

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

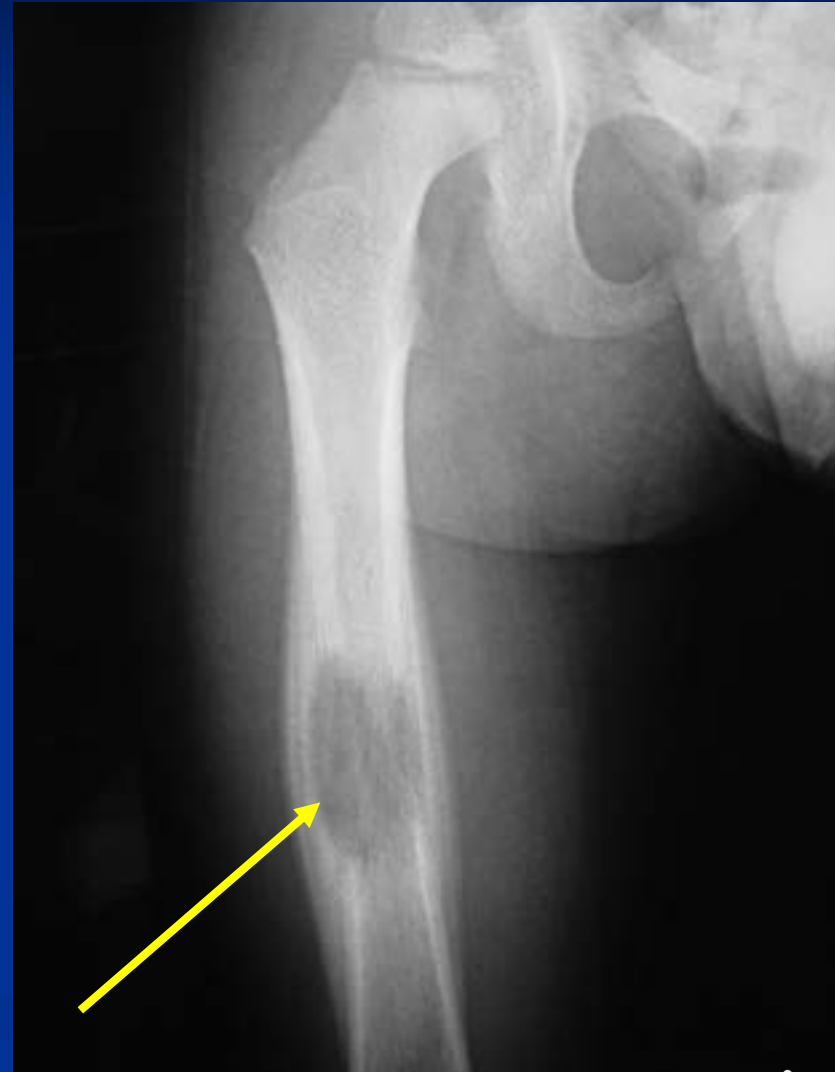
- Develops in 1st year of life
- Disseminated disease and small bone lesions
- Fatal in 95% who develop before 1 year of life

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)
- Ring 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

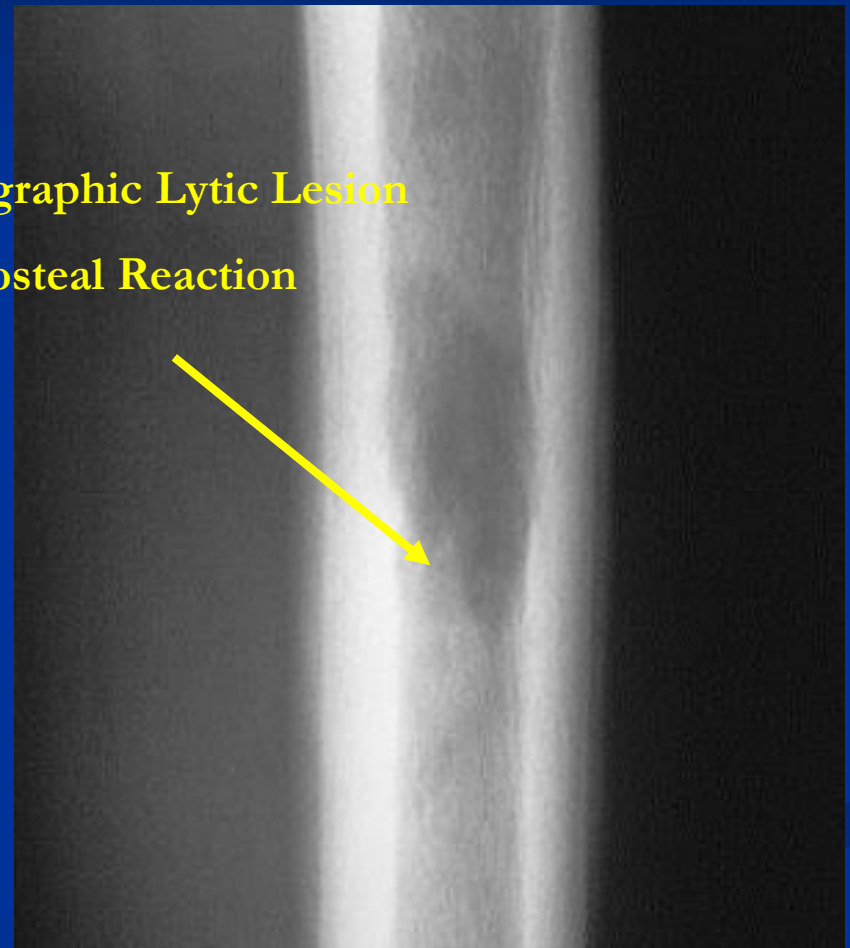


X-ray: Eosinophilic Granuloma of Femur



Geographic Lesion with
Periosteal Reaction

Geographic Lytic Lesion
Periosteal Reaction



X-ray: Eosinophilic Granuloma of Femur

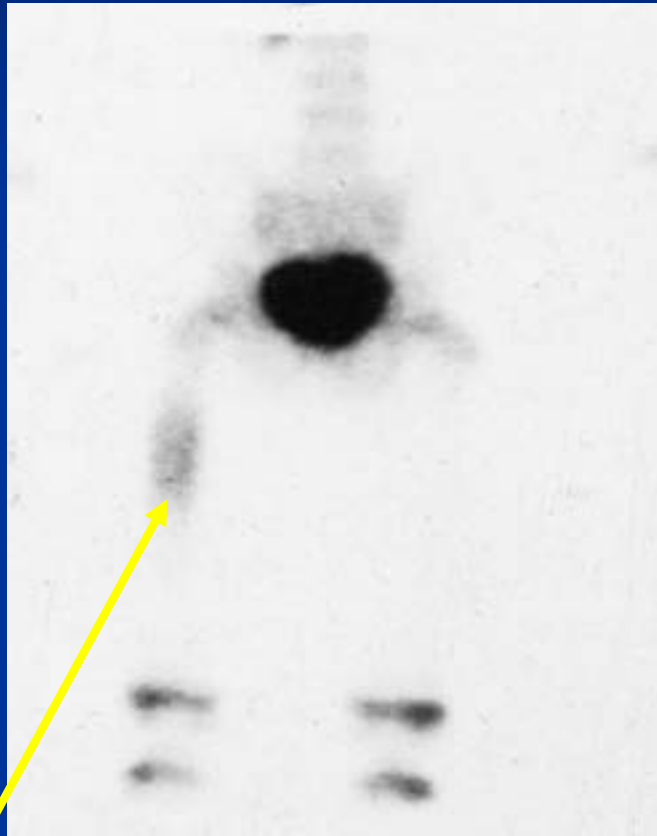


Geographic Lesion

Lamellated Periosteal Reaction

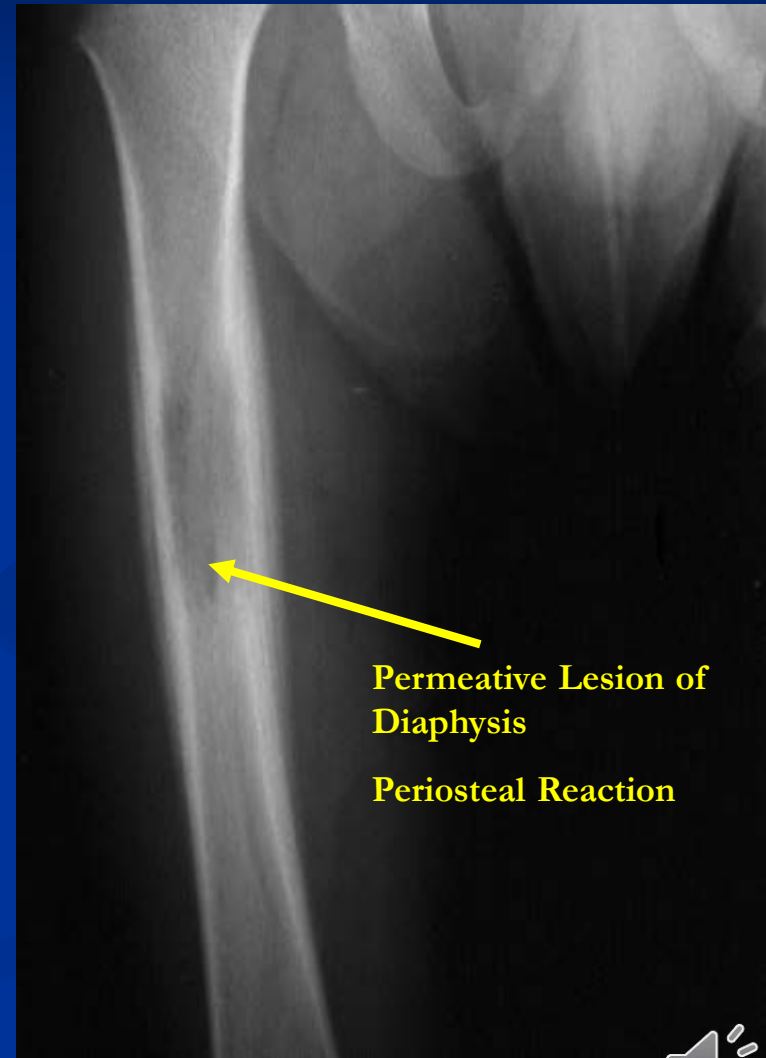


X-ray/Bone Scan: Eosinophilic Granuloma of Femur



Bone Scan is Variable

Uptake Intense, Mild or Cold



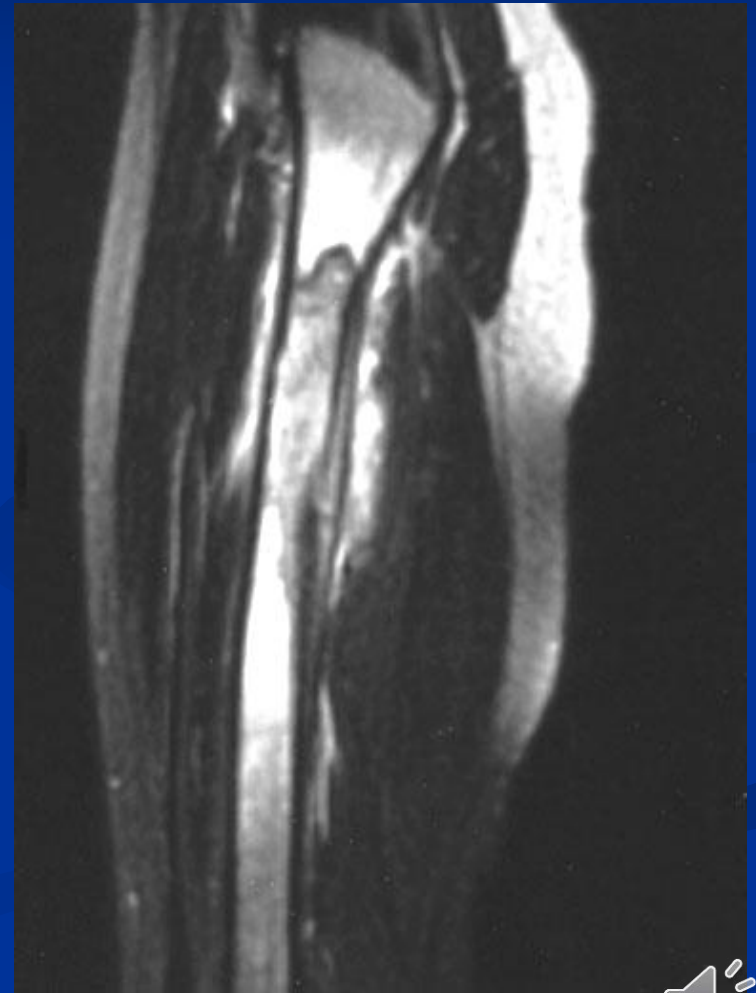
Permeative Lesion of
Diaphysis
Periosteal Reaction



