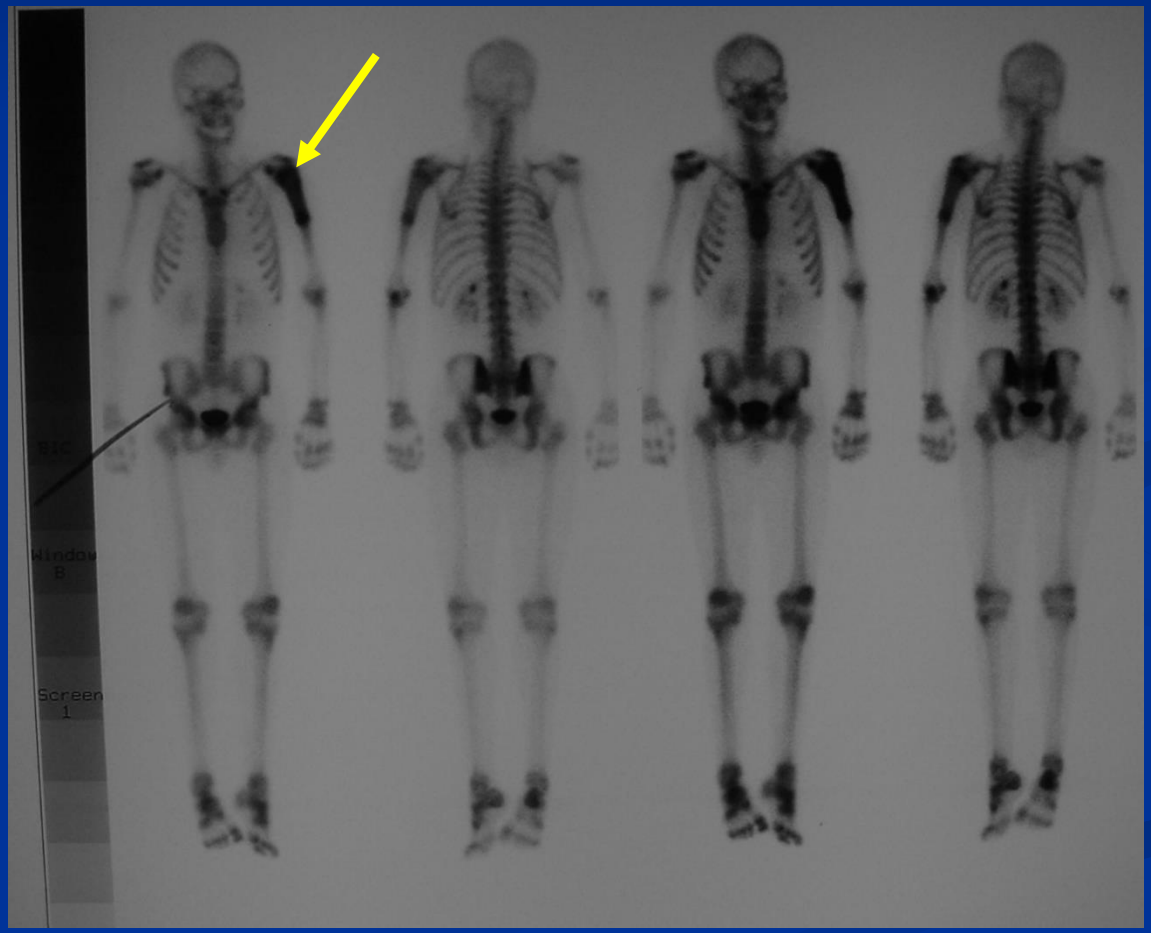
- Permeative lesion left humeral shaft
- Pathological fracture (10% of cases)
- Soft tissue mass proximal humerus
- No mineralization
- Subtle "Hair on End" periosteal reaction



MRI T2: Ewing Sarcoma of Left Humerus



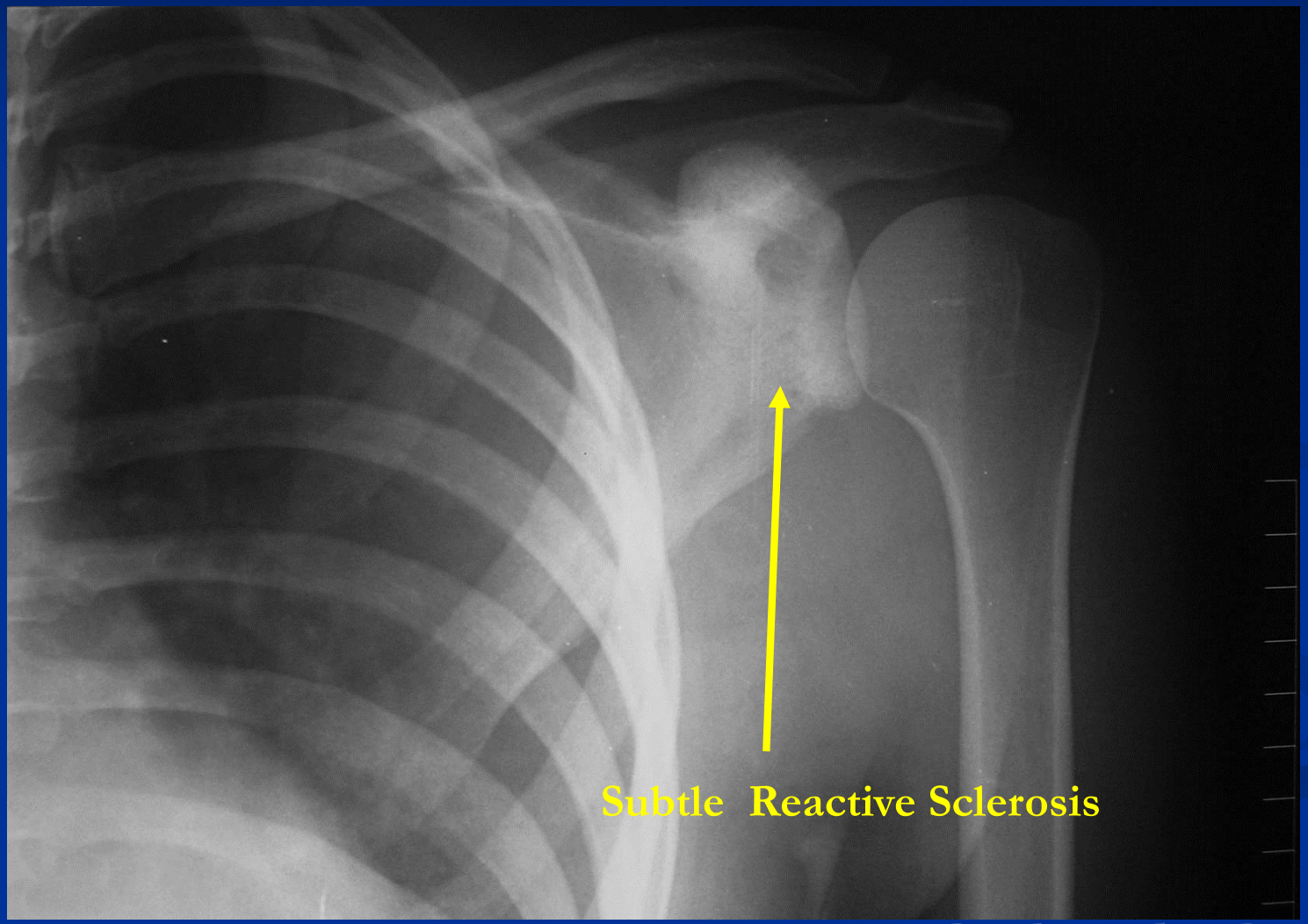
Bone Scan: Ewing Sarcoma of Left Humerus demonstrates Intense Uptake



X-ray: Ewing Sarcoma of Scapula

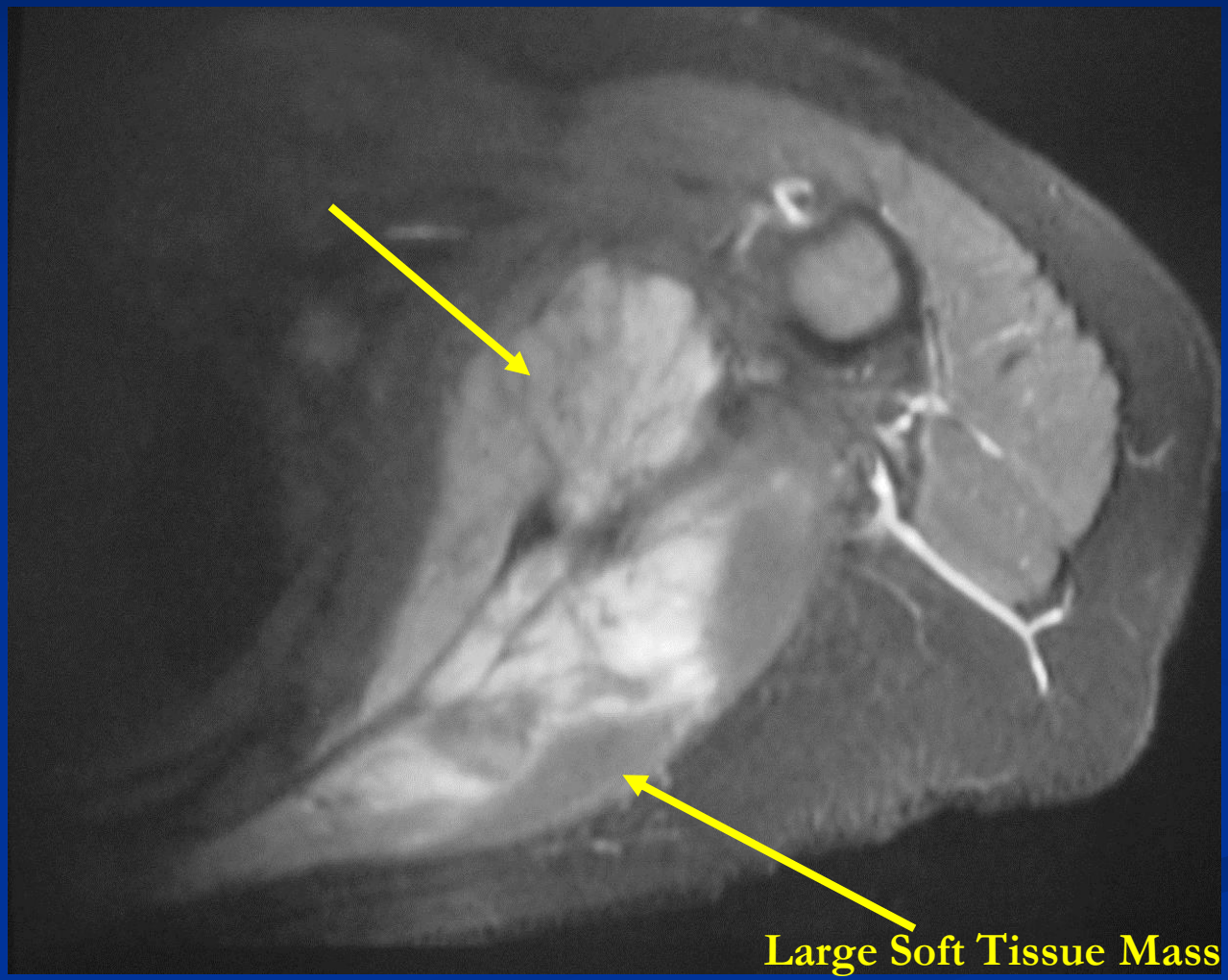
There is subtle reactive sclerosis in the scapula neck and glenoid

The lesion is barely discernible on X-ray



MRI: Ewing Sarcoma of Scapula

There is a large soft tissue component surrounding the scapula

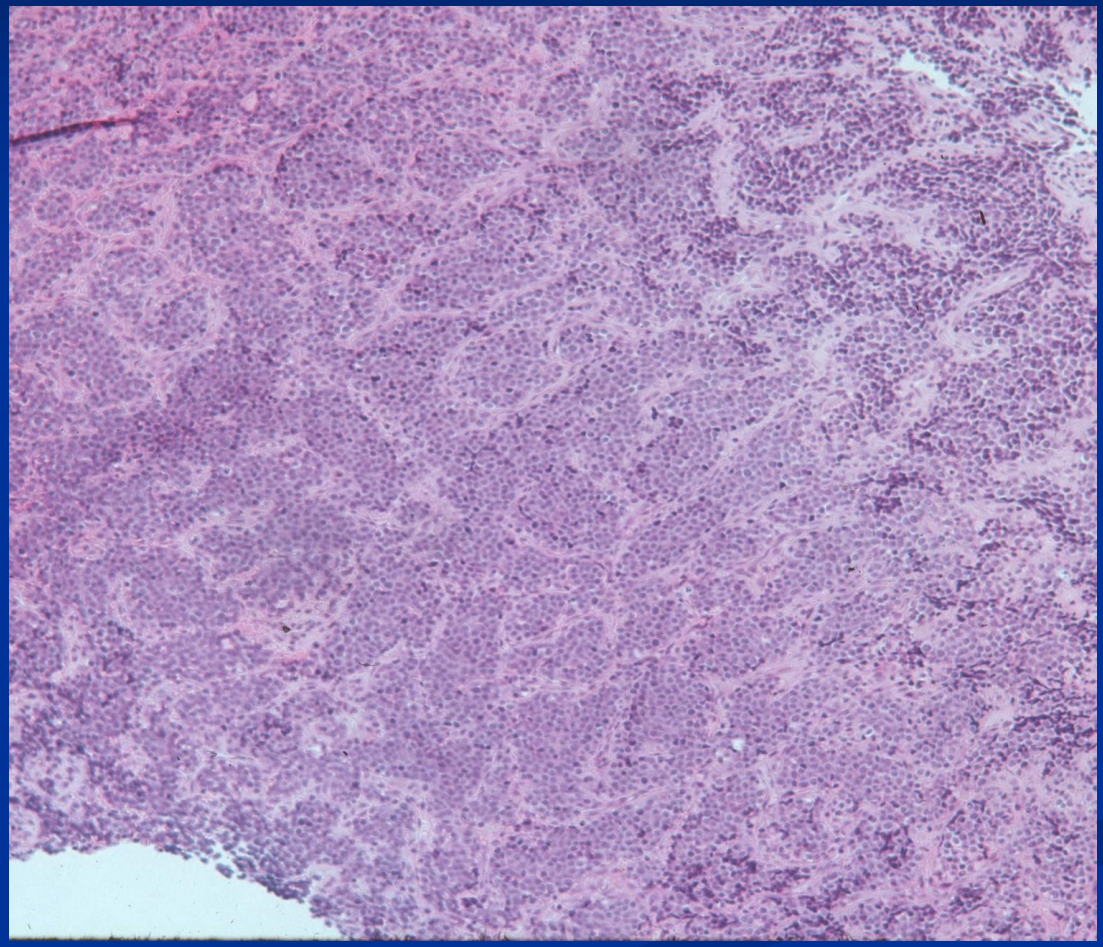


Microscopic Pathology

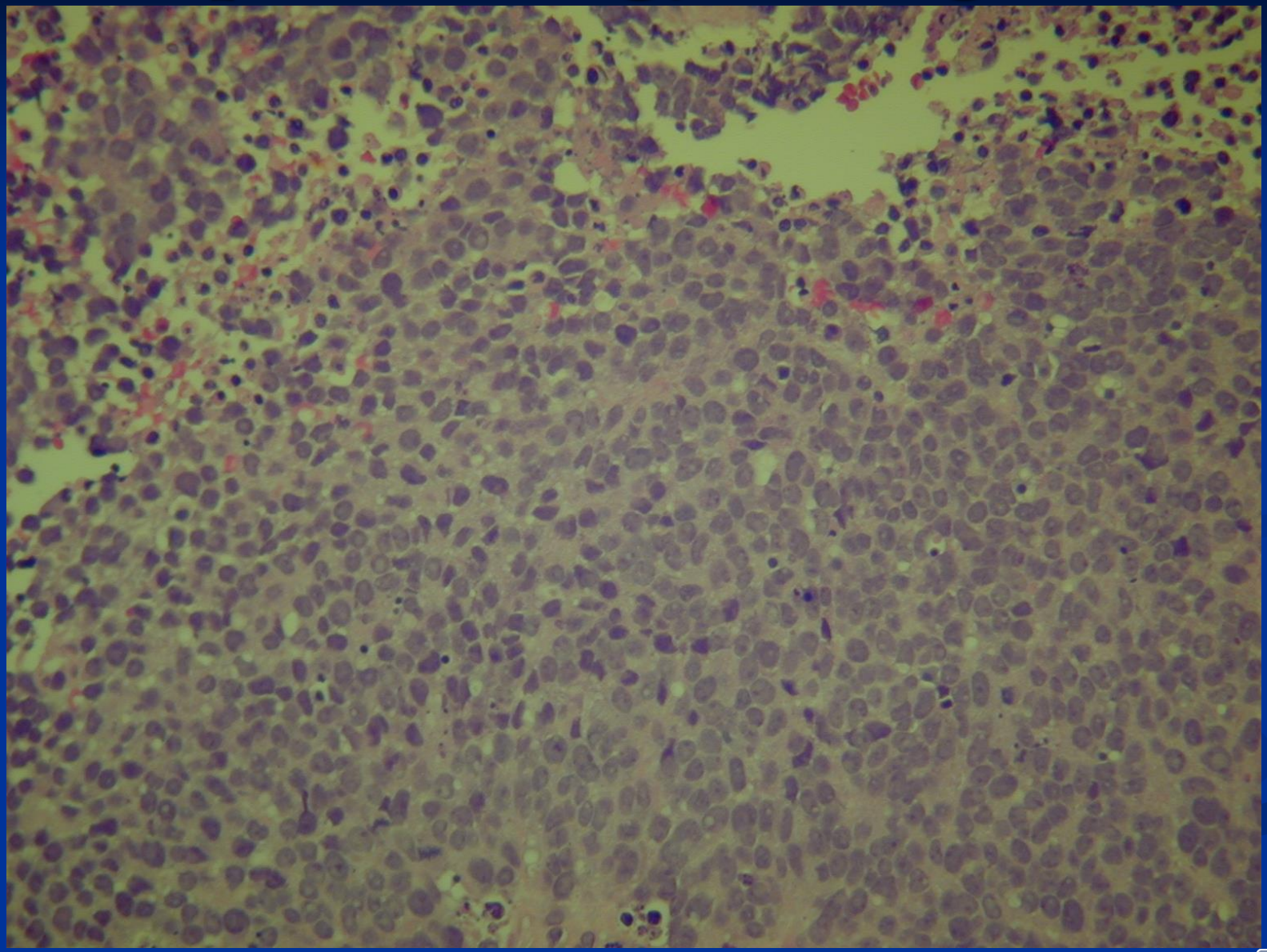
- Undifferentiated, small round, blue cells rich in glycogen
- Uniform cells with scanty pale cytoplasm and indistinct cell borders
- No Matrix
- Virtually no cytoplasm
- Cells are similar in appearance
- **Chromosomal Translocation t(11;22)(q24;q12)**
- PAS positive (glycogen positive); Reticulin stain poor
- Immunostains: Vimentin (+), CD99+, HBA-71 (+); Leukocyte Antigen Negative
- Overexpress MIC2 detected by CD99, HBA-71