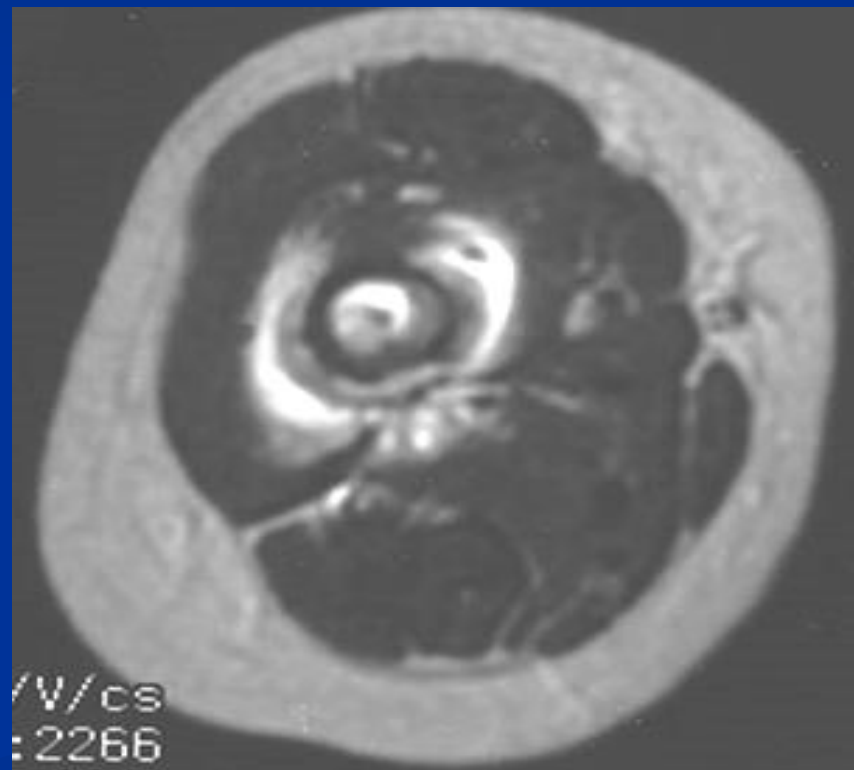
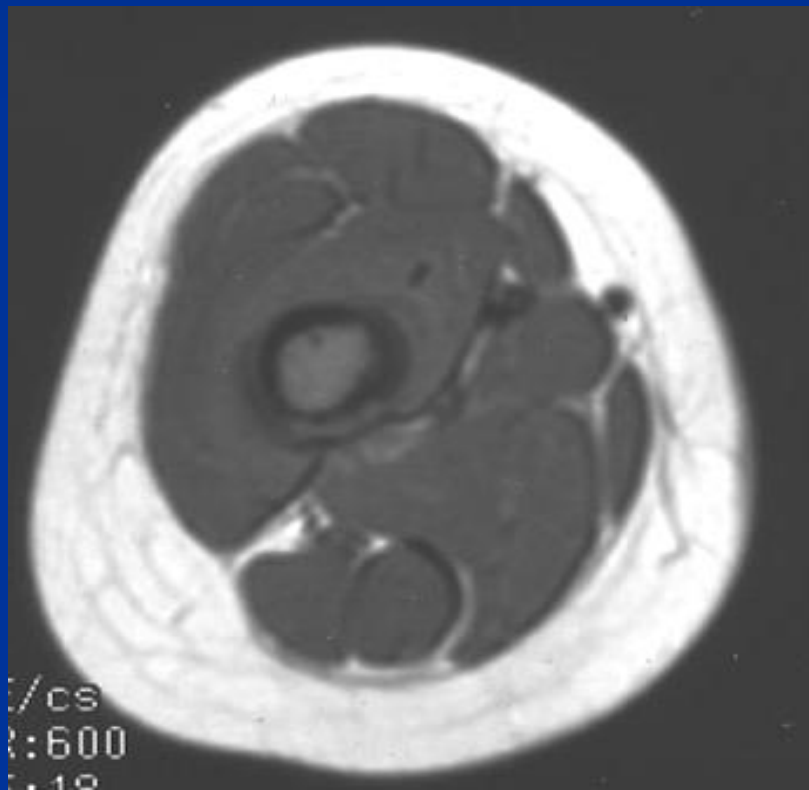
MRI: Eosinophilic Granuloma