Microscopic Pathology: Ewing Sarcoma

- Small Round Blue Cells
- No Matrix
- Large Nuclei
- No Cytoplasm

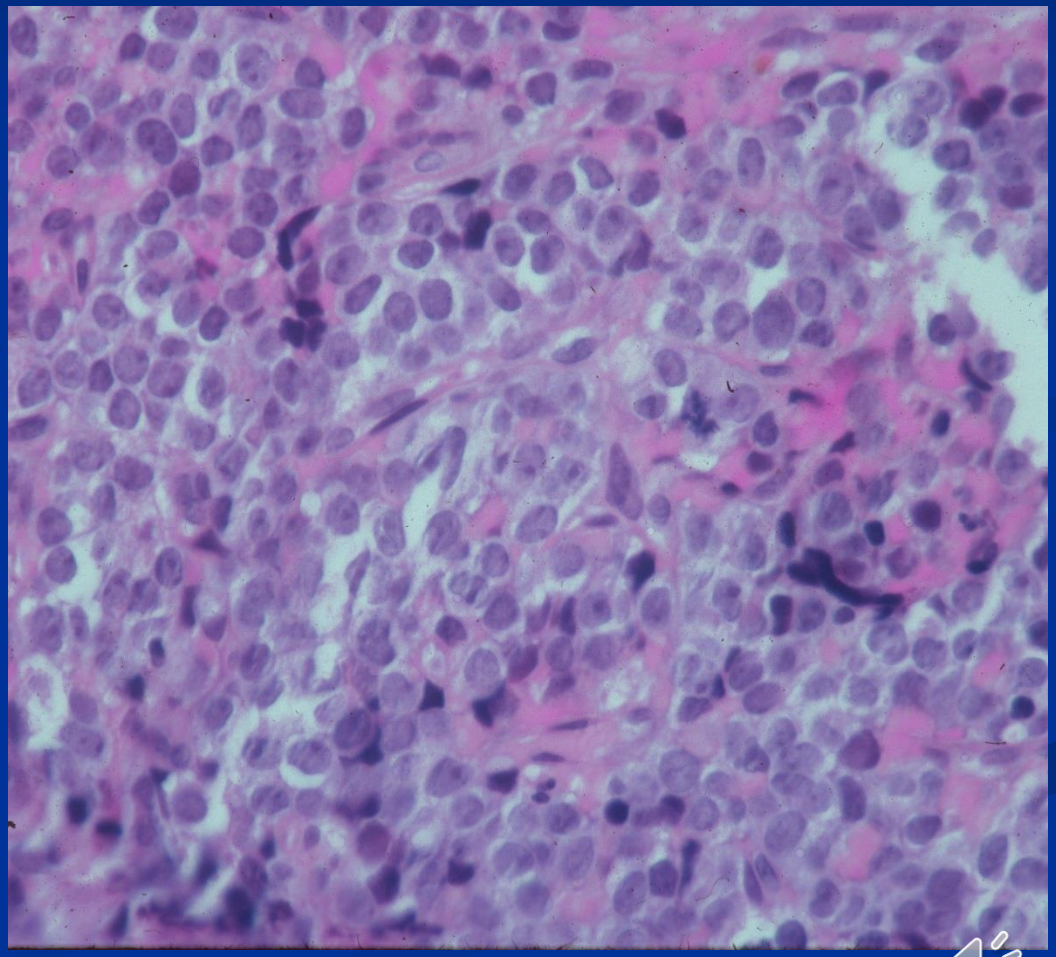


Microscopic Pathology: Ewing Sarcoma

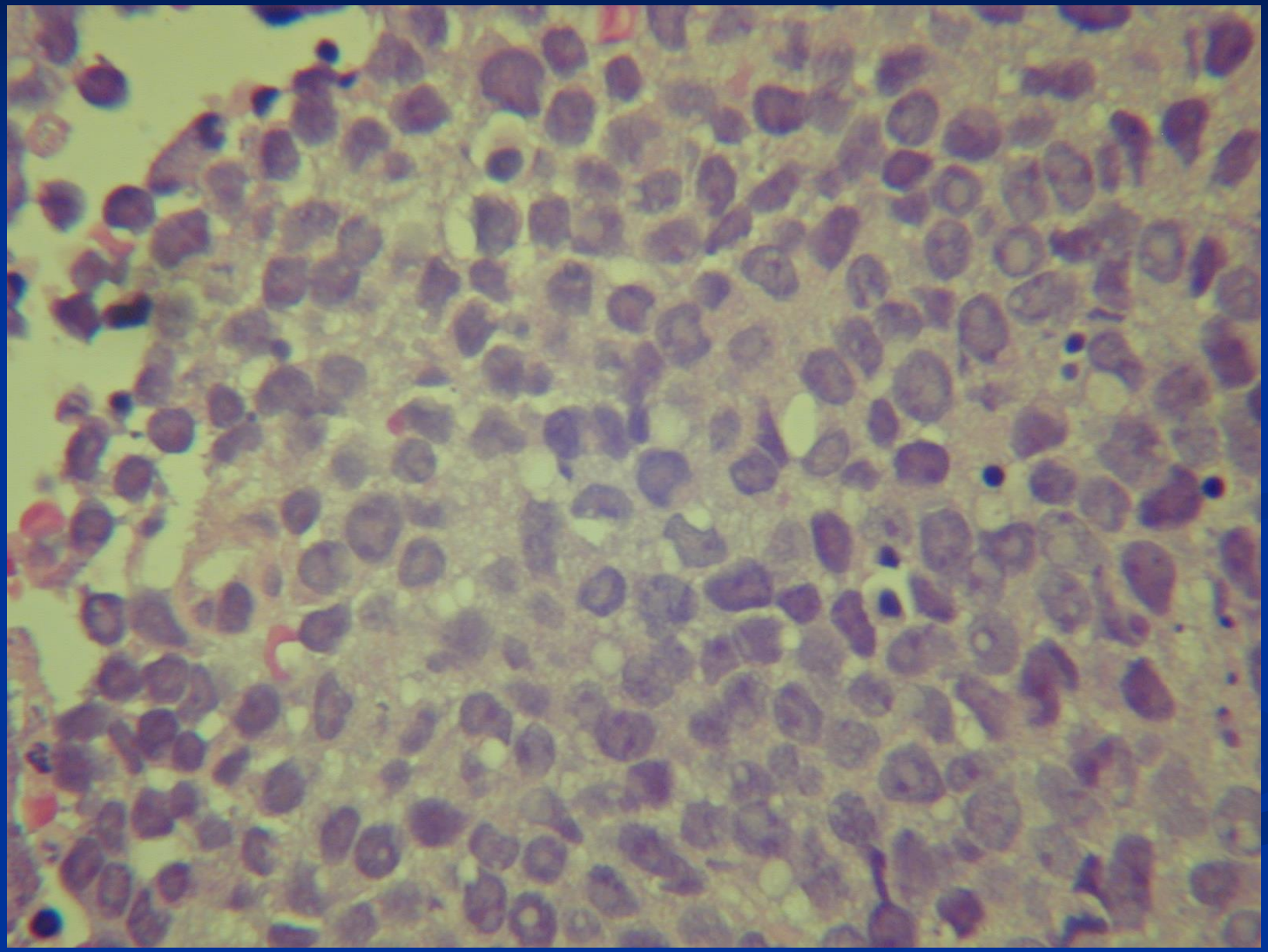


Microscopic Pathology: Ewing Sarcoma

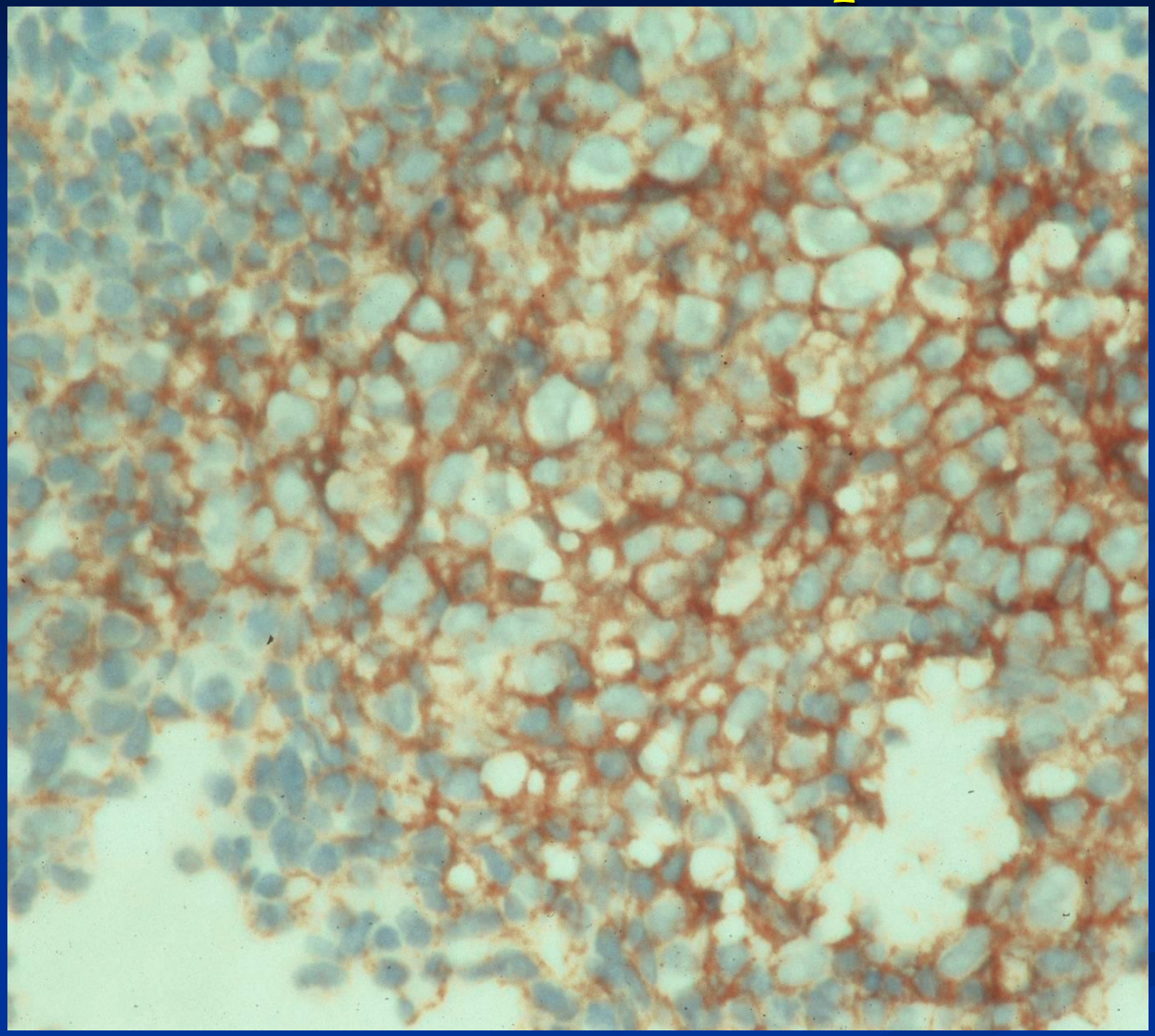
- Uniform small round blue cells
- Few mitoses
- Large nuclei and virtually no cytoplasm
- No matrix
- Pink staining filaments