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

MRI: Eosinophilic Granuloma of Femur



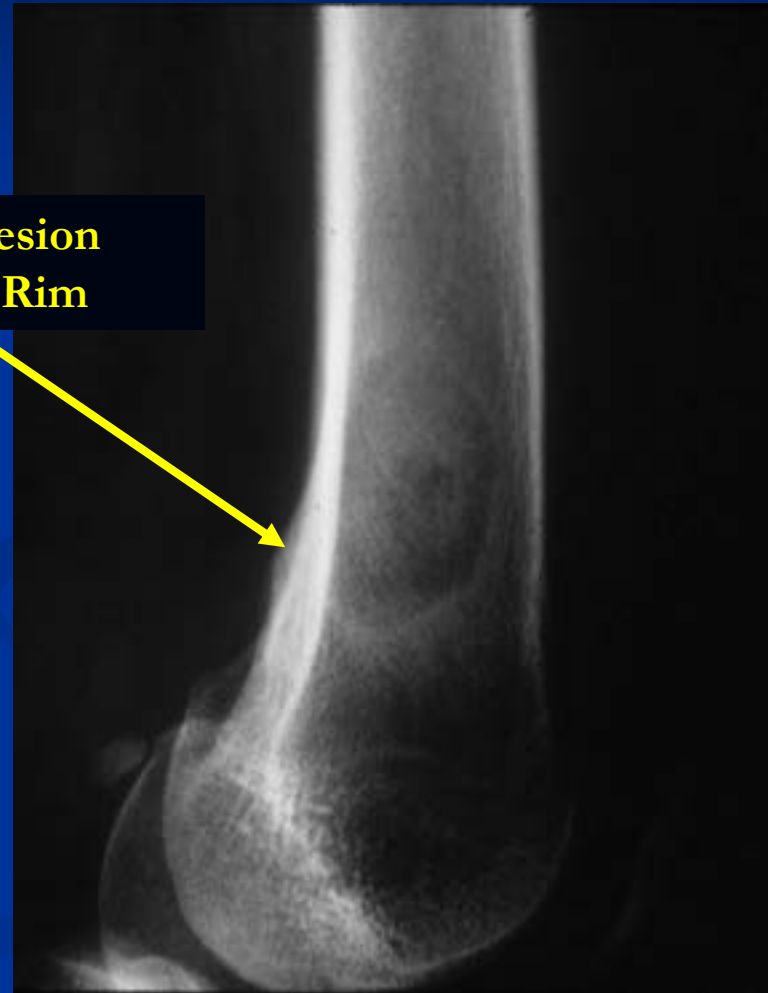
Langerhans Cell Histiocytosis



X-ray: Eosinophilic Granuloma of Femur



Geographic Lesion
with Sclerotic Rim



X-ray: Eosinophilic Granuloma of Clavicle Permeative Lesion

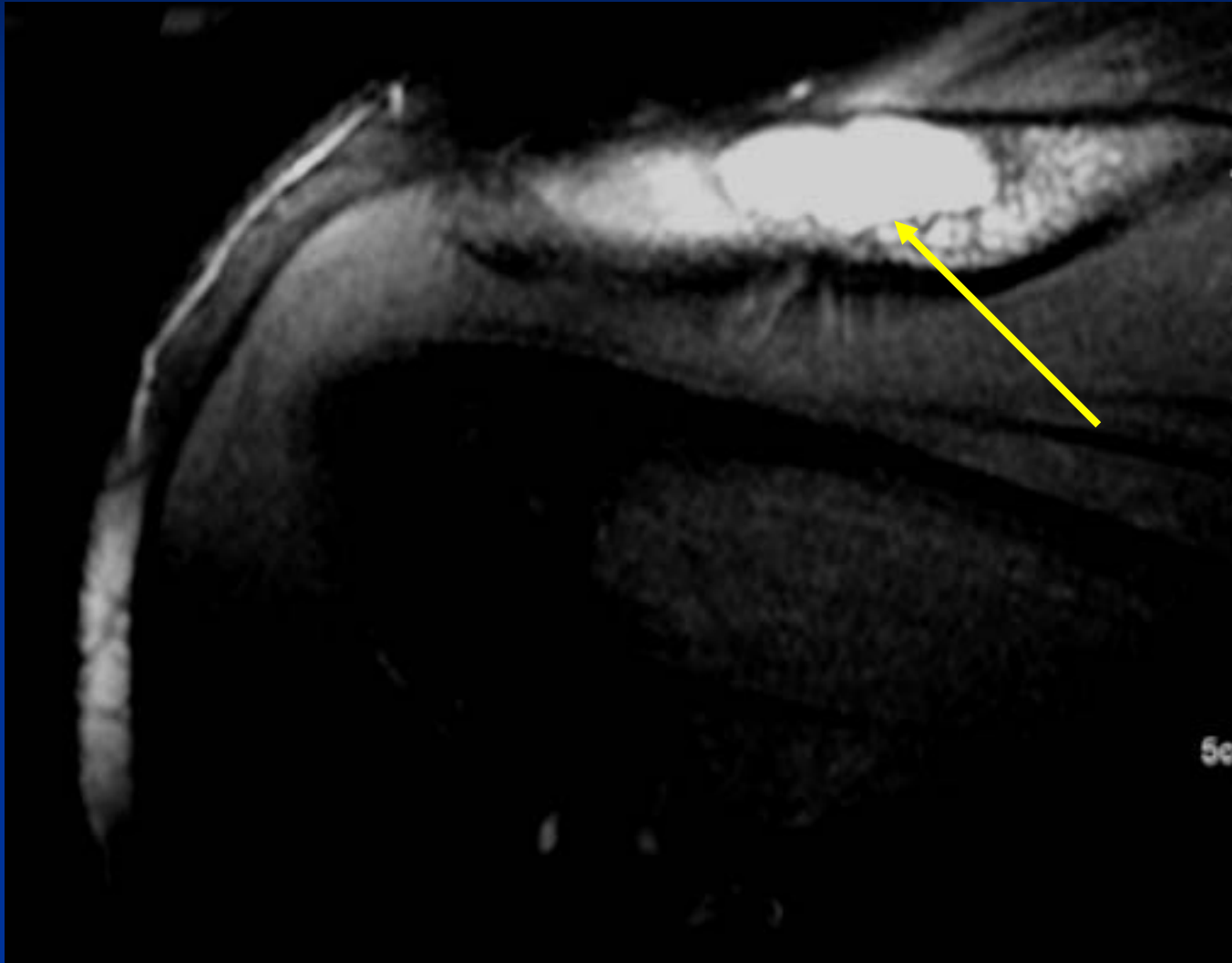


Plain X-ray: Eosinophilic Granuloma of Humerus

Permeative Lesion



MRI T2: Eosinophilic Granuloma of Scapula Spine

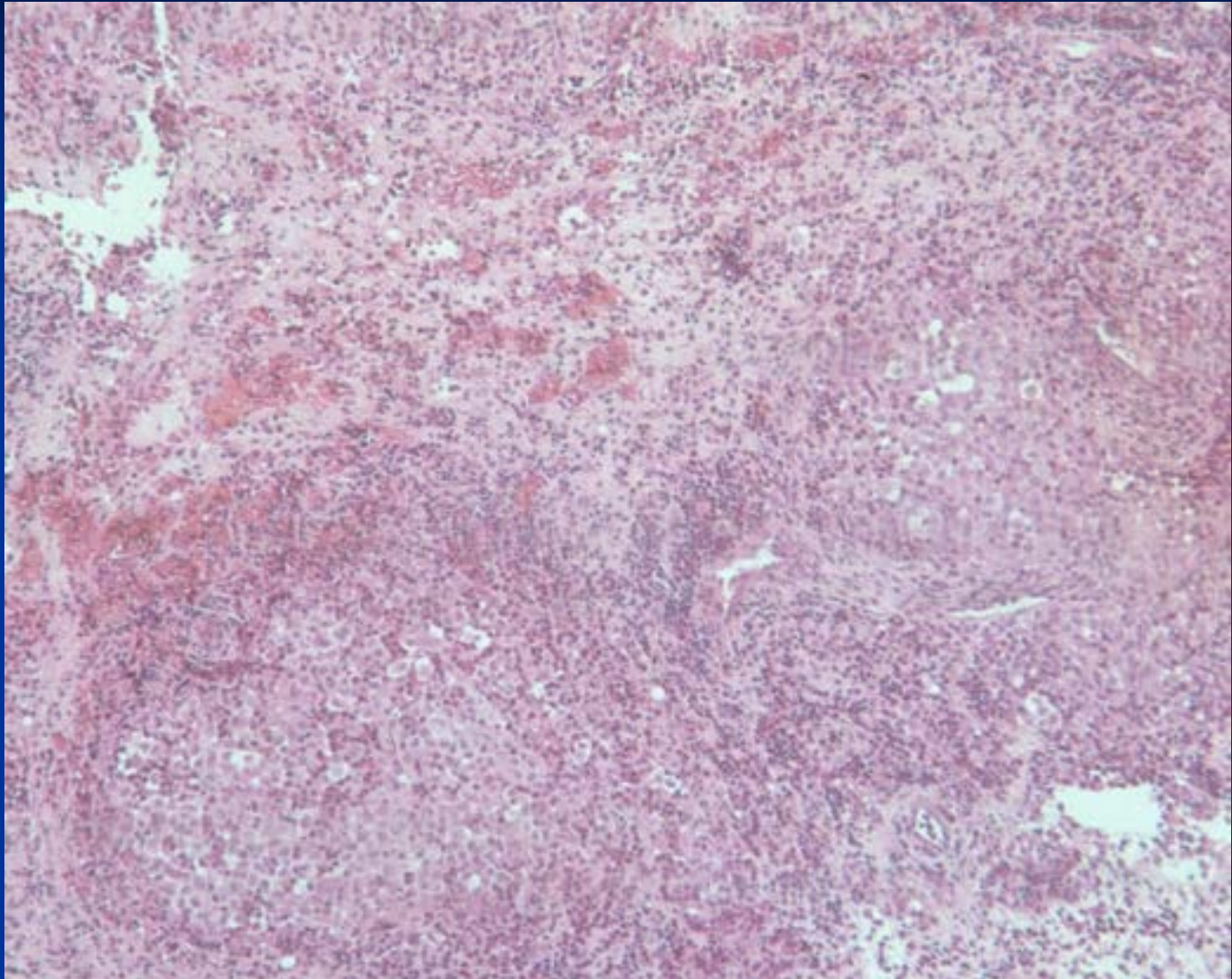


Microscopic Pathology

- 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

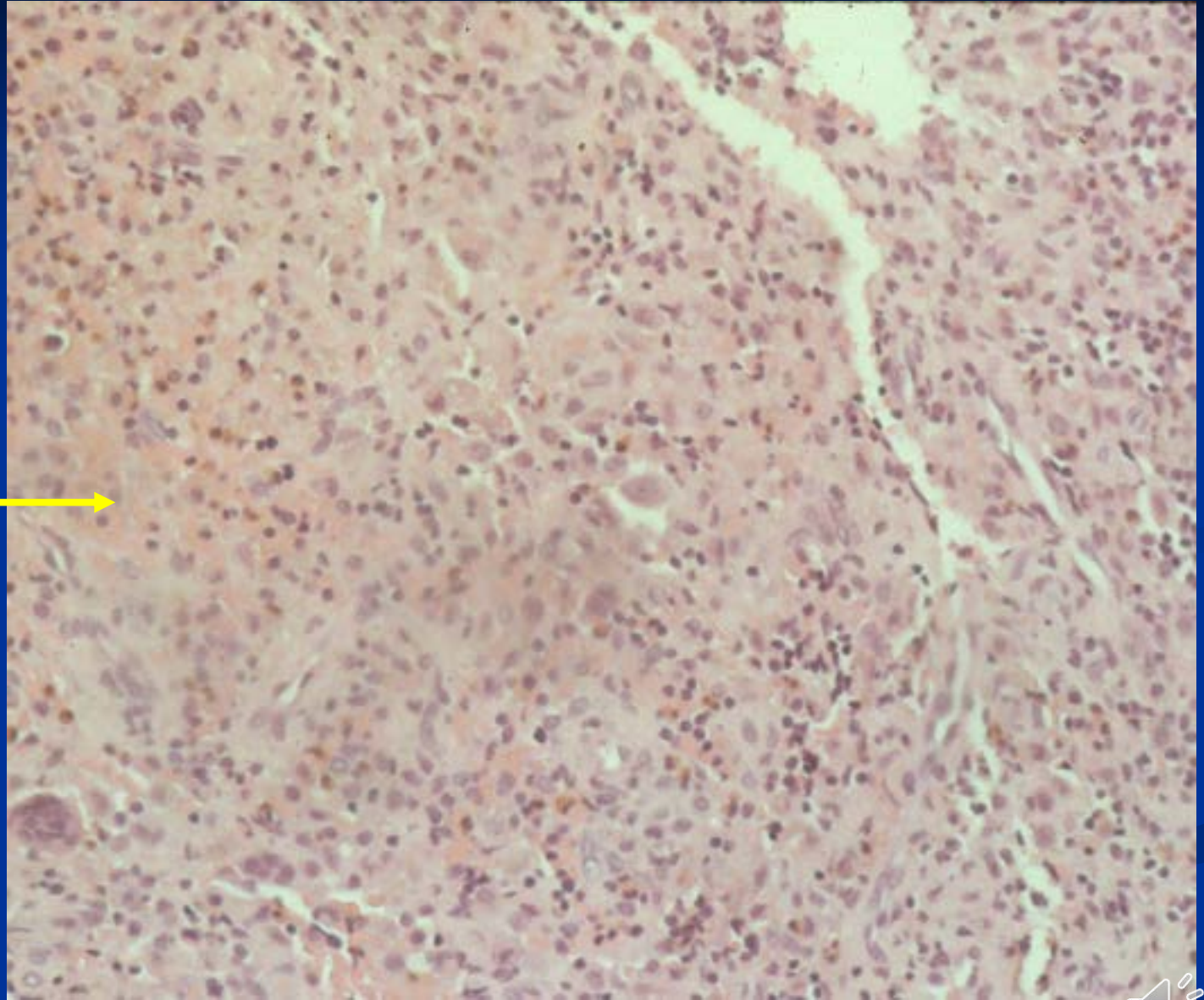
Microscopic Pathology: Eosinophilic Granuloma

Cells and No Matrix



Microscopic Pathology: Eosinophilic Granuloma

Eosinophils →



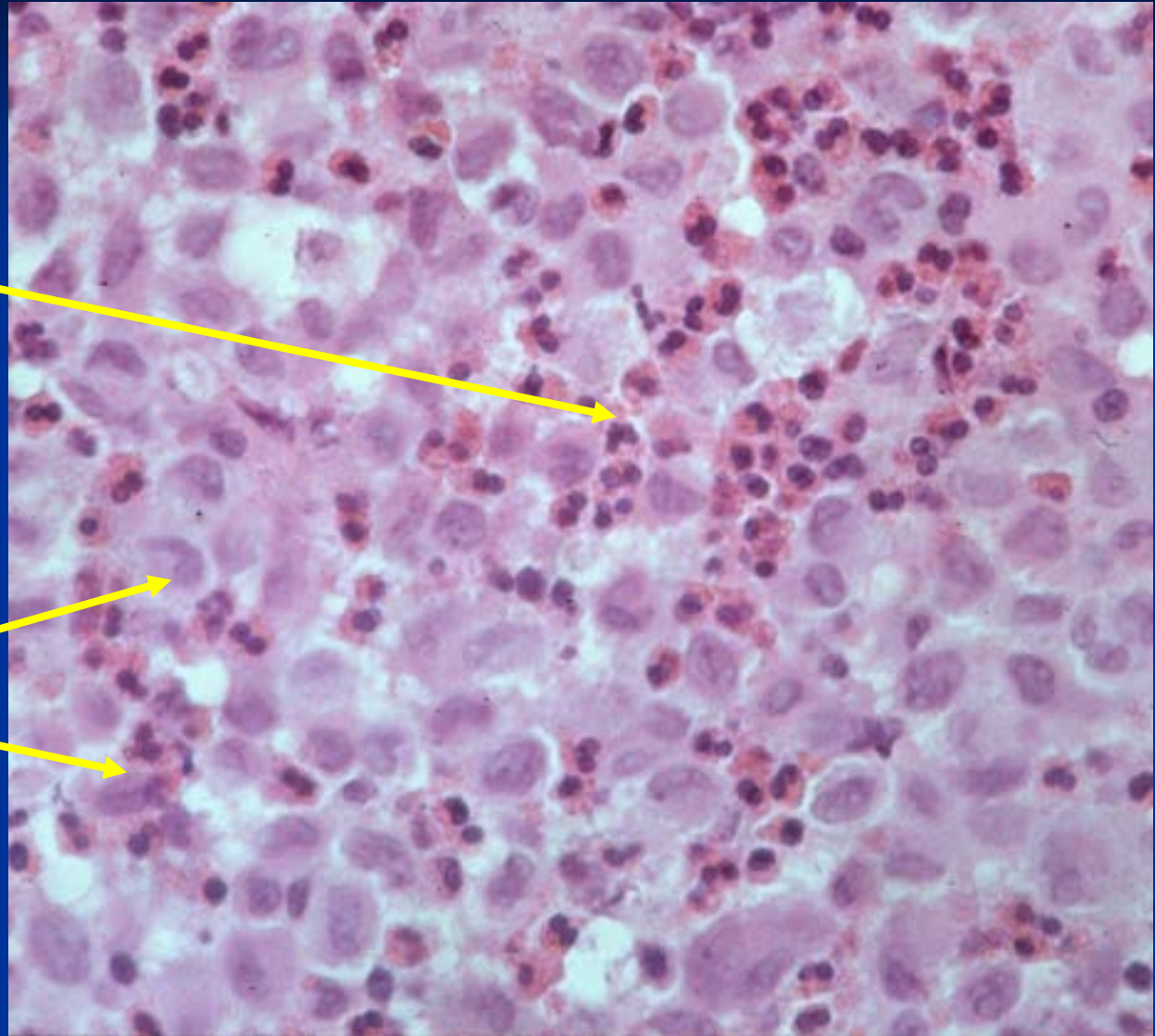
Microscopic Pathology: Eosinophilic Granuloma