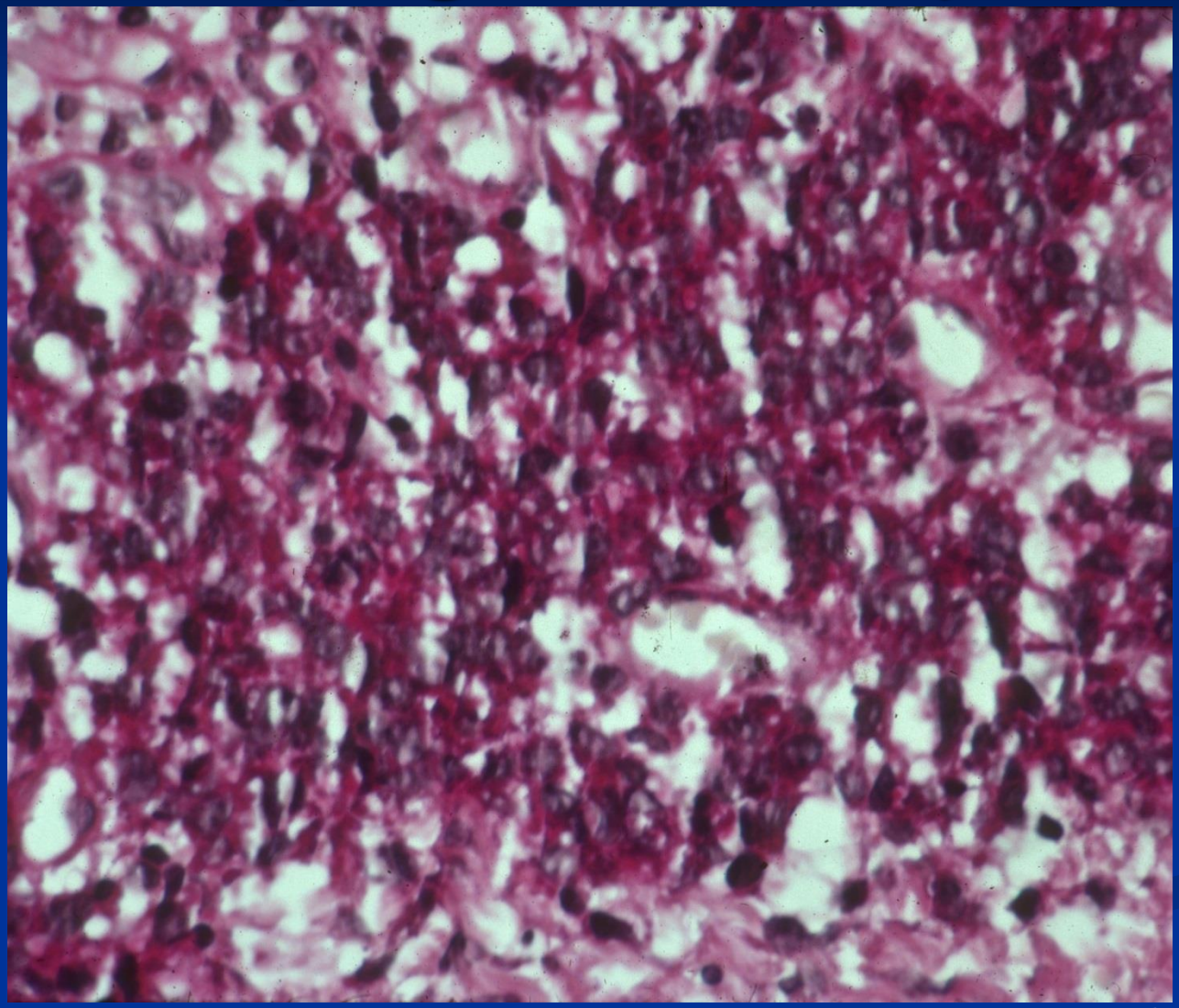
Microscopic Pathology: Ewing Sarcoma



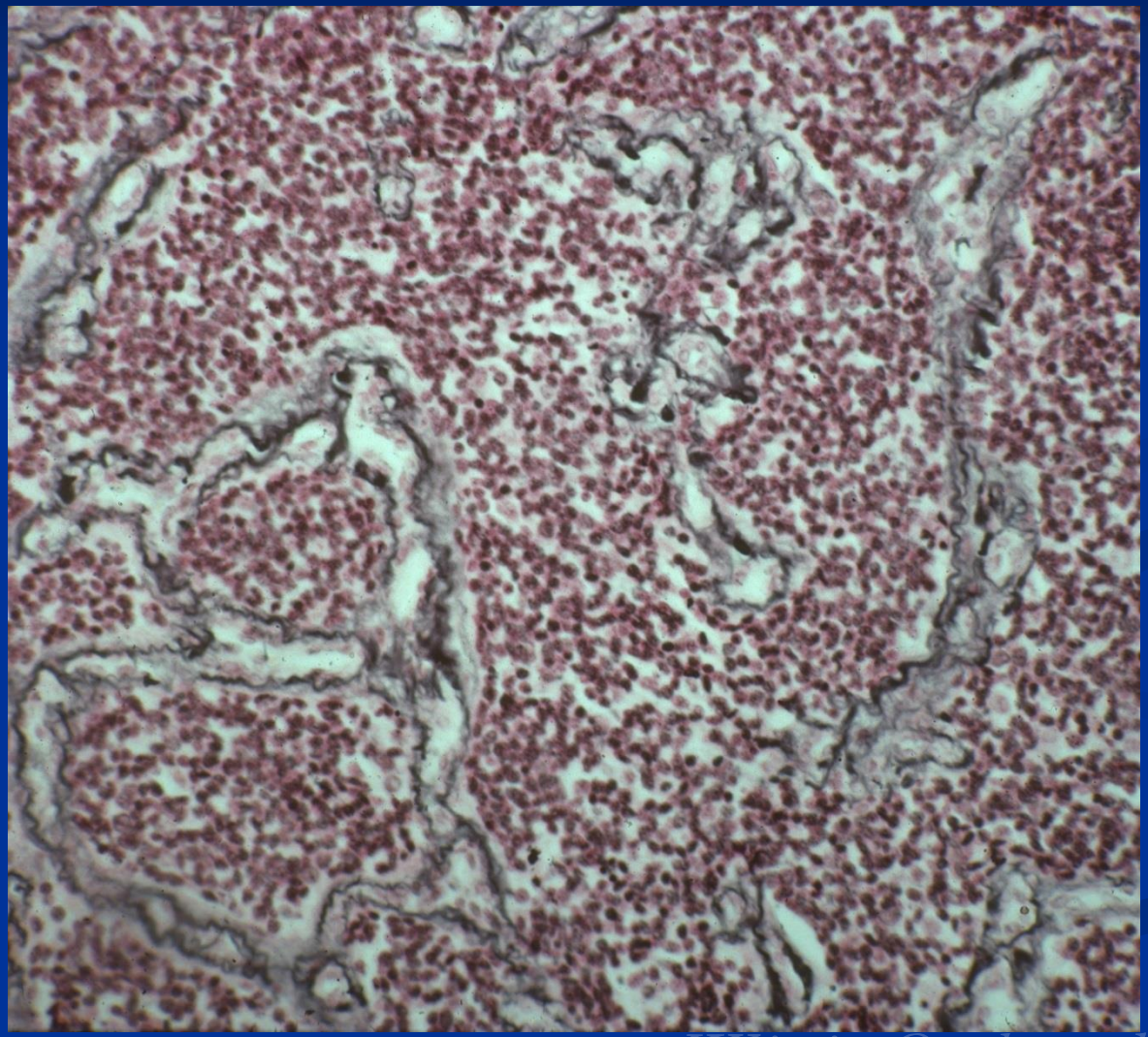
Ewing Sarcoma: CD 99 Identifies MIC2 Overexpression



Ewing Sarcoma: PAS Positive Glycogen Positivity

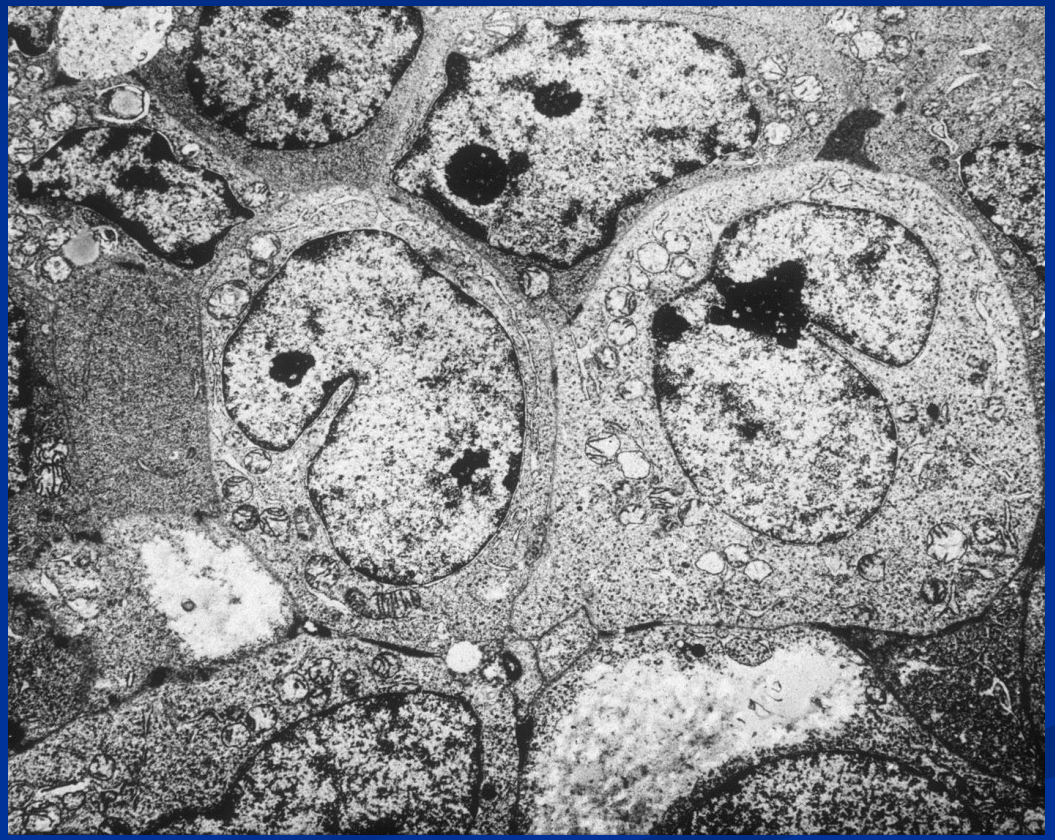


Ewing Sarcoma: Reticulin Poor



Ewing Sarcoma: Electron Microscope

- Large nucleus with small nucleoli and fine granular chromatin
- Minimal cytoplasm
- Few cytoplasmic organelles
- Glycogen granules in cytoplasm



Biological Behavior

- Ewing sarcoma is one of the most aggressive tumors
- High propensity for:
  - Local recurrences
  - Distant metastases (predominantly in lungs and other bones)
- Noted for its lack of immunologic staining

Treatment

- Multiagent chemotherapy
  - Most common chemotherapy agents utilized include: Vincristine, Adriamycin, Cyclophosphamide, Actinomycin-D, Ifosfamide, Etoposide
- Surgical resection (Most patients are treated with surgery)
  - Limb sparing surgery (most cases can be treated with limb sparing surgery)
  - Rarely ever an amputation since Ewing sarcoma are sensitive to radiation
- If surgical resection is not feasible, radiation may be utilized for local control (instead of an amputation) since Ewing sarcoma is highly sensitive to radiation

Prognosis

- Patients with localized, resectable disease
  - 5 year survival 54%-74% (65%)
- Patients with disseminated disease at diagnosis
  - 5 year survival 30%
- Surgical removal of resectable lung metastases improves survival
- Pelvic Ewing sarcoma have a worse prognosis than other areas
- Response to preoperative chemotherapy: Greater than 90% tumor necrosis (Good response) correlates with a better prognosis

Other Important Information

- Patients under 5 years of age should be carefully evaluated to exclude metastatic neuroblastoma
- Large cell variant of Ewing sarcoma exists, which may be confused with large cell lymphoma

Lymphoma of Bone

General Information

- Primary lymphoma of bone is defined as lymphoma arising within the medullary cavity of a bone in the absence of lymph node or organ involvement for at least 6 months after diagnosis
- Primary lymphoma of bone is rare (3% of primary bone tumors)
- Most lymphomas that involve bone are metastatic from lymph node
- Most primary lymphomas of bone are Non Hodgkin's, large cell lymphomas
- In U.S. majority are B-cell proliferations
- Must rule out presence of extraskeletal disease
- May be misdiagnosed as chronic osteomyelitis

Clinical Presentation

- **Signs/Symptoms:**
  - Localized dull or aching pain
  - Palpable mass or swelling
  - Usually no general symptoms and appear healthy
  - Pathological fractures in 25% of cases
- **Age:**
  - Most occur after second decade with 50% occurring above 40 years
  - Rare in children
- **Sites:** Any bone can be involved
  - Lower extremities involved most often especially femur and pelvis
  - More common in appendicular than axial skeleton (opposite of metastatic lymphoma)

Radiographic Presentation: Primary Lymphoma of Bone

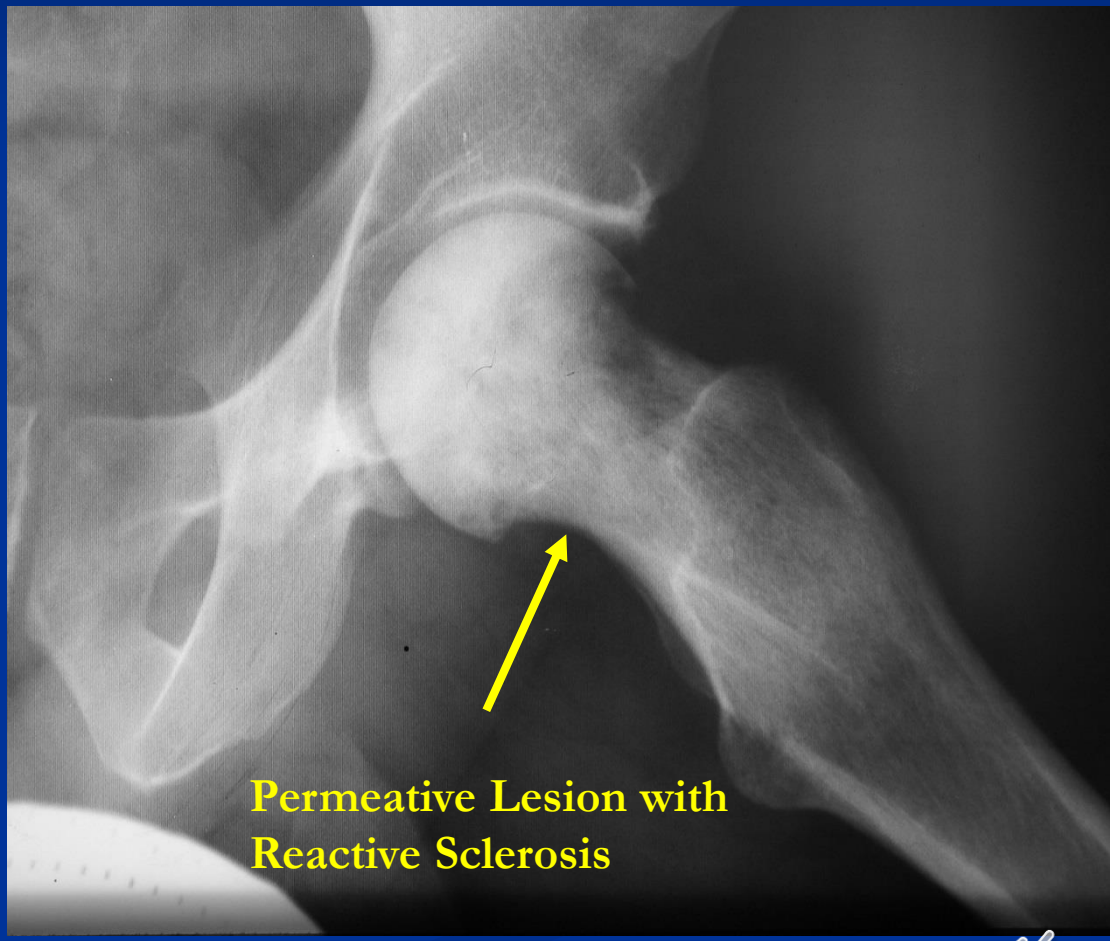
- **Permeative or moth eaten bone destruction**
  - Geographic (11%); Blow out (1%); Blastic (2%); Normal XR (5%)
- **Metadiaphysis** (75%)
- **Periosteal reaction—may look benign**
  - **Interrupted or solid single layer (66%)**
  - Onion Skin 10%
  - Sunburst 2%
- **Soft tissue mass**— by CT (80%); by MRI (99%)

Radiographic Presentation: Primary Lymphoma of Bone

- Pathologic Fracture (22%)
- Diff Dx:
  - Metastatic Lymphoma
  - Ewings
  - Neuroblastoma
  - Rhabdomyosarcoma
  - Osteomyelitis
  - Eosinophilic Granuloma

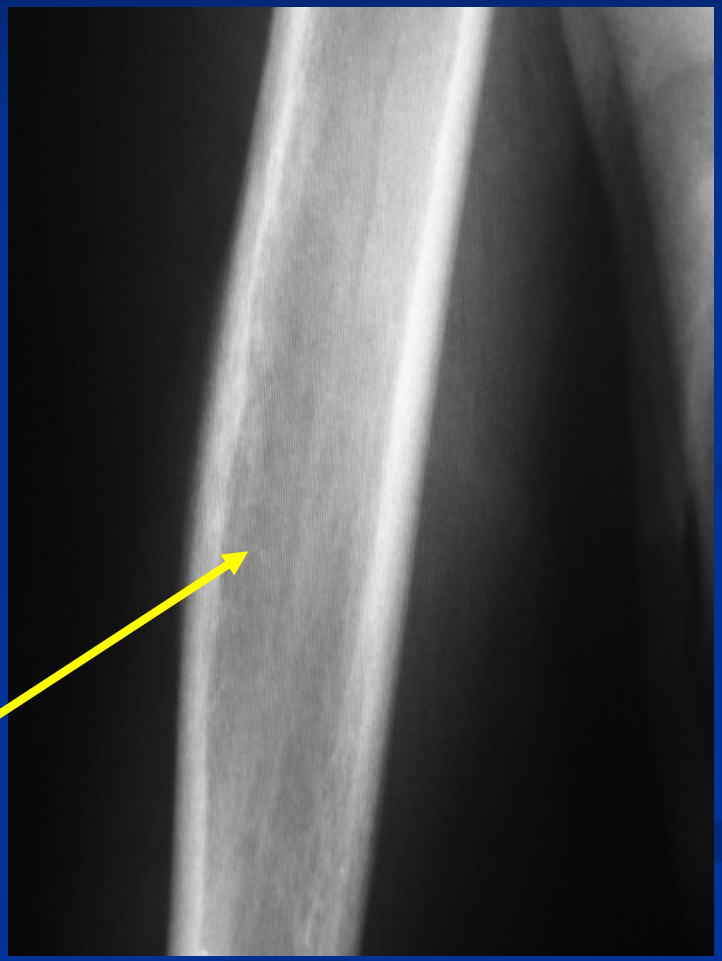
Radiographic Presentation

- Permeative or moth eaten lesion
- Often barely perceptible on X-ray
- Reactive sclerosis (28%)
- Metaphysis or metadiaphysis of long bones
- No Mineralization
- Soft tissue mass common
- Femur/tibia/humerus



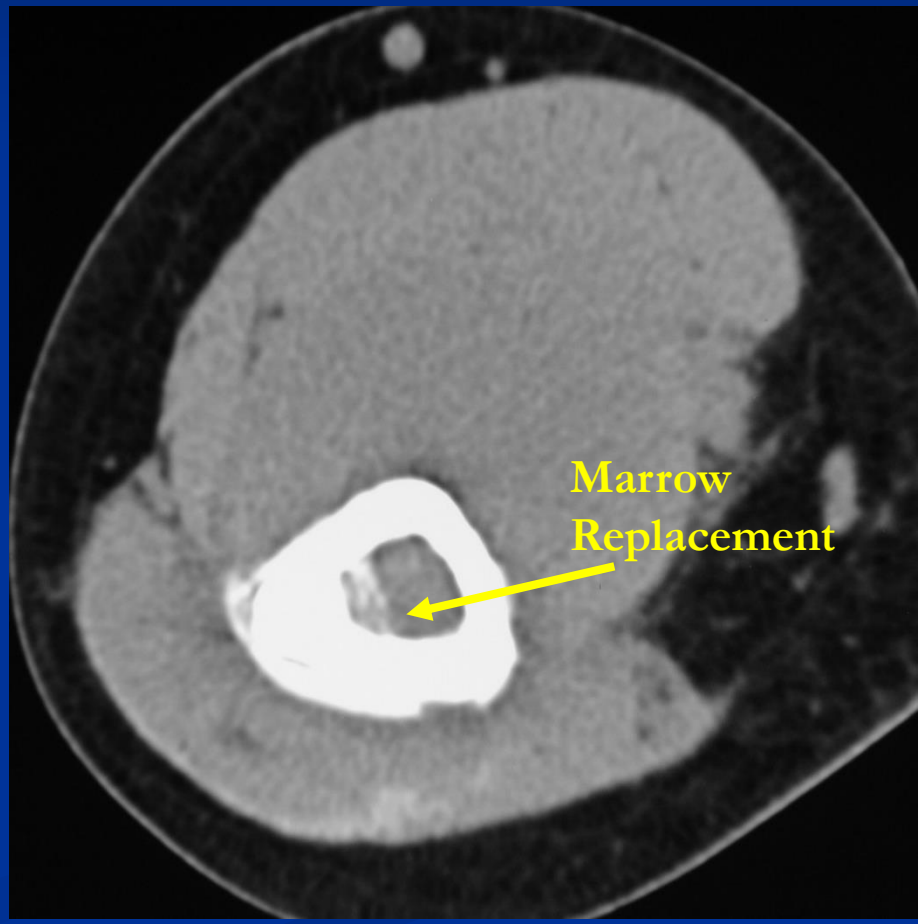
Radiographic Presentation: Primary Lymphoma of Bone

- 25% involve flat bones (pelvis, sacrum, ribs)
- Mixed lysis/sclerosis in 28%
- Aggressive or nonaggressive PR common



Radiographic Presentation: Primary Lymphoma of Bone

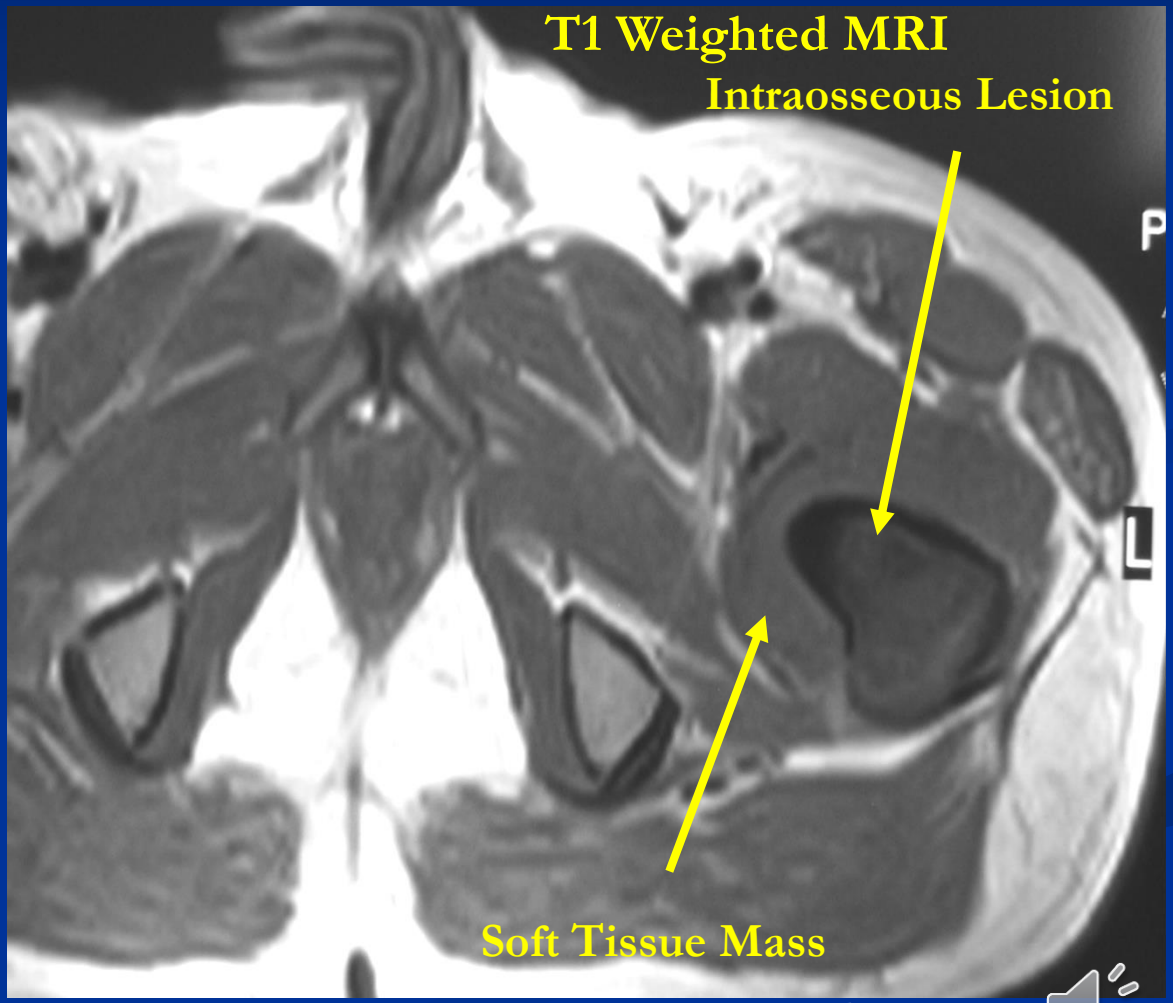
- Increased activity on bone scan
- *Increased activity on scintigraphy and normal XR highly suggestive of lymphoma*
- Marrow replacement, cortical destruction and ST mass on CT
- Sequestra formation in 11-16%



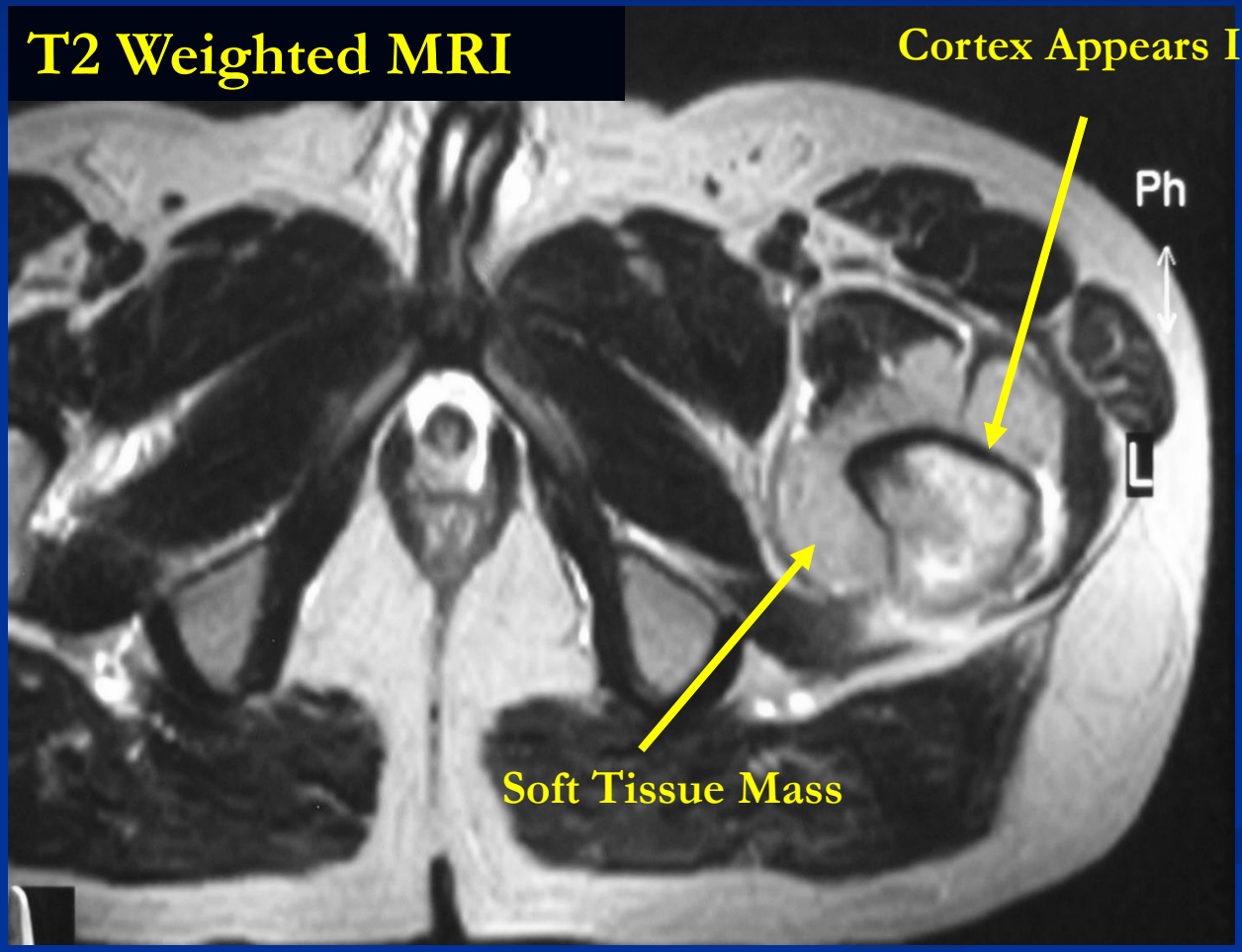
Radiographic Presentation: Primary Lymphoma of Bone

- Variable SI MR
  - Intermediate on T1
  - High on T2
- ST mass common

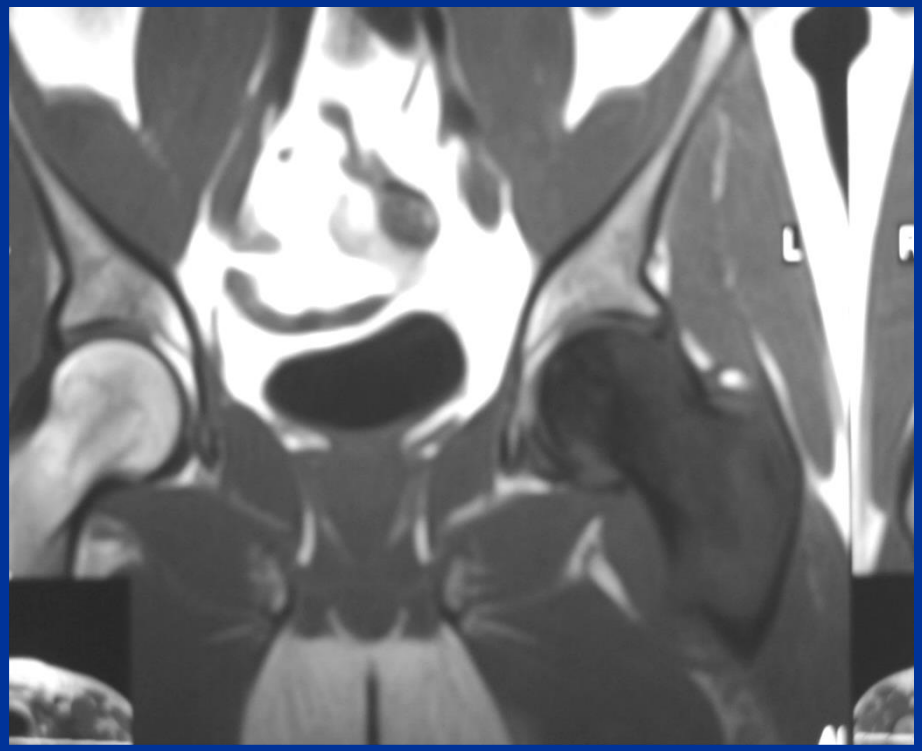
(permeation of tumor cells through small vascular channels in the cortical bone without frank cortical breakthrough (also seen with Ewing/PNET))



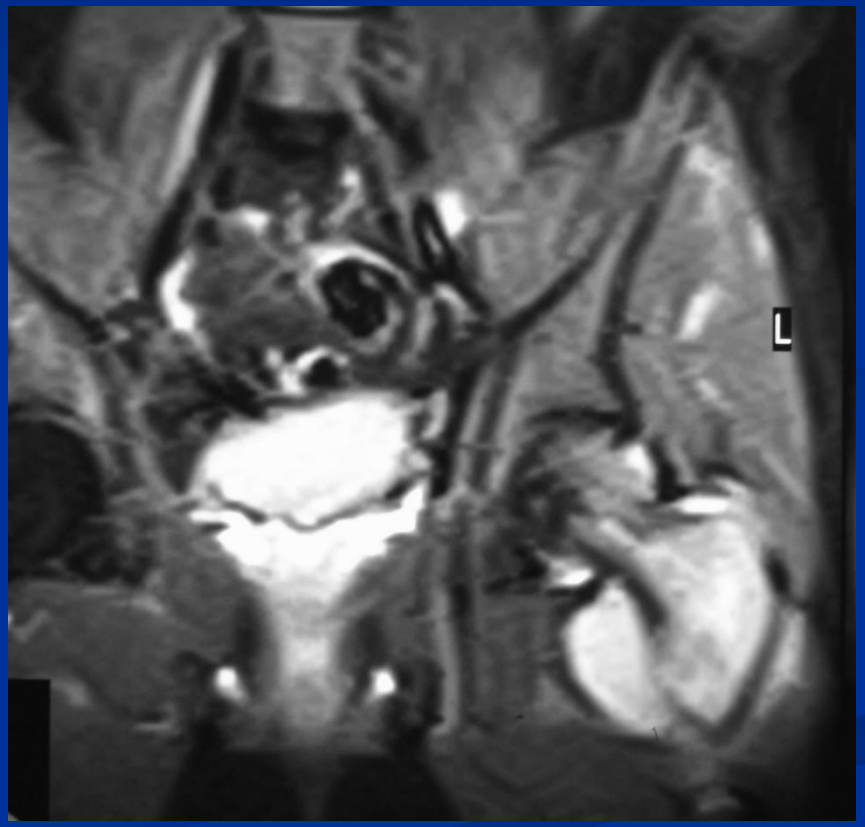
Radiographic Presentation: Primary Lymphoma of Bone