Eosinophils

Langerhans Cells

Coffee Bean

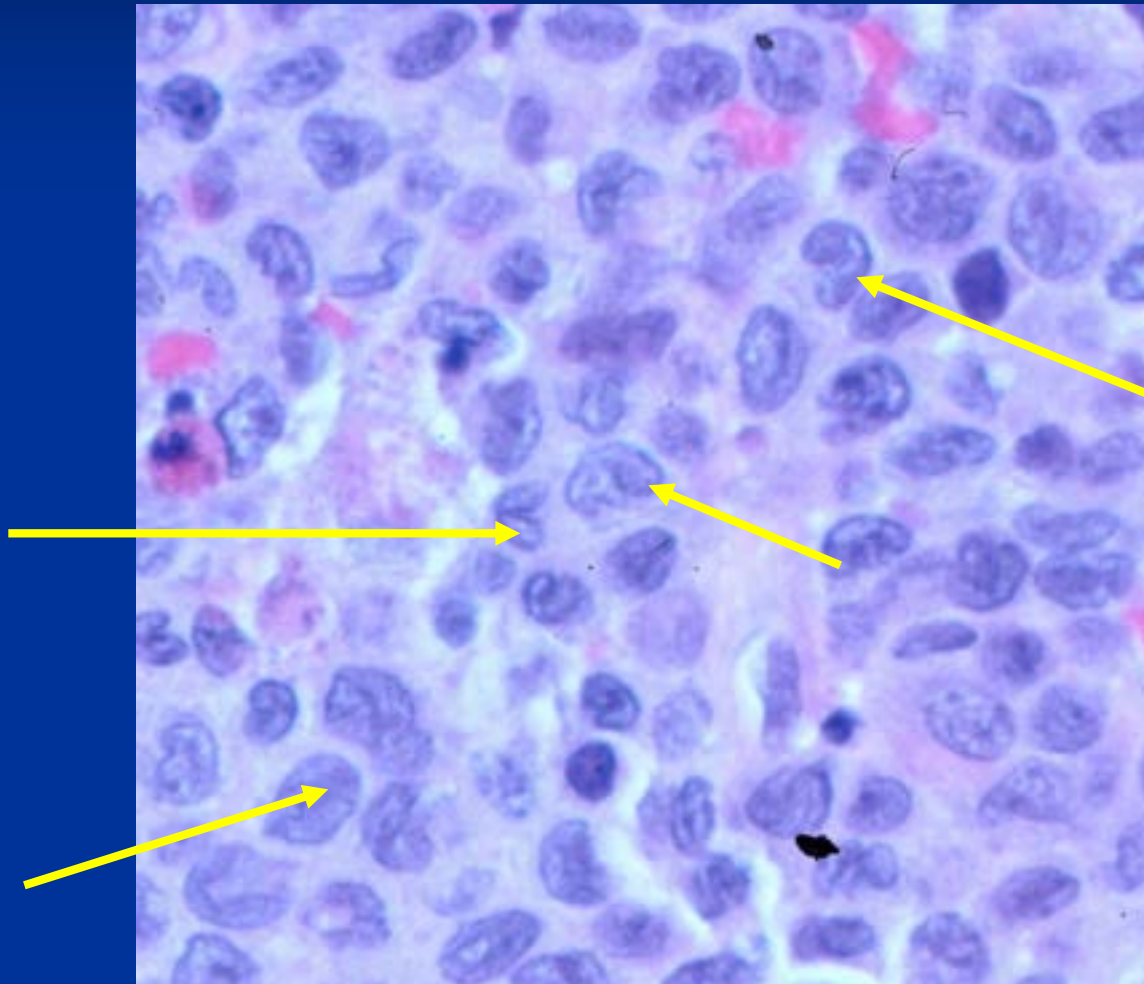
Indented
Nucleus



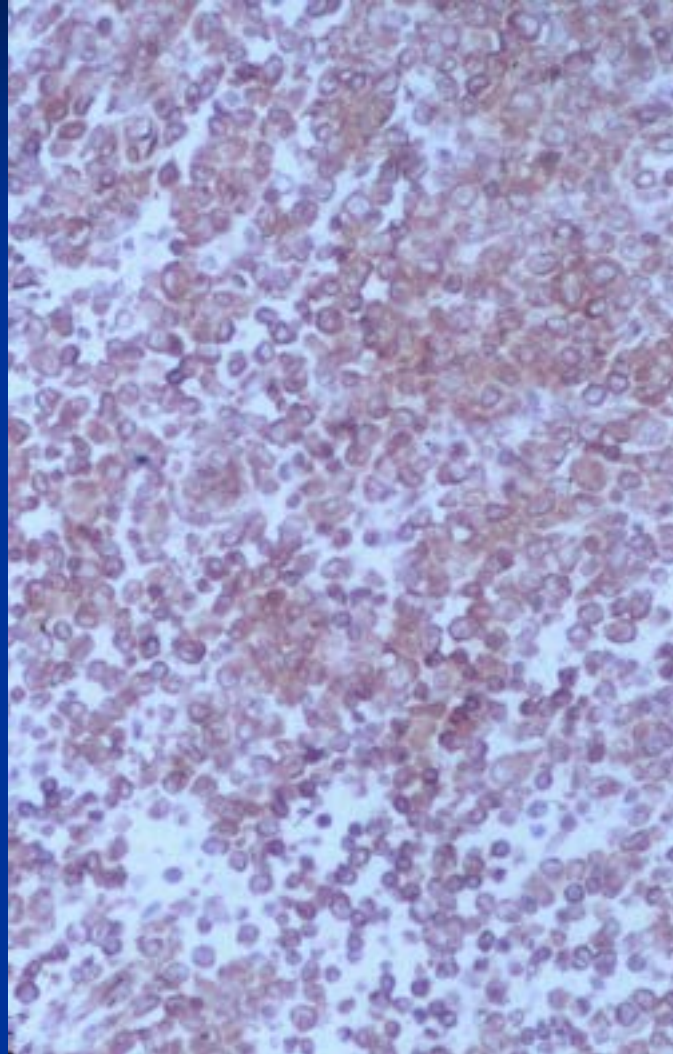
Microscopic Pathology: Eosinophilic Granuloma

High power

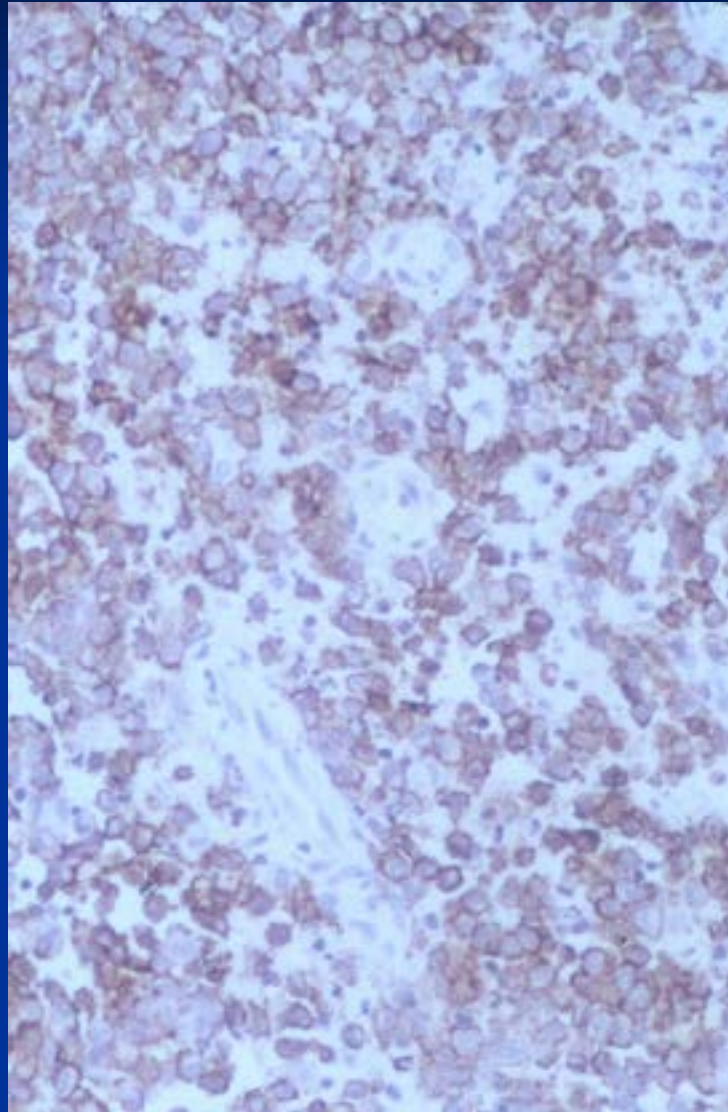
Coffee Bean/Indented Nuclei of Langerhans Cells