MRI: Primary Lymphoma of Bone



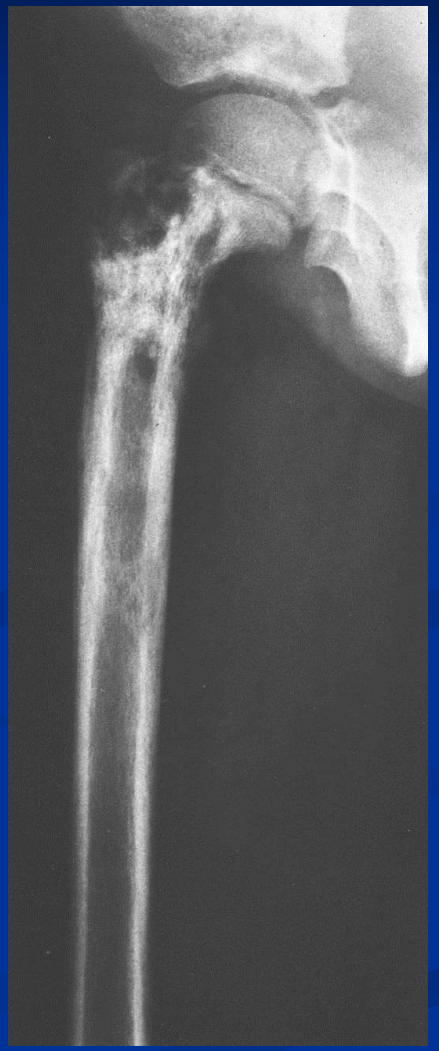
T1 Weighted MRI



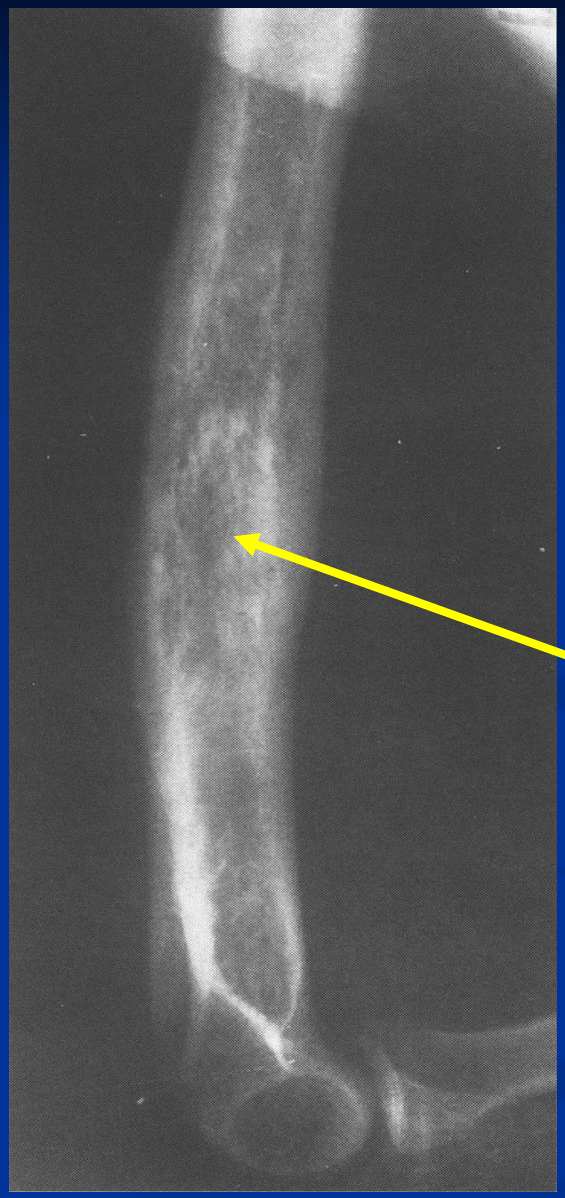
T2 Weighted MRI

X-ray: Primary Lymphoma of Femur

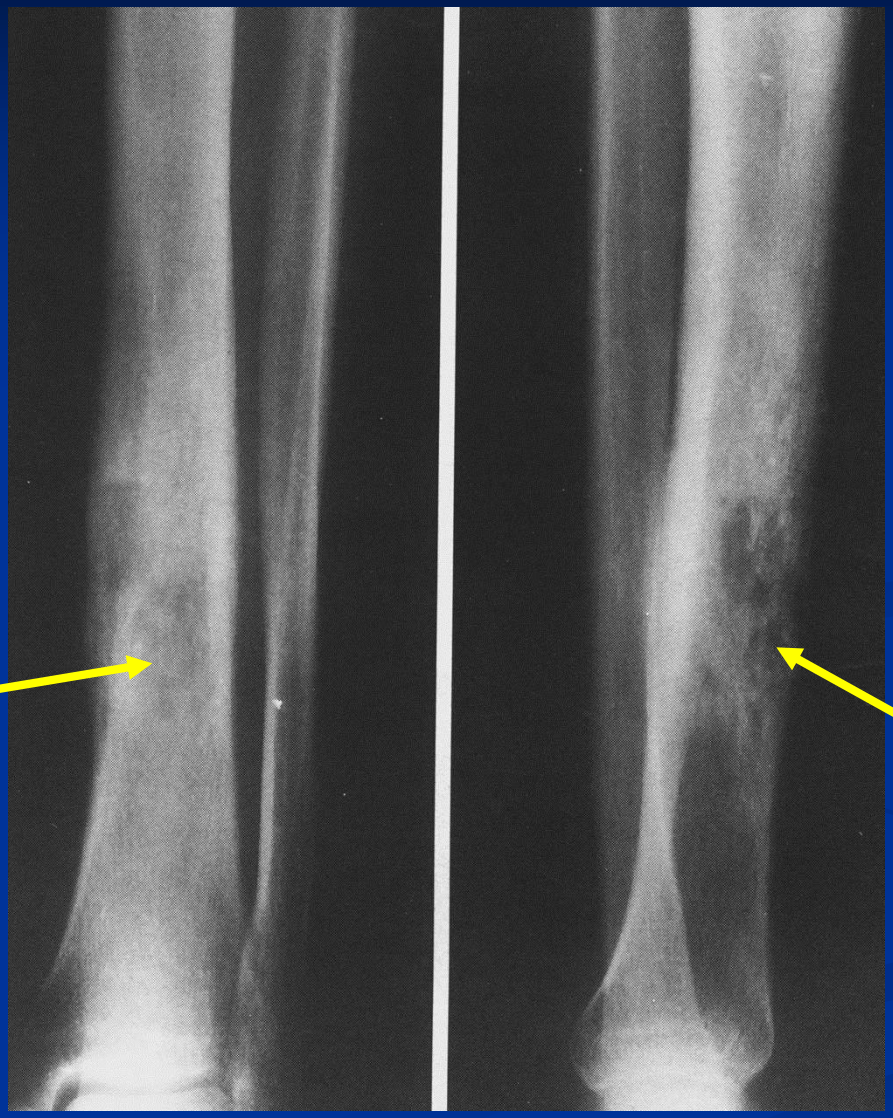
- Permeative/Moth eaten lesion
- Reactive sclerosis (mixed lysis and sclerosis)
- Slight periosteal reaction



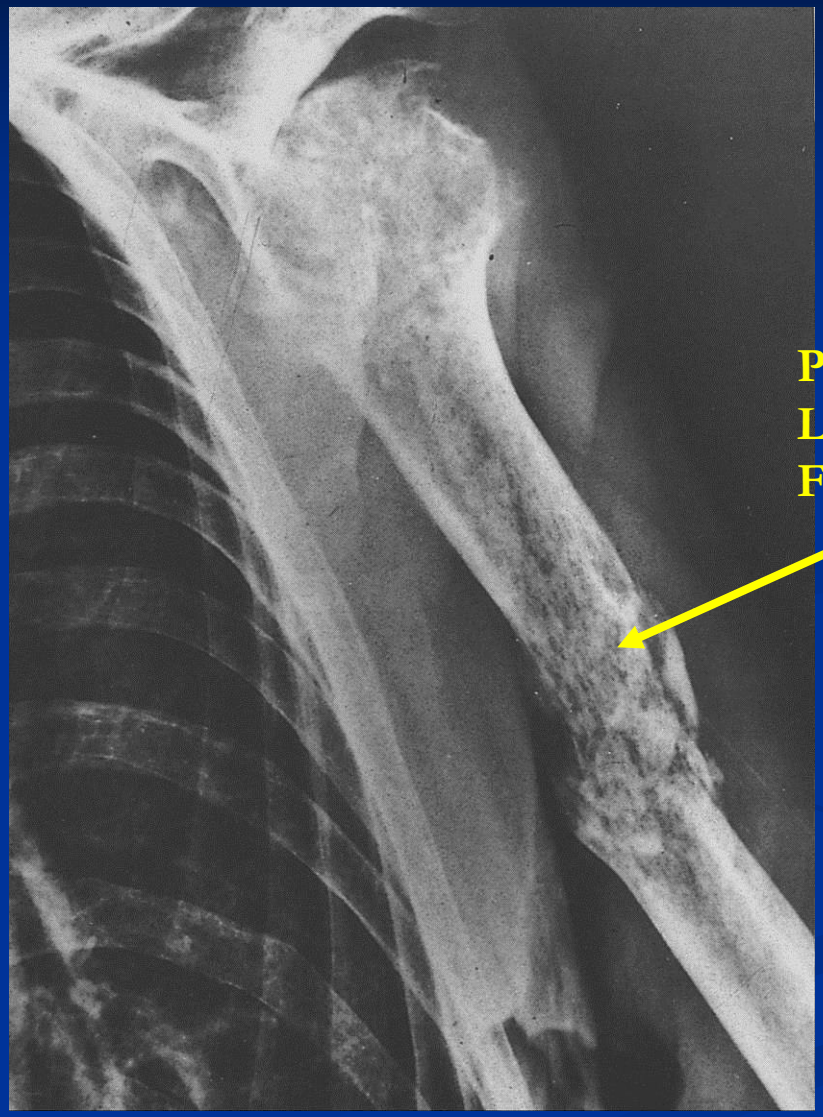
X-ray: Primary Lymphoma of Distal Humerus



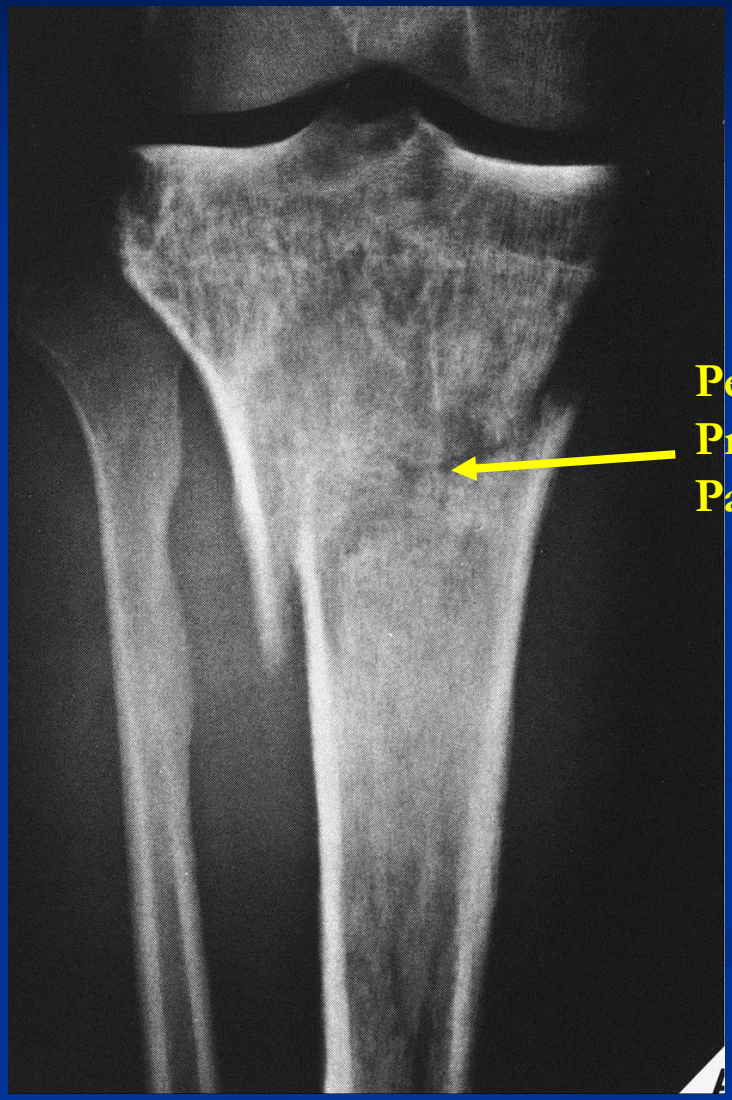
X-ray: Primary Lymphoma of Tibia



X-ray: Primary Lymphoma of Humerus



X-Ray: Primary Lymphoma of Proximal Tibia



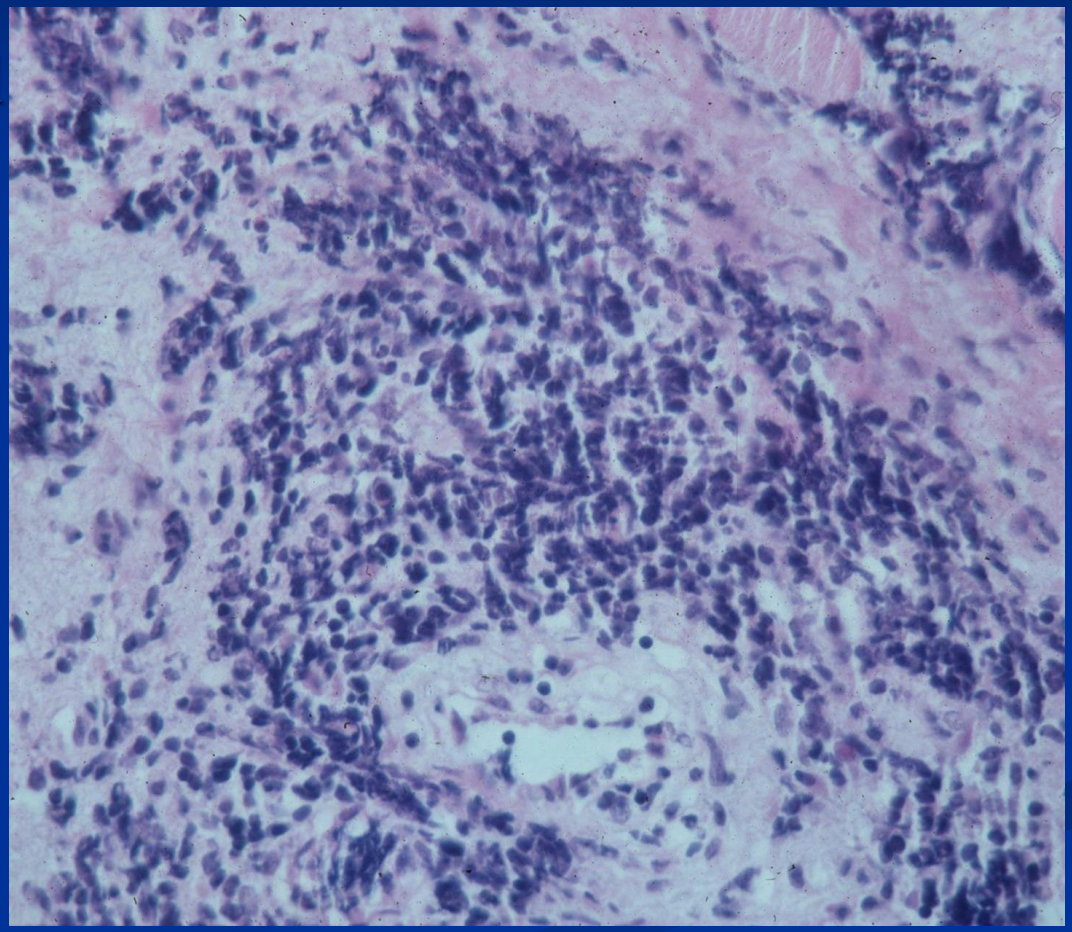
Permeative Lesion of Proximal Tibia with Pathological Fracture

Microscopic Pathology

- Diffuse growth pattern
- Mixture of small lymphocytic cells and larger histiocytic components (Large Malignant B Cells)
- Cells and **no matrix**
- Nuclei
  - **Vary in shape and size**
  - Grooved vesicular nuclei
  - Prominant nucleoli
- Cytoplasmic glycogen is absent
- Complex reticulin framework
- CD5 and Leukocyte Common Antigen Positive
- CD20 and CD45 for B Cell Lymphoma; CD3 for Rare T-Cell

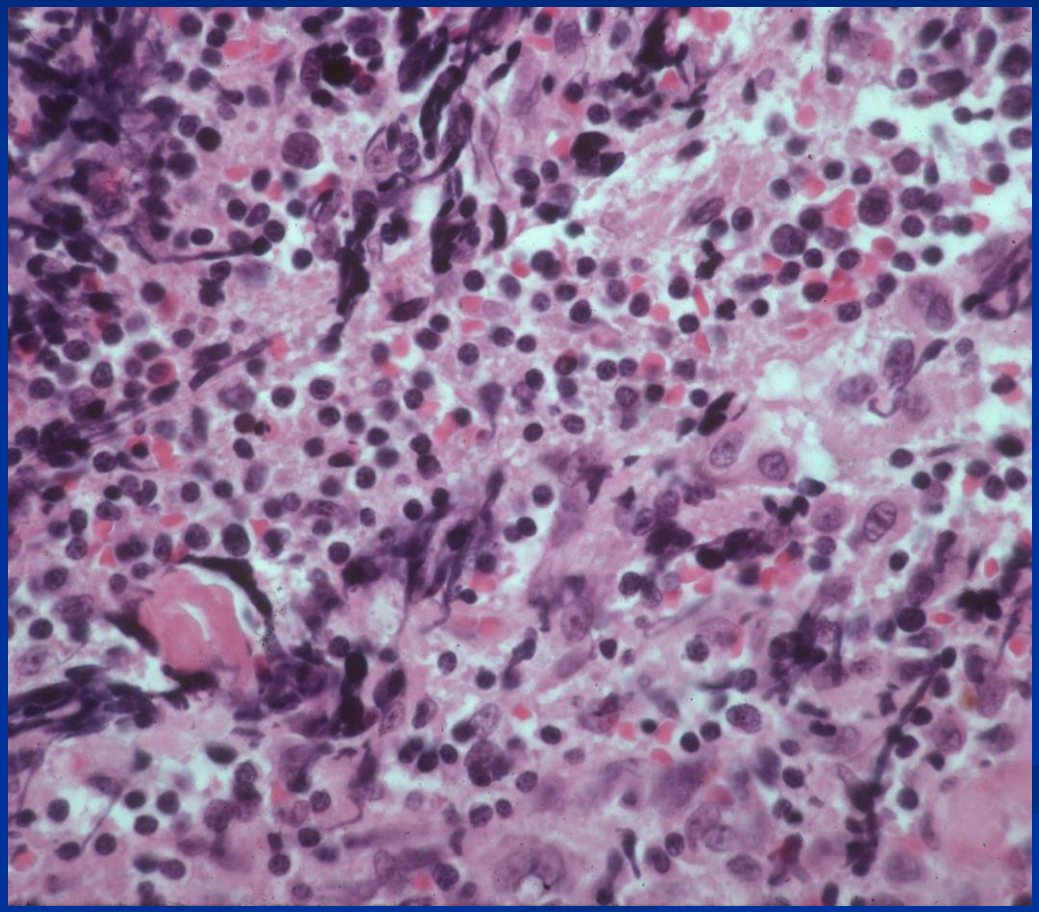
Microscopic Pathology: Lymphoma

- Small Round Blue Cell Tumor
- Cells without Matrix
- Crush artifact
- Cells are different sizes and shapes

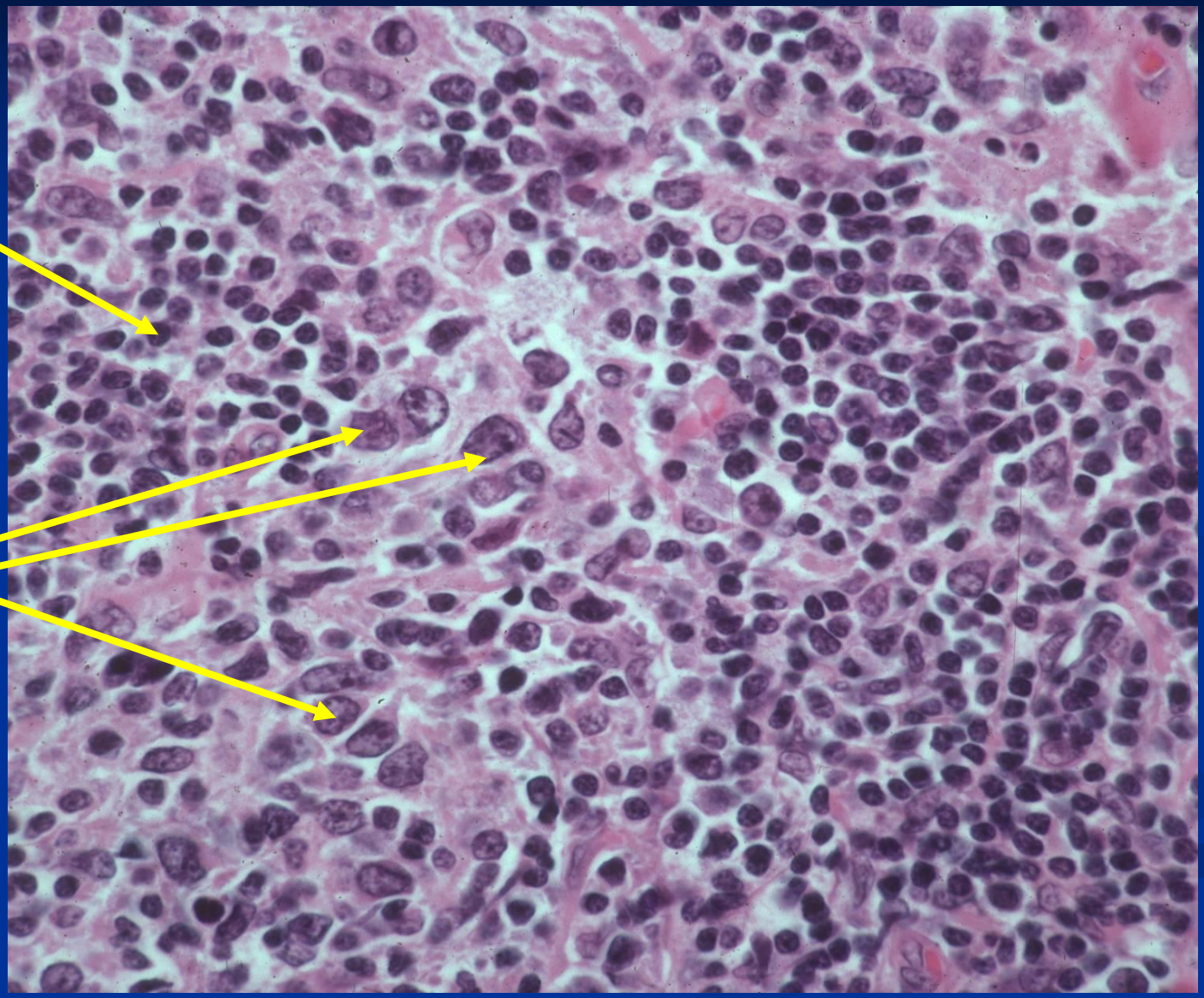


Microscopic Pathology: Lymphoma

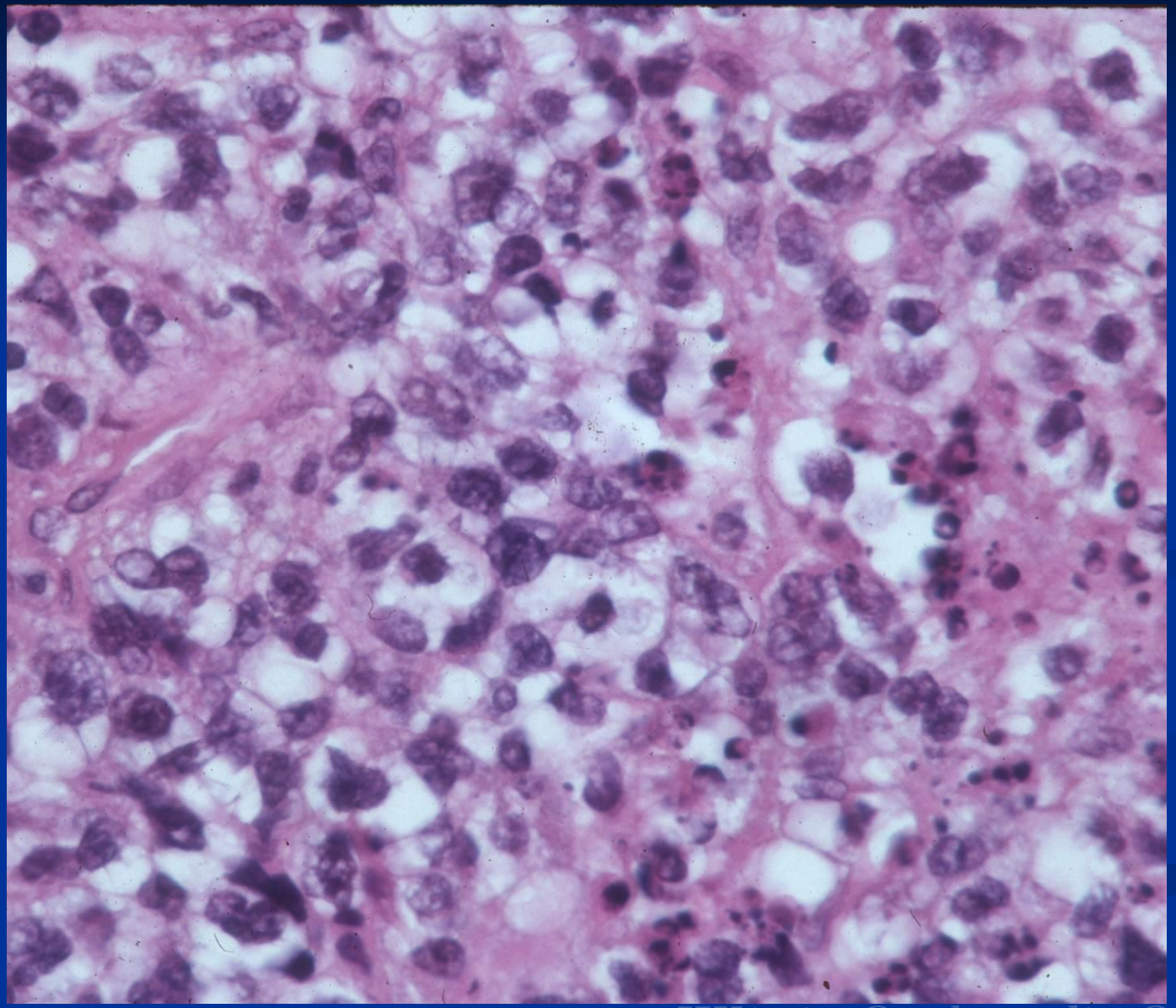
- Mixture of small round blue cells of different sizes and shapes
- No Matrix production
- Large B-Cells mixed with reactive inflammatory infiltrate leads to different cell types



Microscopic Pathology: Lymphoma



Microscopic Pathology: Lymphoma



Differential Diagnosis

- Ewing Sarcoma
- Chronic Osteomyelitis
- Leukemia

Treatment

- Chemotherapy and radiation

Myeloma

General Information

- Myeloma is a malignant proliferation of plasma cells
- There are 2 types:
  - **Multiple myeloma**
    - Intraosseous plasma cell neoplasm
    - Produces multiple lesions
    - Found in bone marrow
  - **Solitary myeloma (Plasmacytoma)**
    - Neoplasm of plasma cells
    - Produces single osseous lesion
    - Not detected in bone marrow
    - Also known as *solitary plasmacytoma of bone*
    - Most patients with an isolated plasmacytoma eventually develop myeloma

Clinical Presentation

Signs/Symptoms:

- Many different symptoms
  - Bone pain
  - Anemia
  - Pathologic fracture
  - Neurologic complaints from spinal cord compression or neuropathy
  - Fever
  - Hypercalcemia
  - Renal failure /Proteinuria
  - Amyloidosis (10% of patients)
  - Coagulopathy
  - Immune Dysfunction

Prevalence:

- Most common primary neoplasm of bone
- Slight male predominance

Age:

- All ages can be affected
  - Most common over age of 50

Sites:

- Multiple myeloma
  - May occur in all bones of body
- Solitary myeloma
  - Most common in thoracic vertebra
  - May also occur in lumbar vertebra, ribs, scapula, pelvic bones, skull, mandible, and long bones

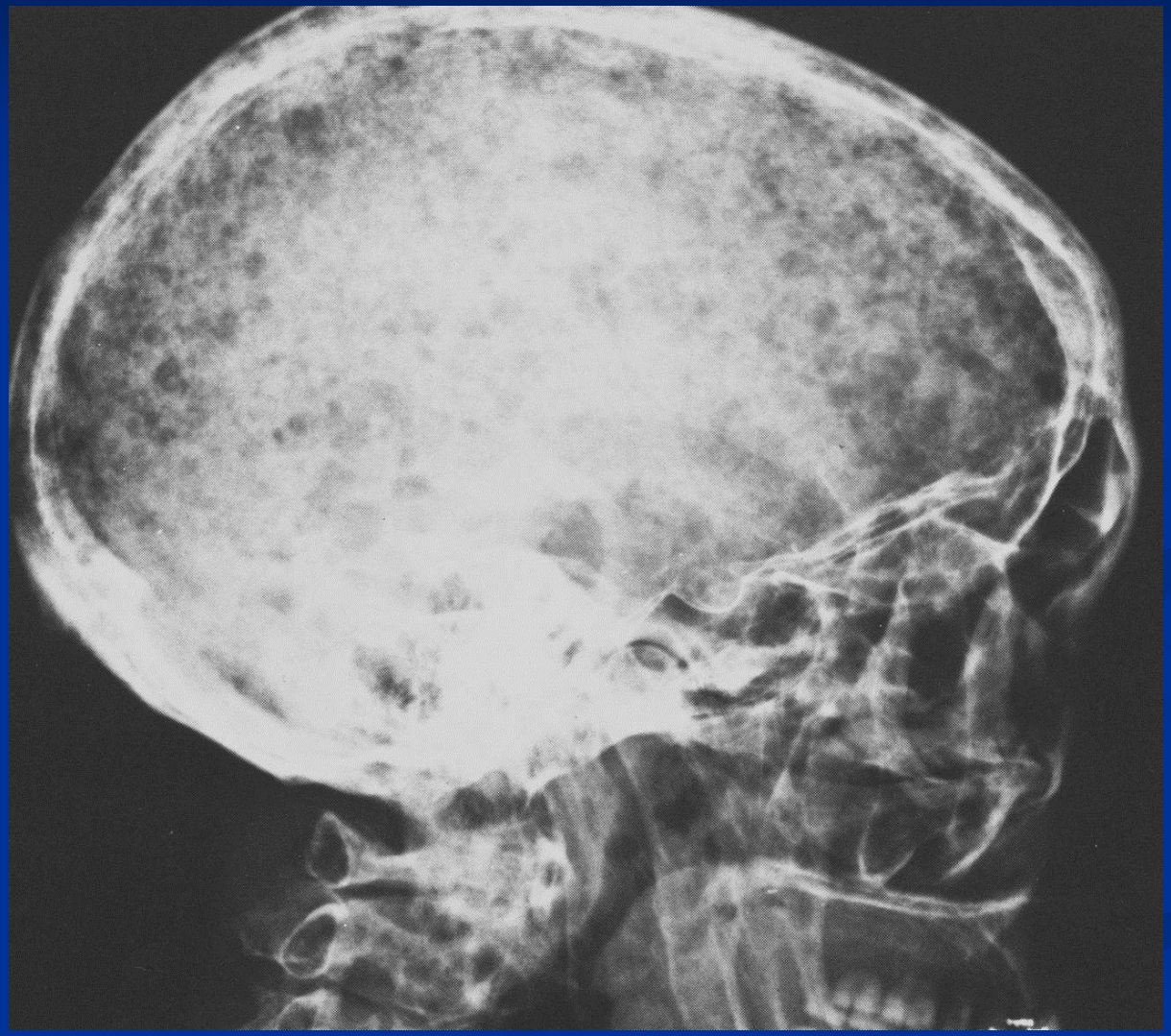
Myeloma

- Labs: monoclonal spike; Bence-Jones proteinuria, anemia, elevated sed rate, hypercalcemia
  - Serum IgG in 55%; IgA (25%); Rarely IgM, D, E
  - In 20% have Bence Jones protein in urine alone without elevated serum immunoglobulins
- 10% with coexisting amyloidosis
- **POEMS Syndrome (Often associated with osteosclerotic myeloma)**
  - Polyneuropathy (100%)
  - Organomegaly (24%)
  - Endocrinopathy (39%)
  - Monoclonal gammopathy (52% IgA; 36% IgG;)
  - Skin Changes (58%)

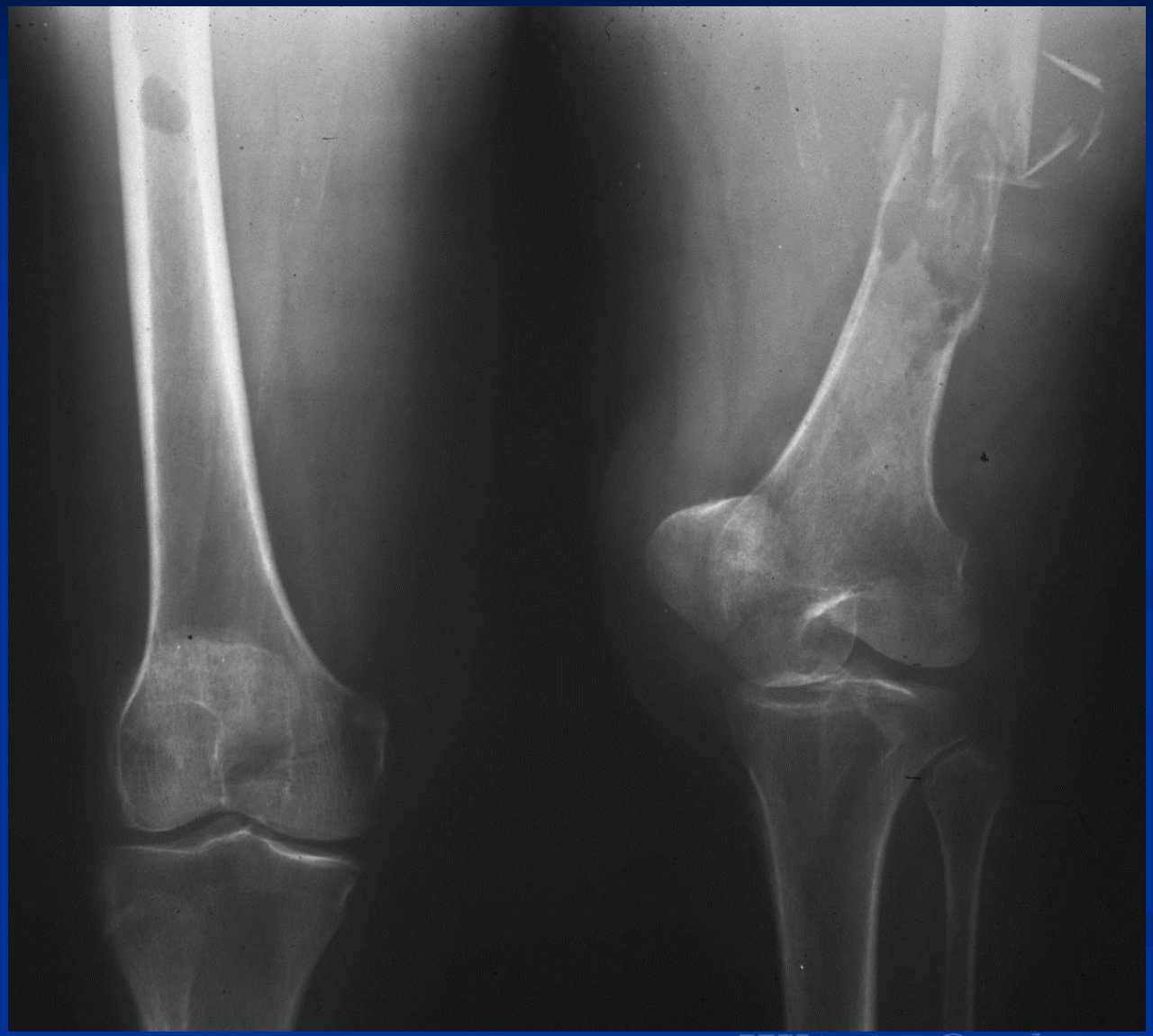
Myeloma

- Bone scan is positive for 80% of lesions
- Skeletal Survey
- Osteosclerotic Myeloma <3%--- associated with POEMS syndrome
  - Sclerotic lesions/Increased density of bones