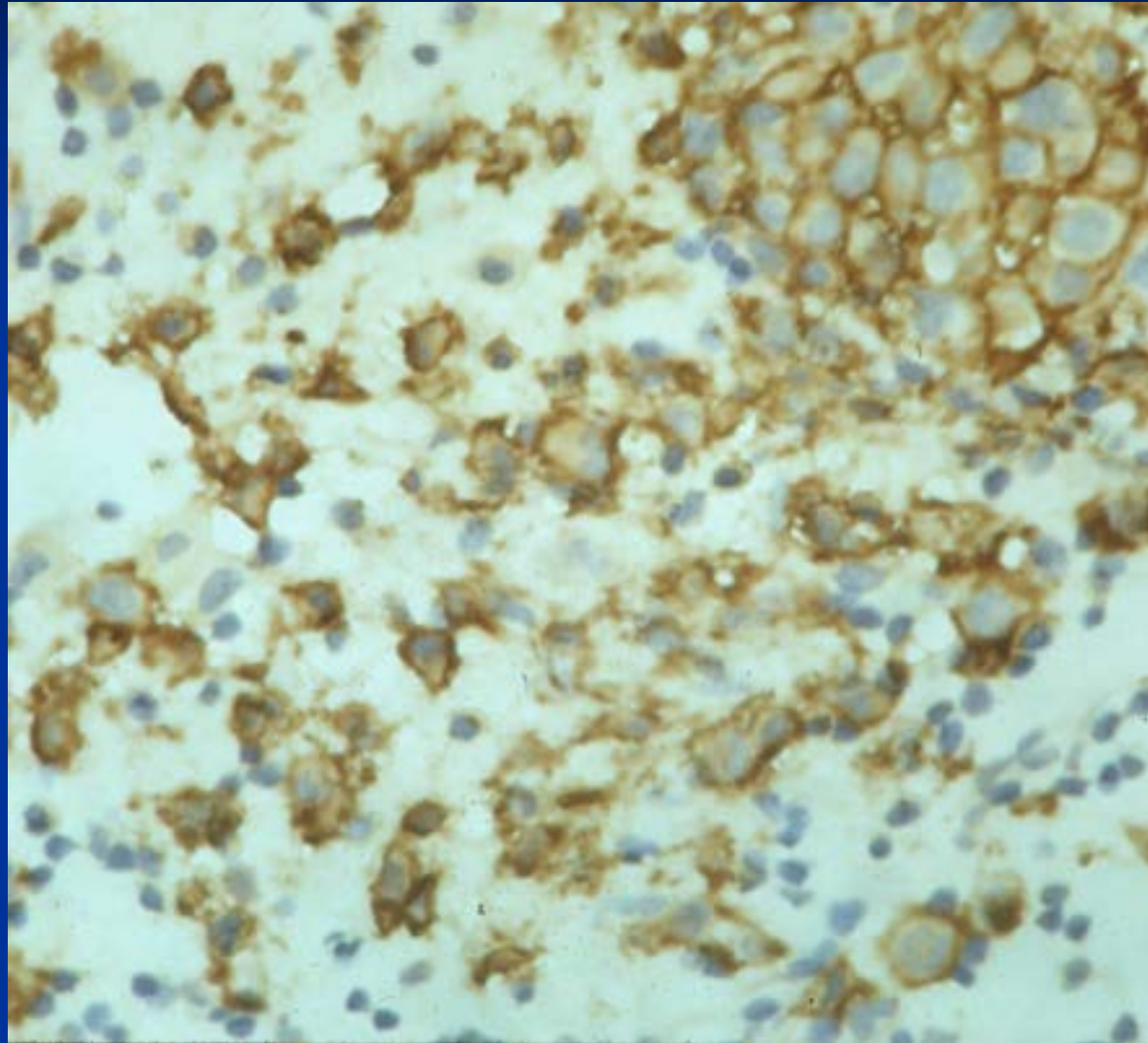
Eosinophilic Granuloma: Vimentin Stain



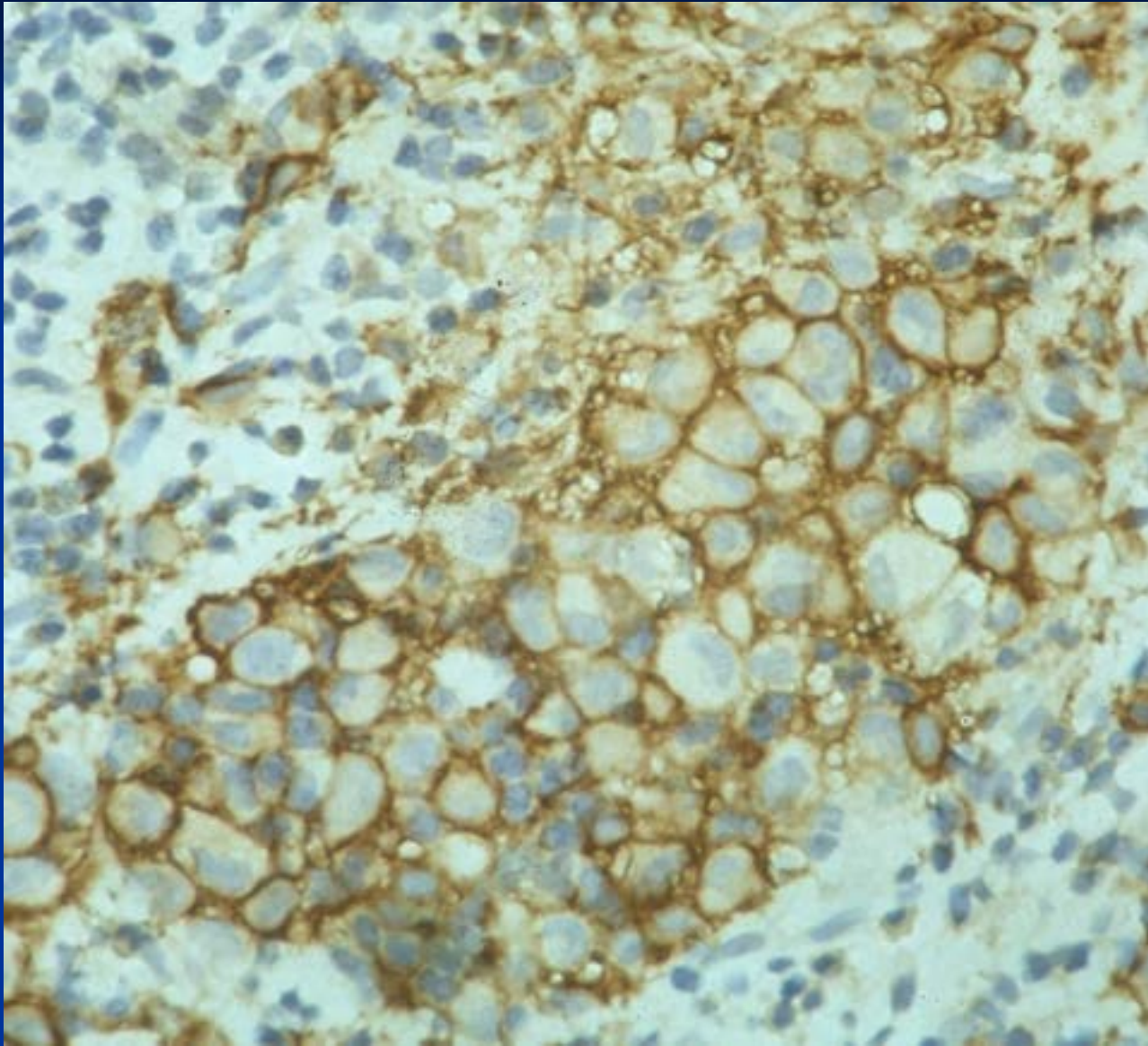
Eosinophilic Granuloma: CD1a Stain



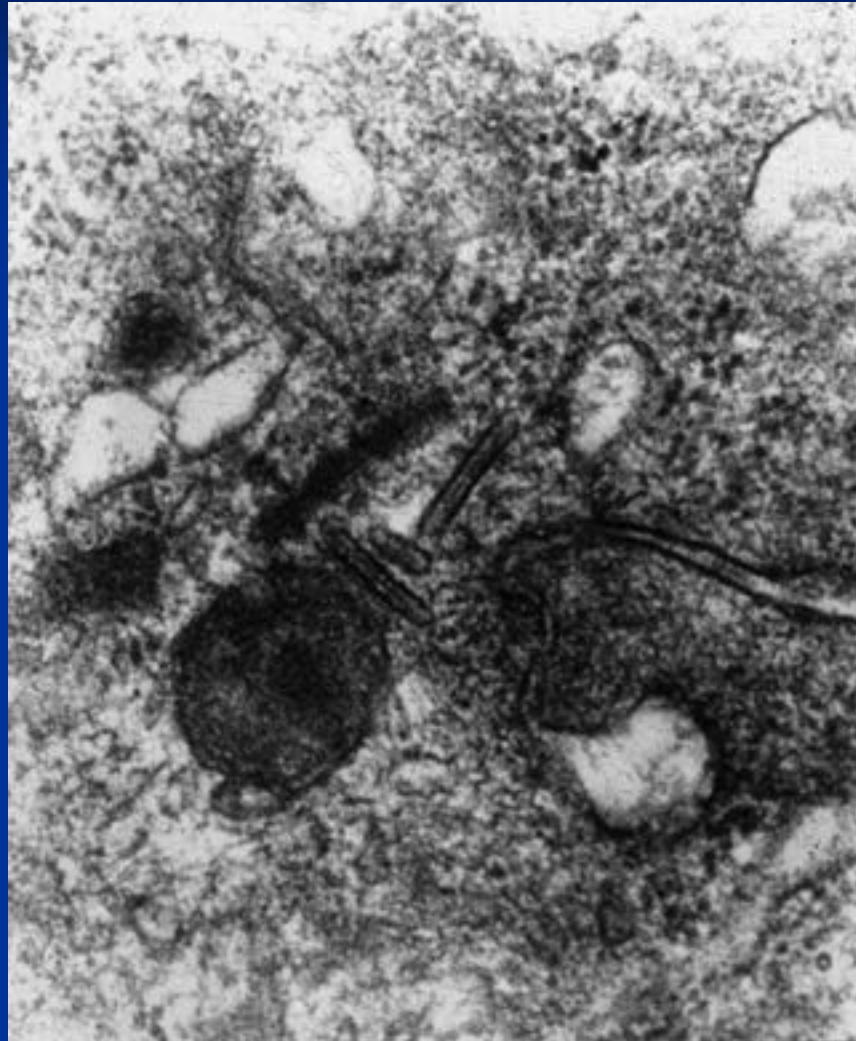
Eosinophilic Granuloma: S-100 Stain



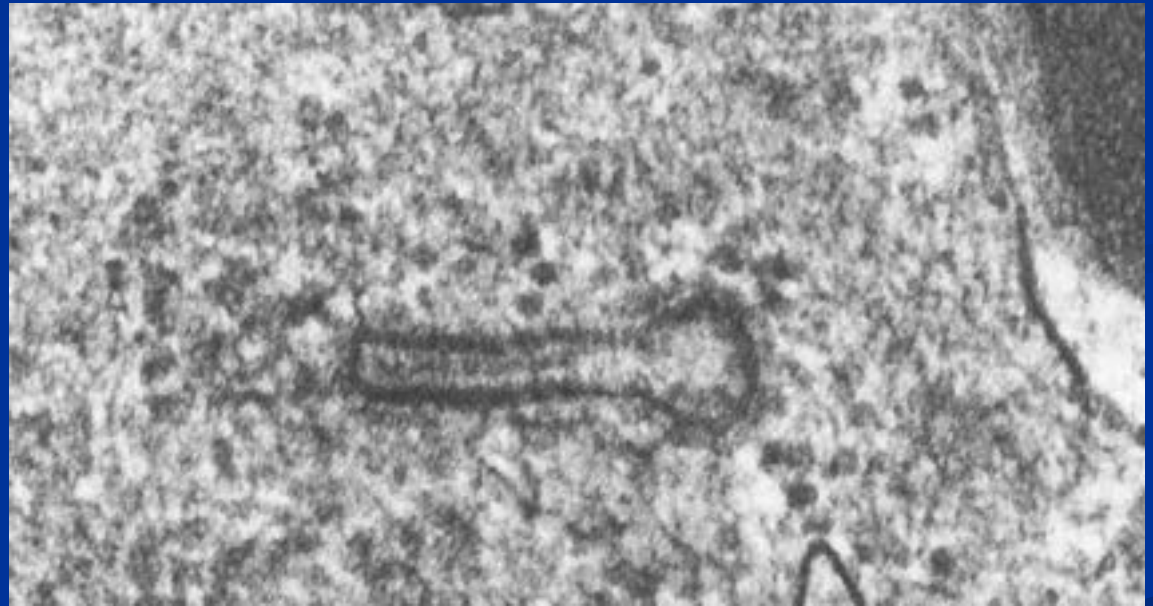
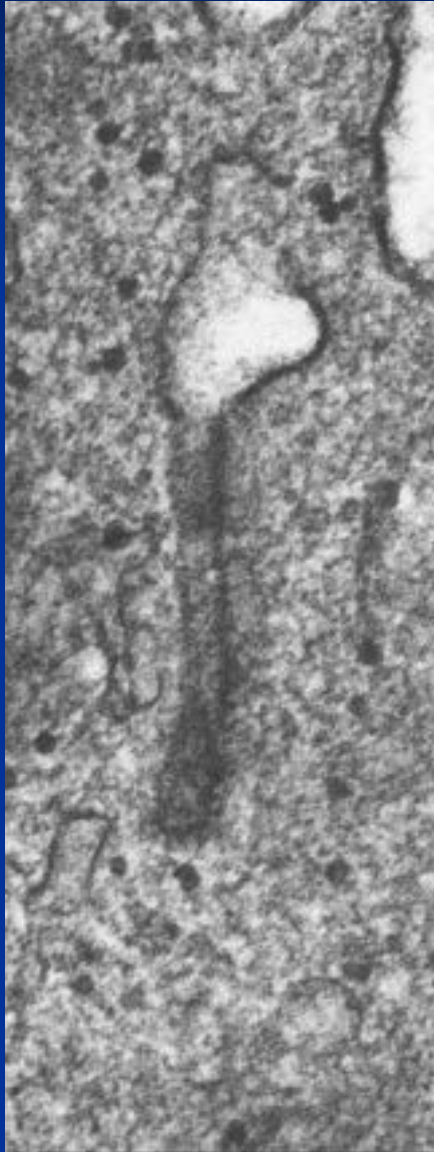
Eosinophilic Granuloma: CD-10 Stain



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

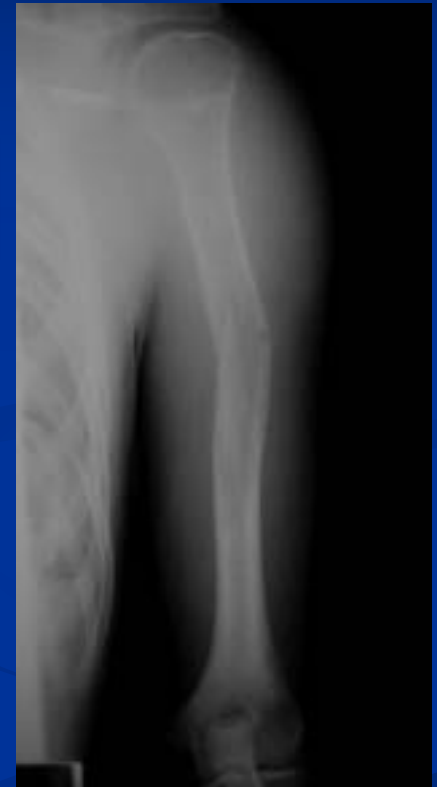
- Uniform, monotonous, small round blue cells without any matrix production
- Fourth most common primary malignancy of bone
- Rare
- Most Ewing sarcoma cases (85%) are associated with a characteristic chromosomal translocation **t(11;22)(q24;q12)** that results in **EWS/FLI-1** chimeric protein

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

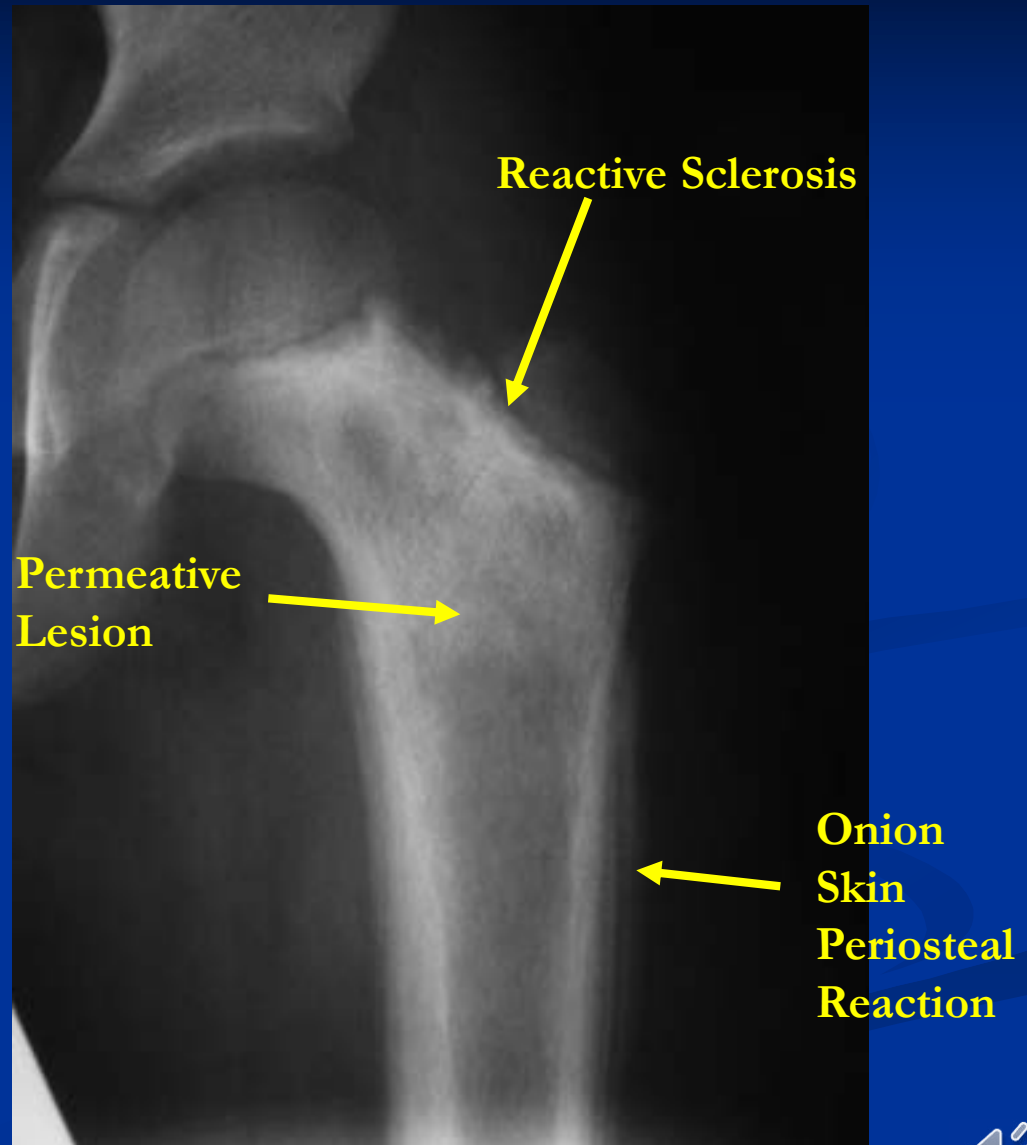
Radiographic Presentation

- Permeative or moth eaten bone destruction
- Soft Tissue Mass in 90% of cases
- Periosteal Reaction in 50% of cases
 - **Onion Skin** (concentric 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