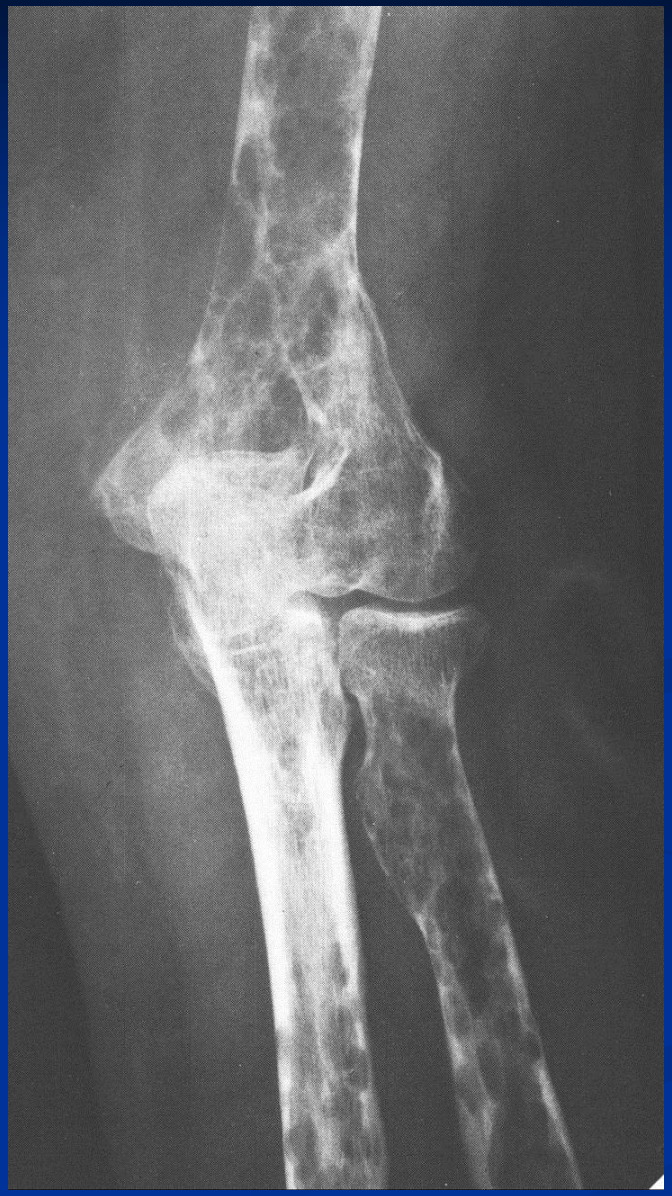
Myeloma



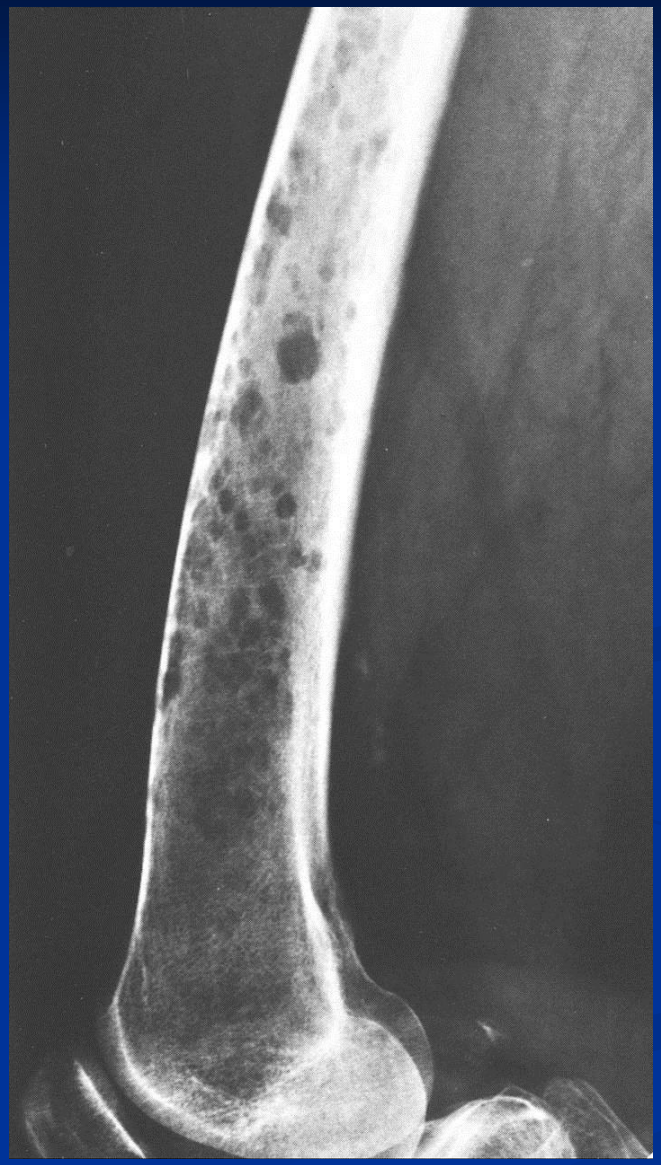
Myeloma



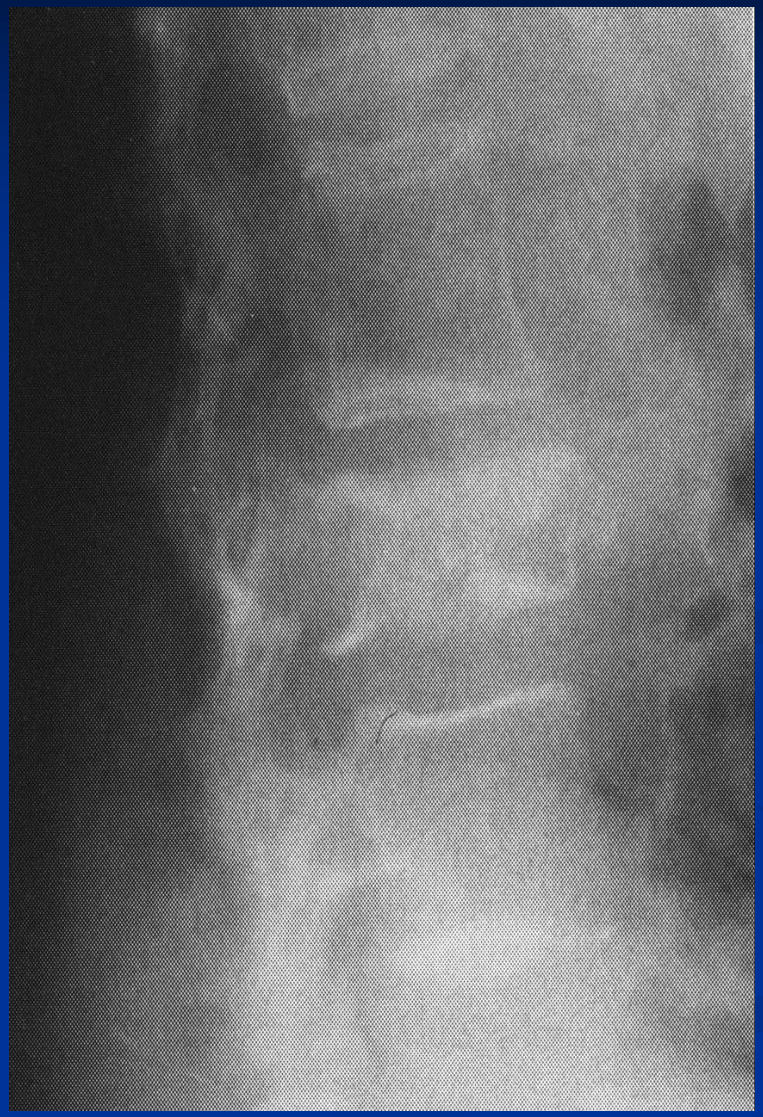
Myeloma



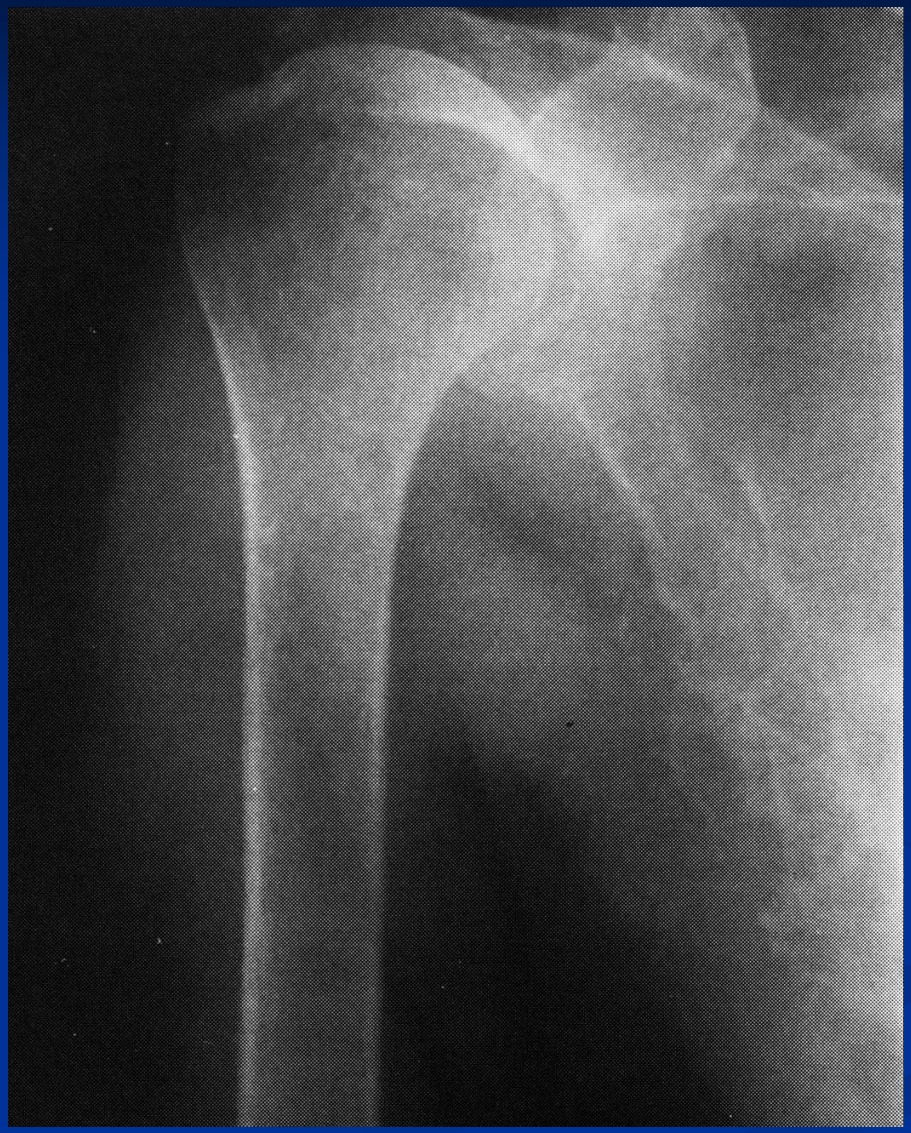
Myeloma



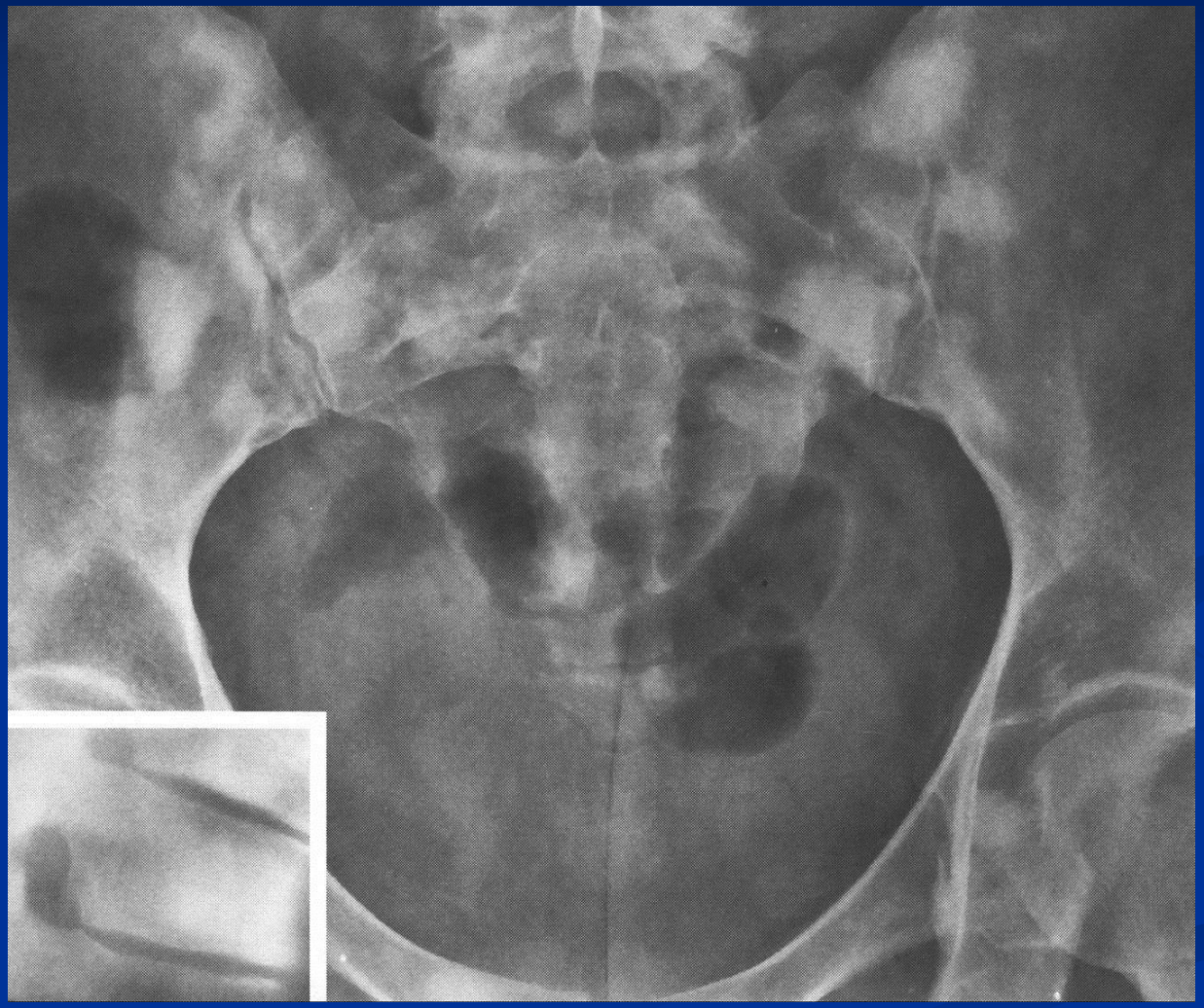
Myeloma



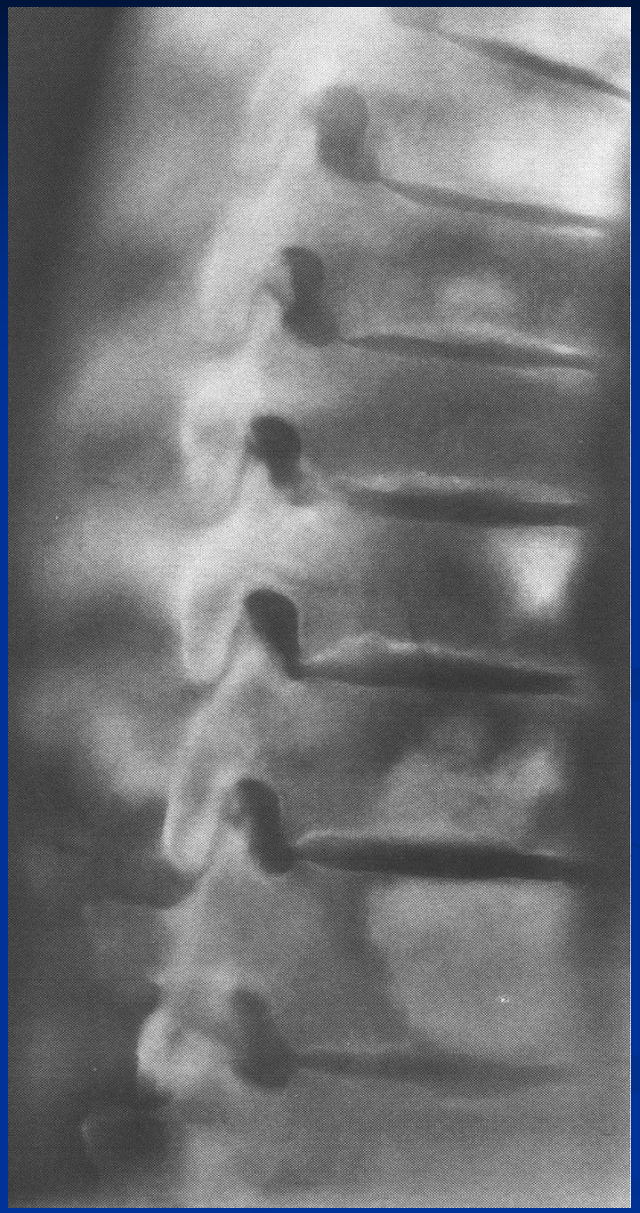
Myeloma



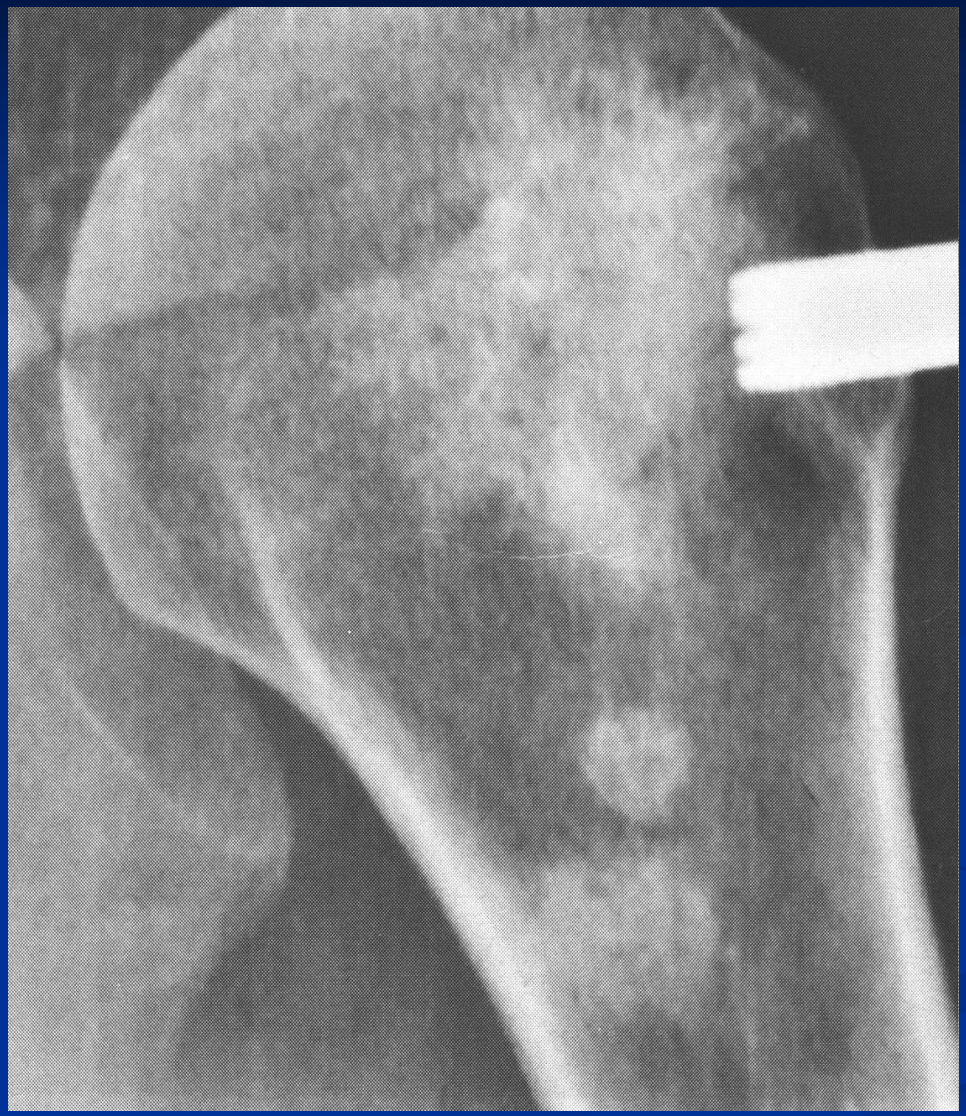
Osteosclerotic Myeloma



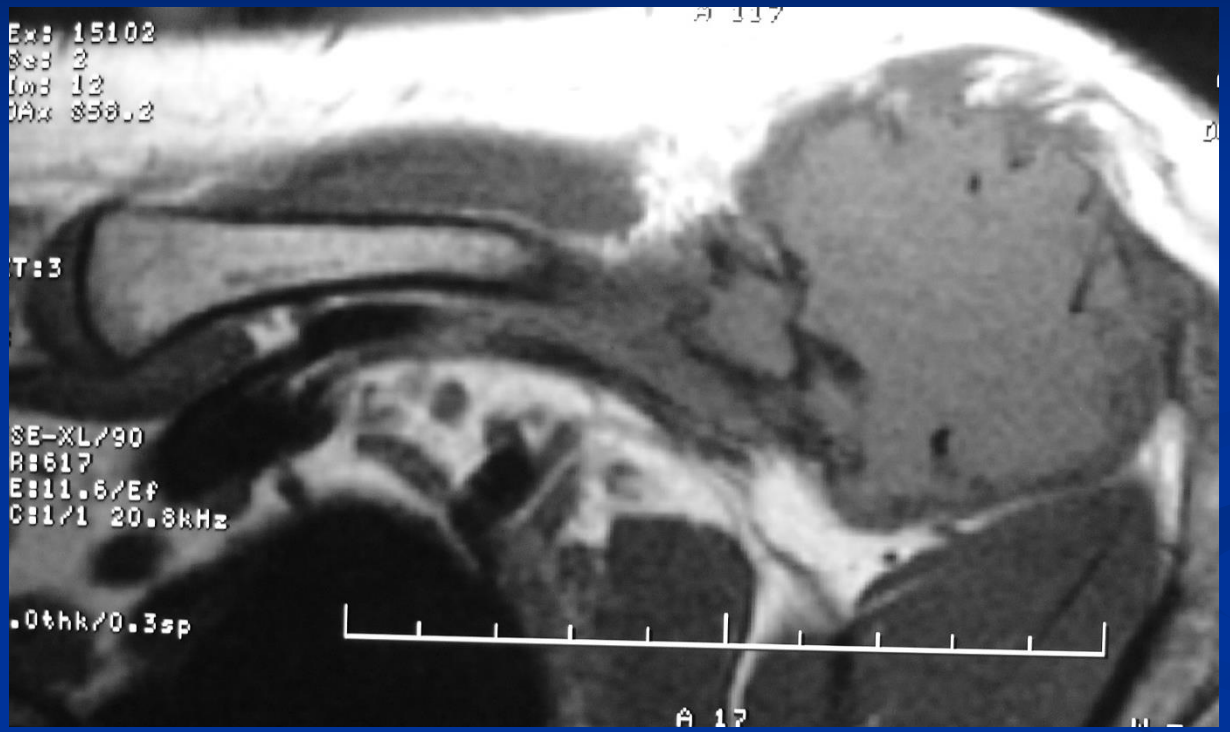
Osteosclerotic Myeloma



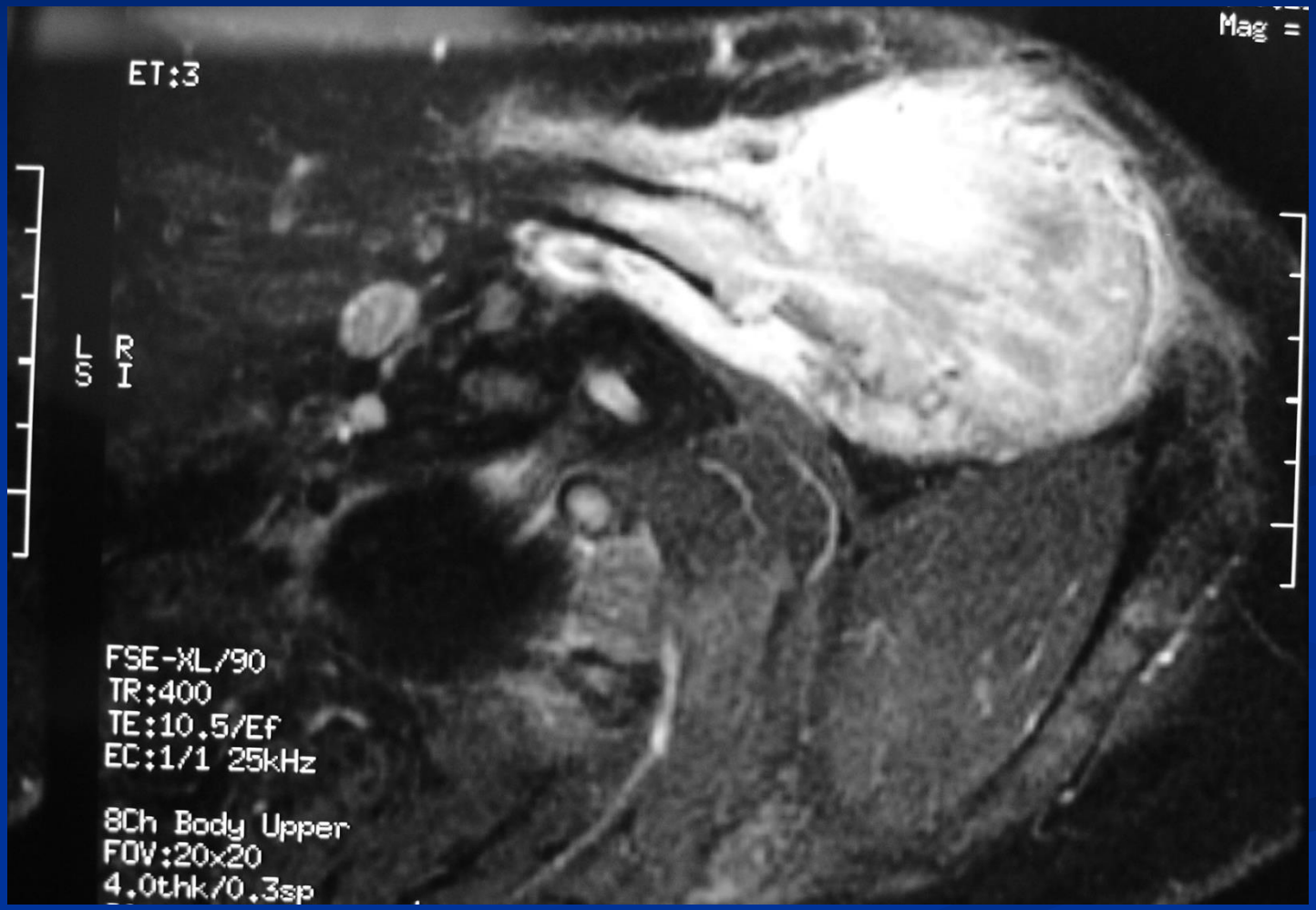
Osteosclerotic Myeloma



Plasmacytoma

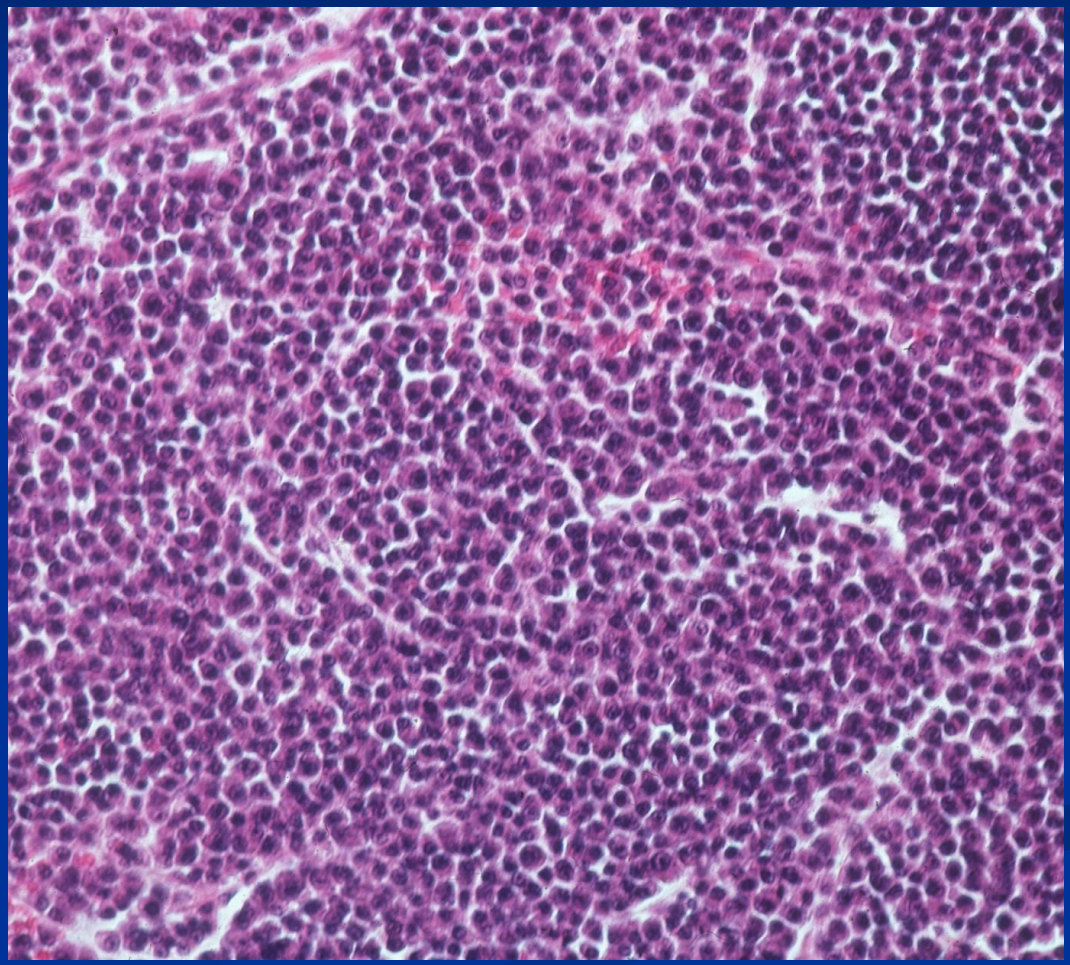


Plasmacytoma

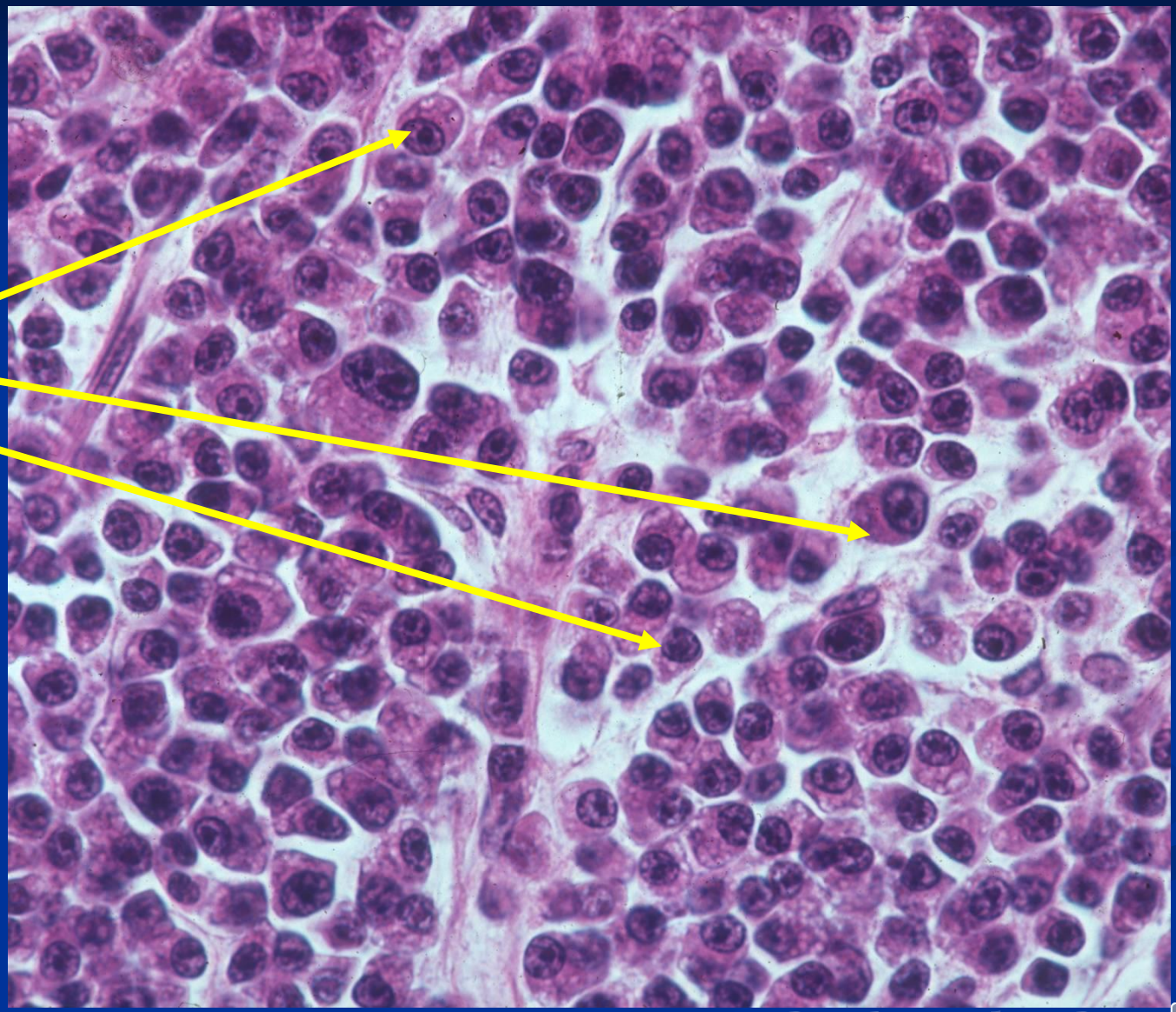


Microscopic Pathology: Myeloma

- Uniform small round blue cells
- No matrix
- Plasma cells with eccentric clock face nucleus and perinuclear halo
- Sheets of cohesive cells similar size and shape



Microscopic Pathology: Myeloma



Treatment & Prognosis

- Prognosis depends on stage of disease and percentage of plasma cells in bone marrow
  - Less than 5% plasma cells in bone marrow is associated with a better prognosis
- Multiple myeloma
  - Surgery for fixation of pathological fractures or impending pathological fractures
  - Chemotherapy
    - Induces remissions in 50-70% of patients
  - Radiotherapy: Indicated for bone pain or impending pathological fracture
    - Effective for individual lesions
  - Most deaths stem from infections or renal failure
- Solitary myeloma (plasmacytoma)
  - 36-54% of solitary myelomas become multiple myelomas within a few years
  - May consider surgery for a solitary myeloma depending on size, location, fracture or impending fracture
  - Radiotherapy
    - Common treatment
    - Usually allows for resolution of the lesion
    - Often only radiation treatment and then patient is observed for development of multiple myeloma

Thank You!

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