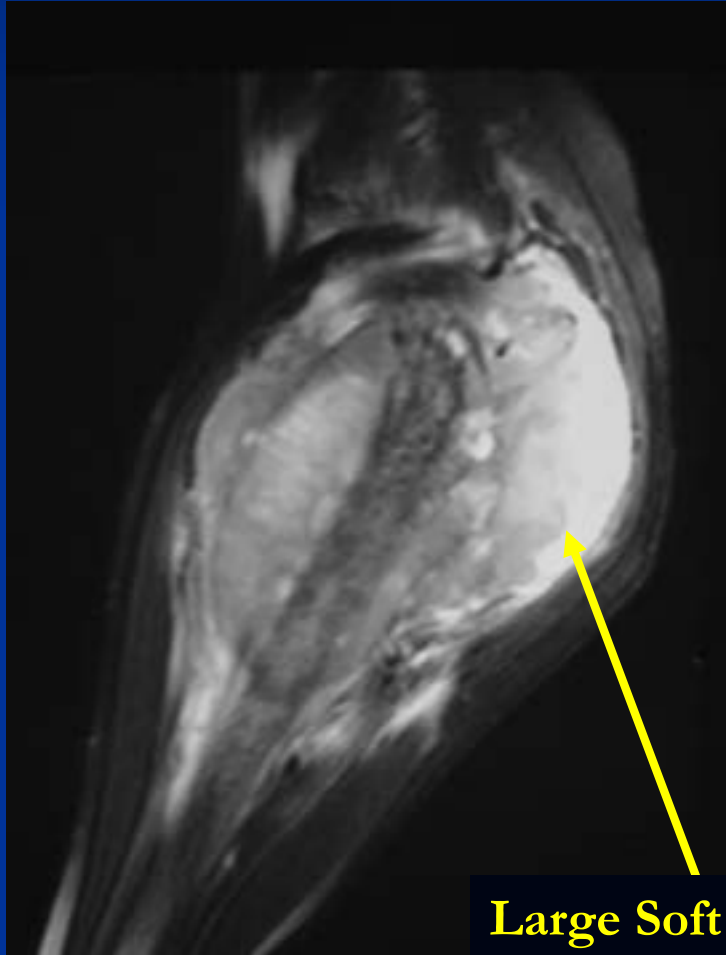
X-ray: Ewing Sarcoma of Proximal Femur

- 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



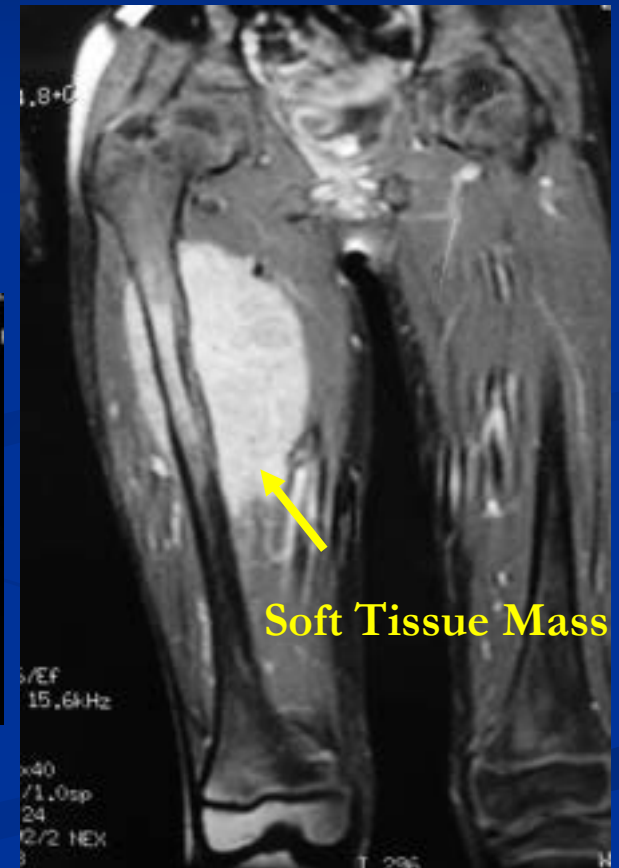
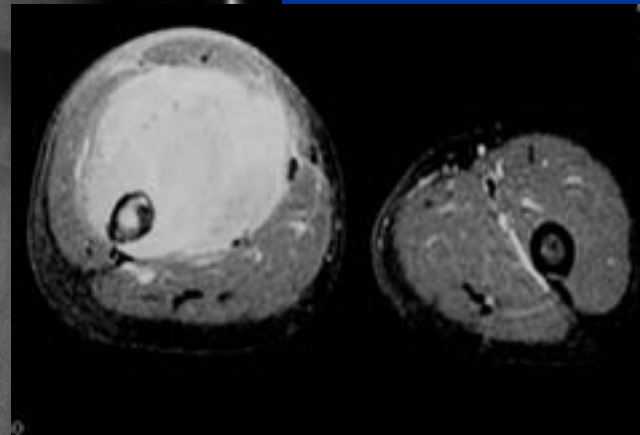
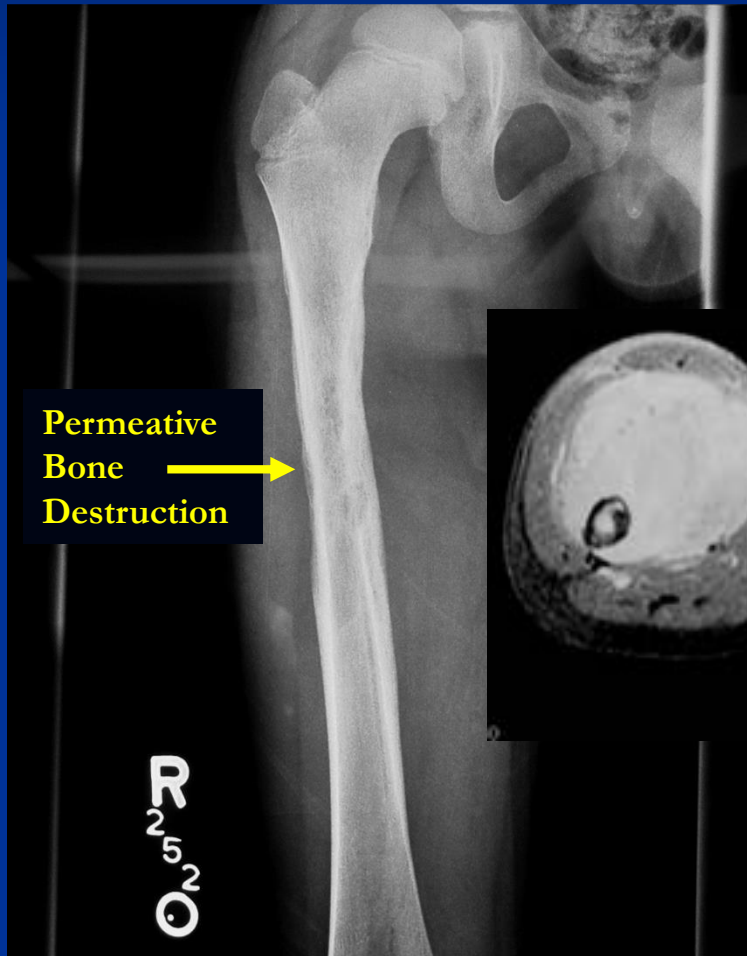
Large Soft Tissue Mass Best Visualized on MRI



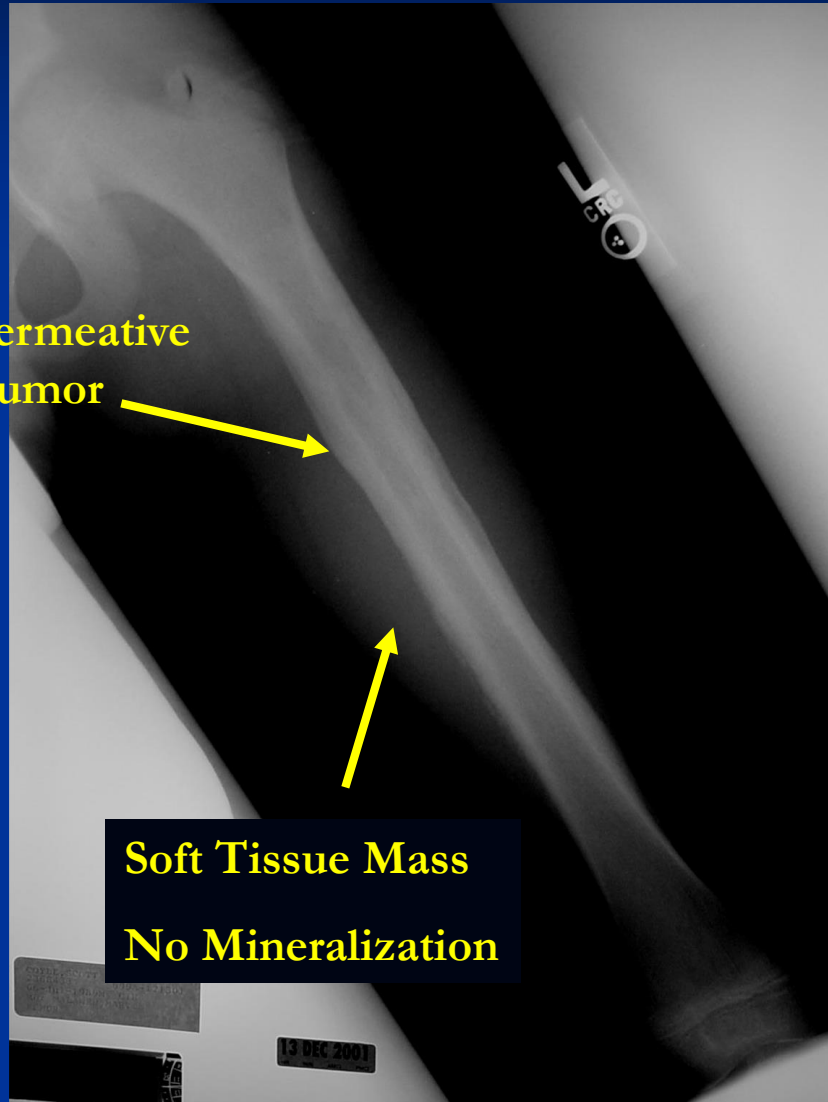
X-ray/MRI: Ewing Sarcoma of Diaphysis of Femur

Tumor Barely Perceptible on X-Ray

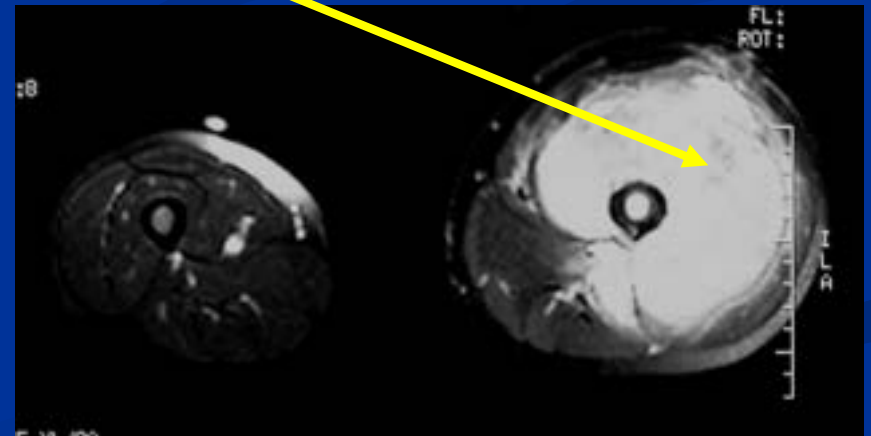
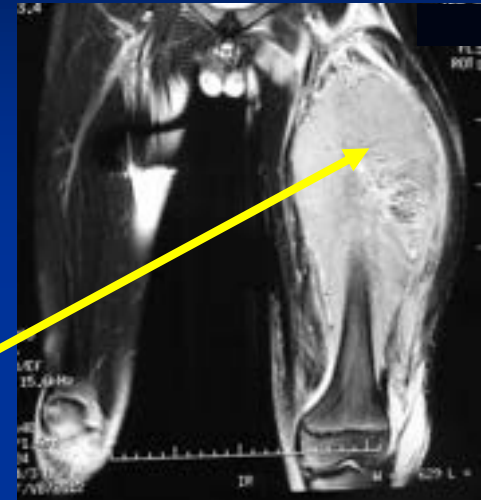
MRI Demonstrates Marrow Involvement and Large Soft Tissue Mass



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



Large Soft Tissue Mass



X-ray: Ewing Sarcoma of Right Femur

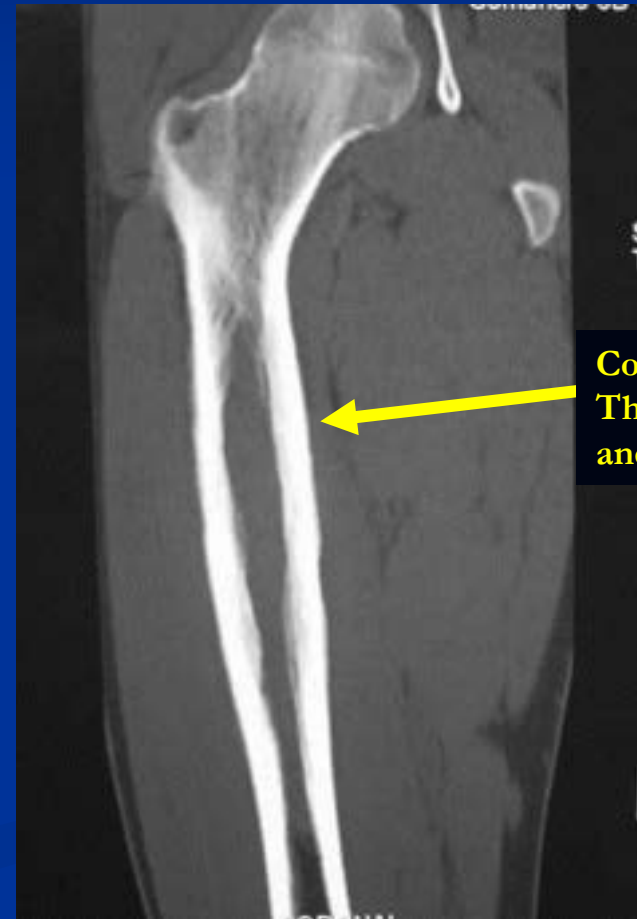
- X-rays demonstrate a **permeative lesion** of the right proximal femur with slight sclerosis
- The lesion is barely perceptible on the Xray
- There is no periosteal reaction in this case



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 1/2 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



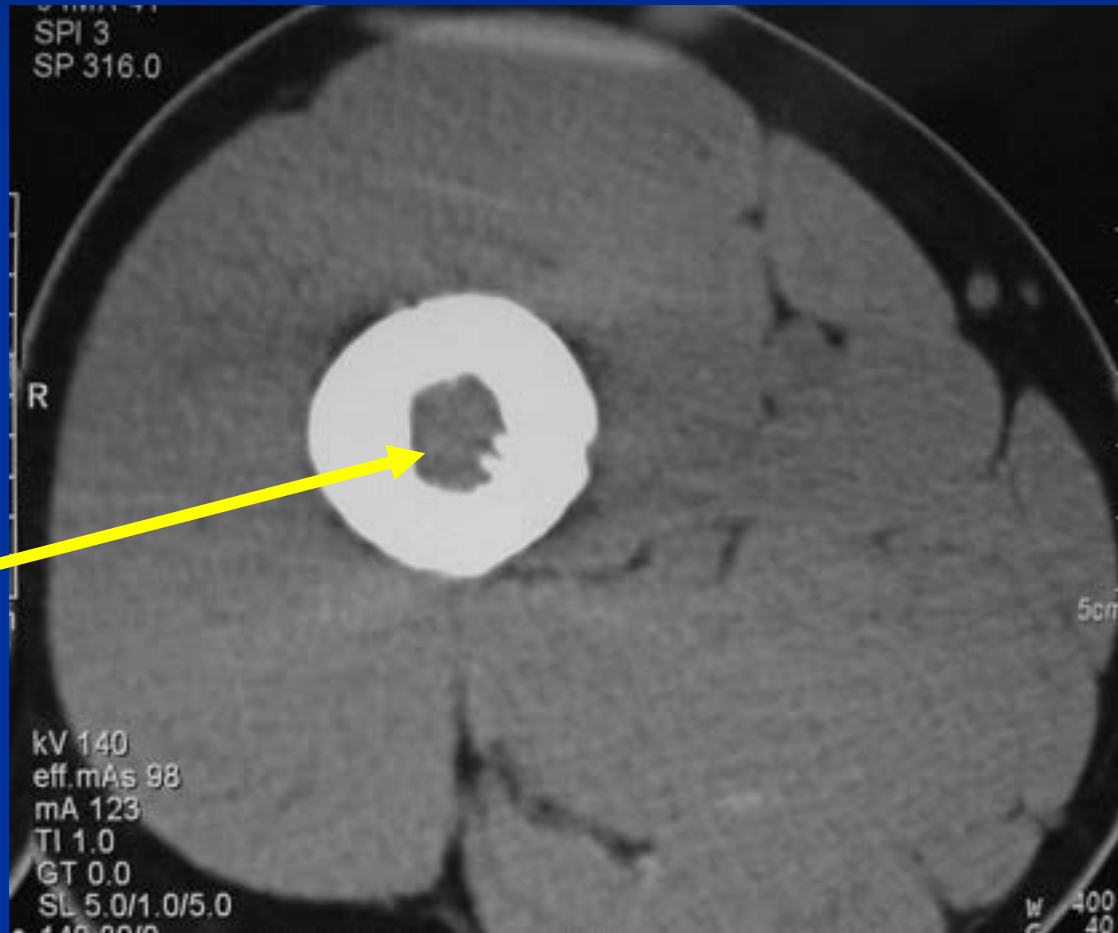
Cortex Mildly Thickened and Expanded



CT Scan: Ewing Sarcoma of Right Femur

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

**Marrow
Replacing
Lesion**



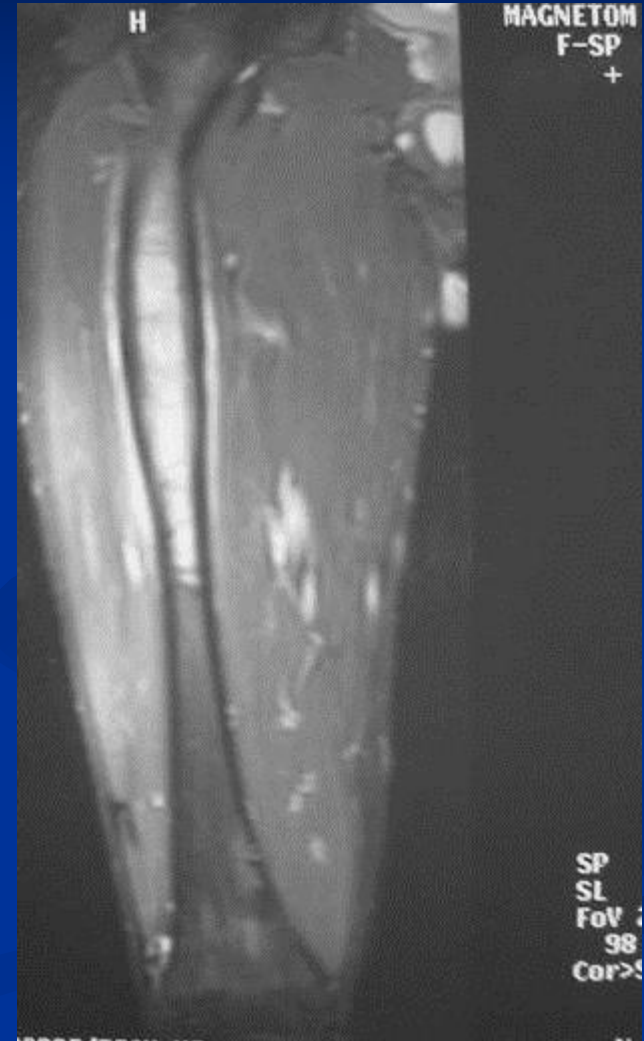
MRI T1 Weighted Image: Ewing Sarcoma of Right Proximal Femur

- The T1 weighted MRI demonstrated a permeative lesion involving the upper 1/2 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



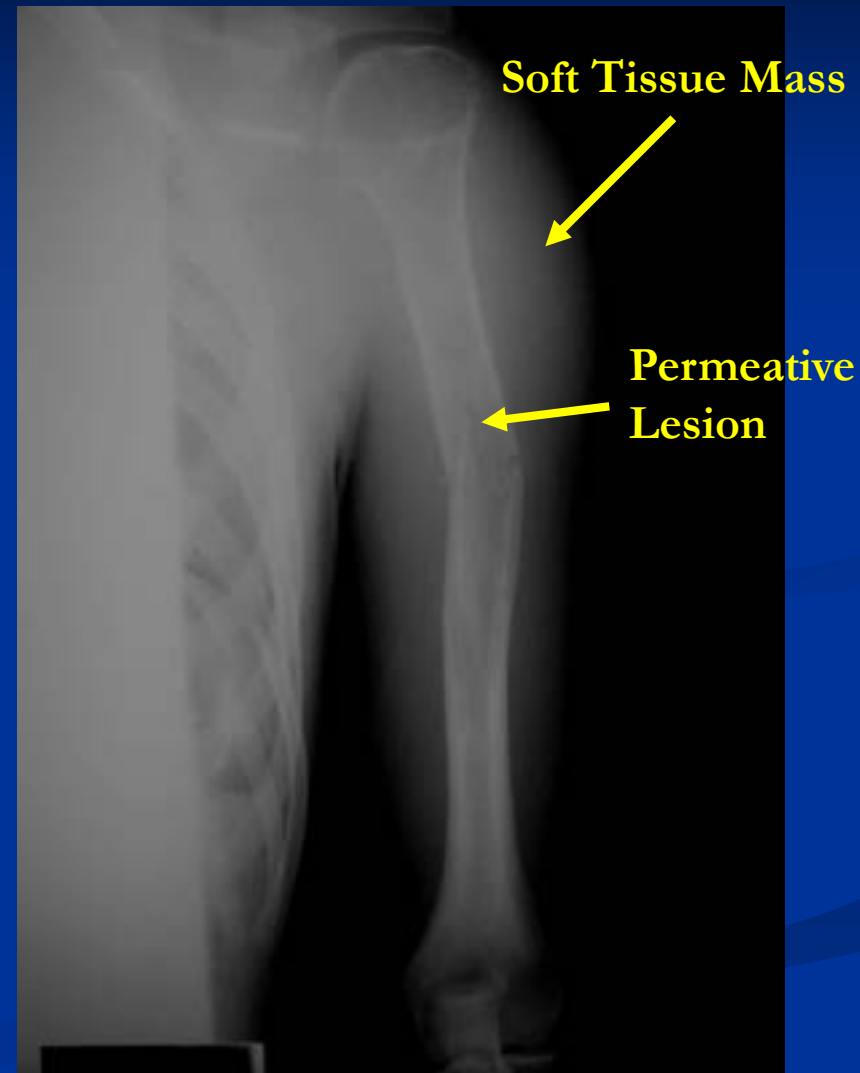
MRI T2 Weighted Image: Ewing Sarcoma of Right Proximal Femur

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

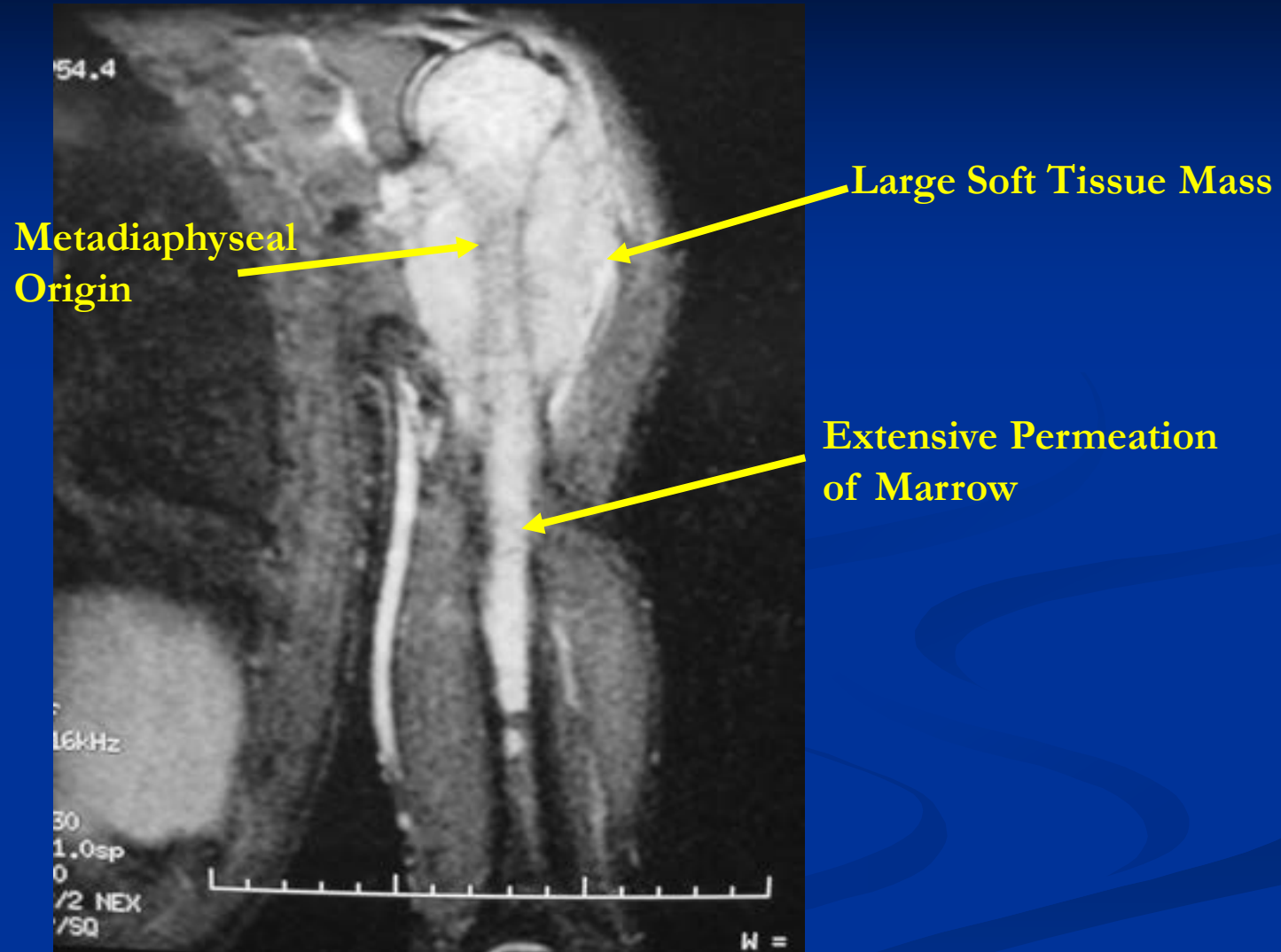


X-ray: Ewing Sarcoma of Left Humerus Metadiaphysis

- 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

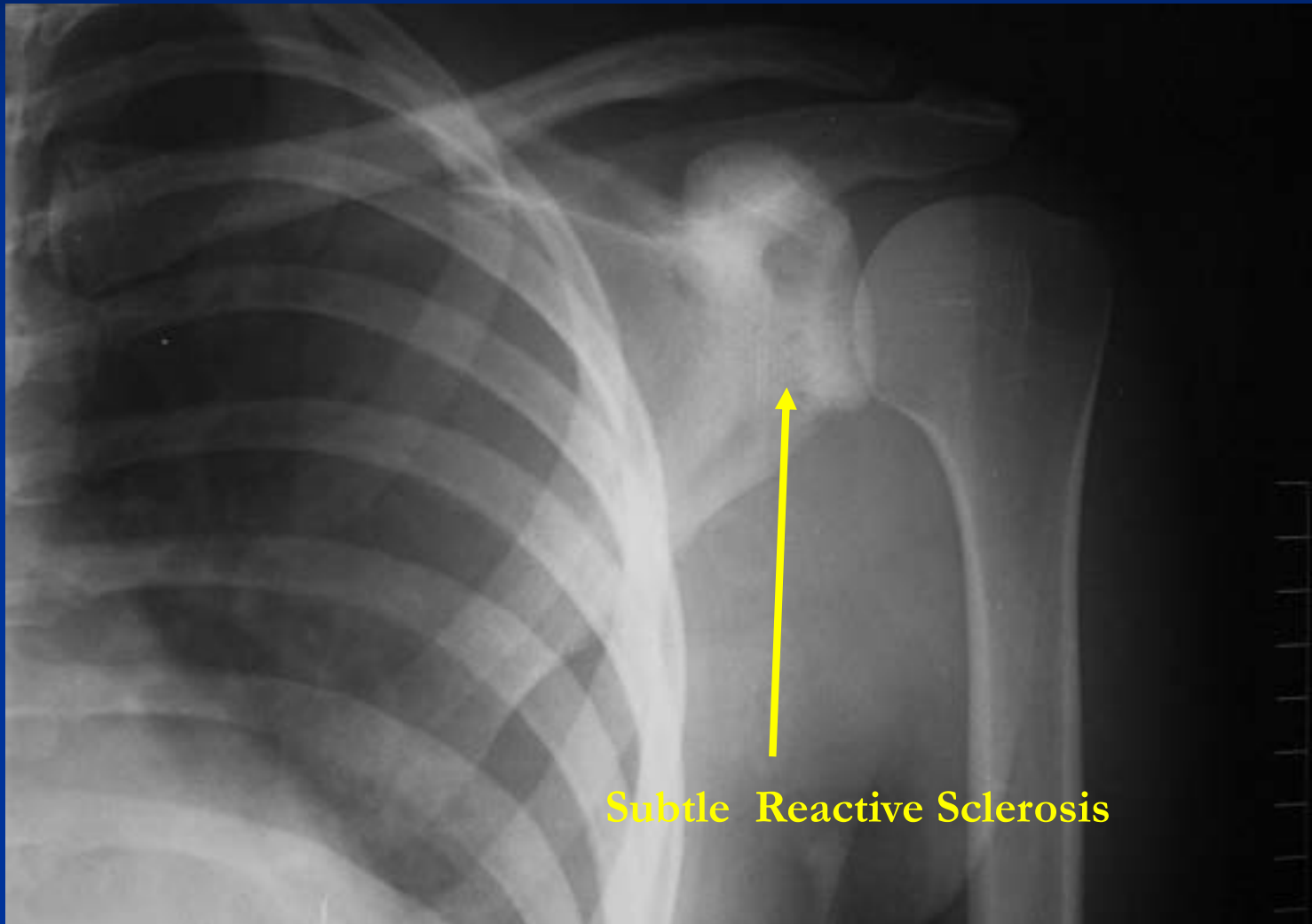


Bone Scan: Ewing Sarcoma of Left Humerus demonstrates Intense Uptake



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

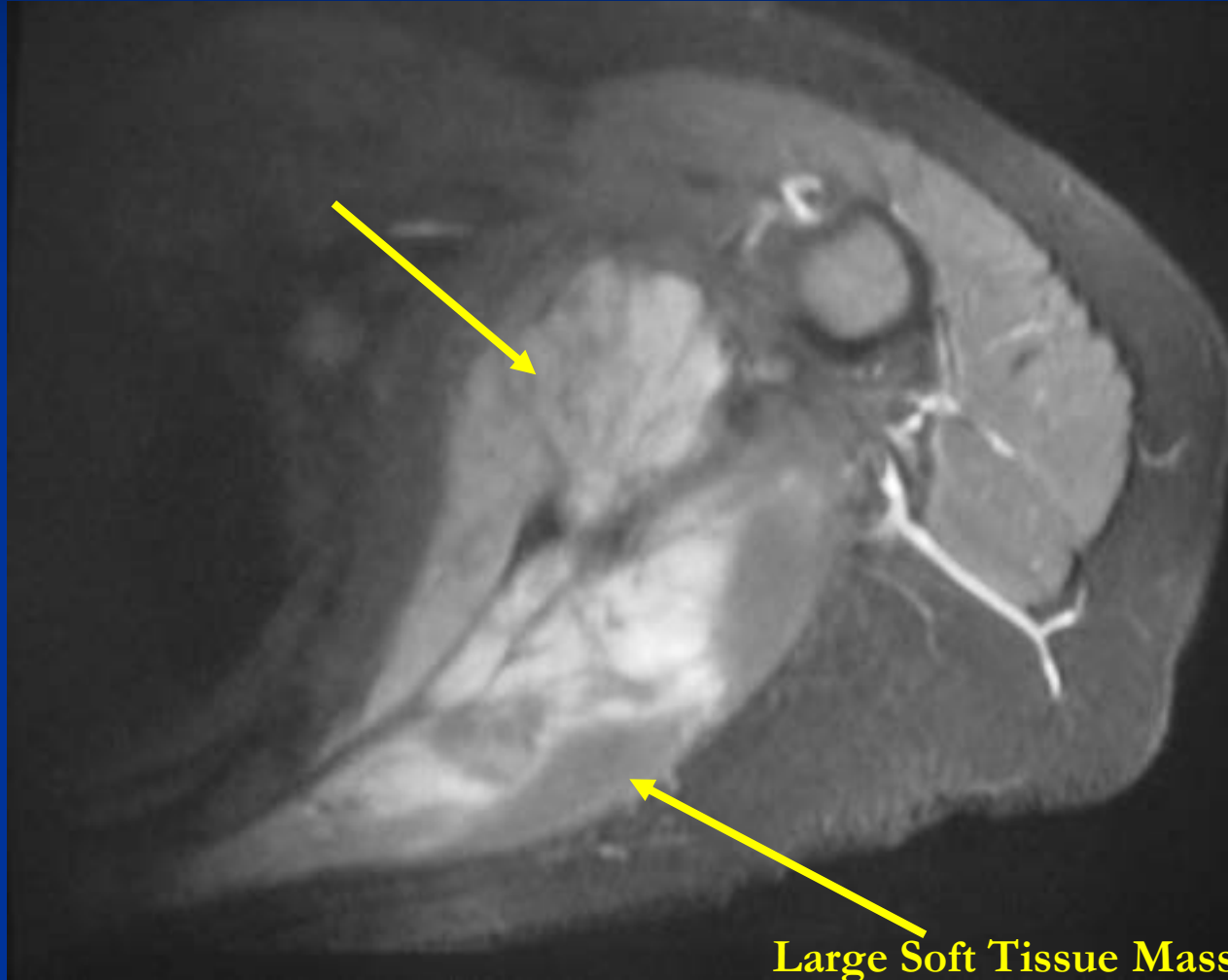


Subtle Reactive Sclerosis



MRI: Ewing Sarcoma of Scapula

There is a large soft tissue component surrounding the scapula



Large Soft Tissue Mass

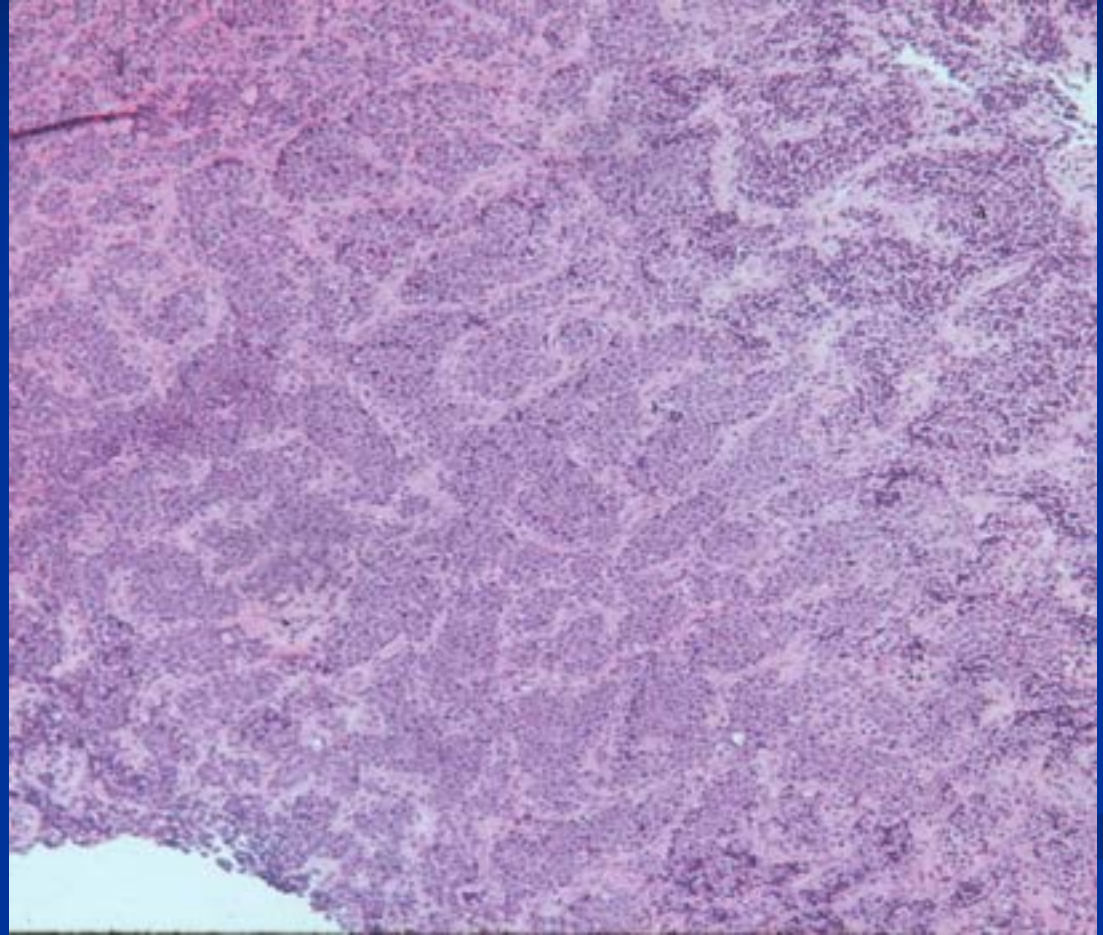


Microscopic Pathology

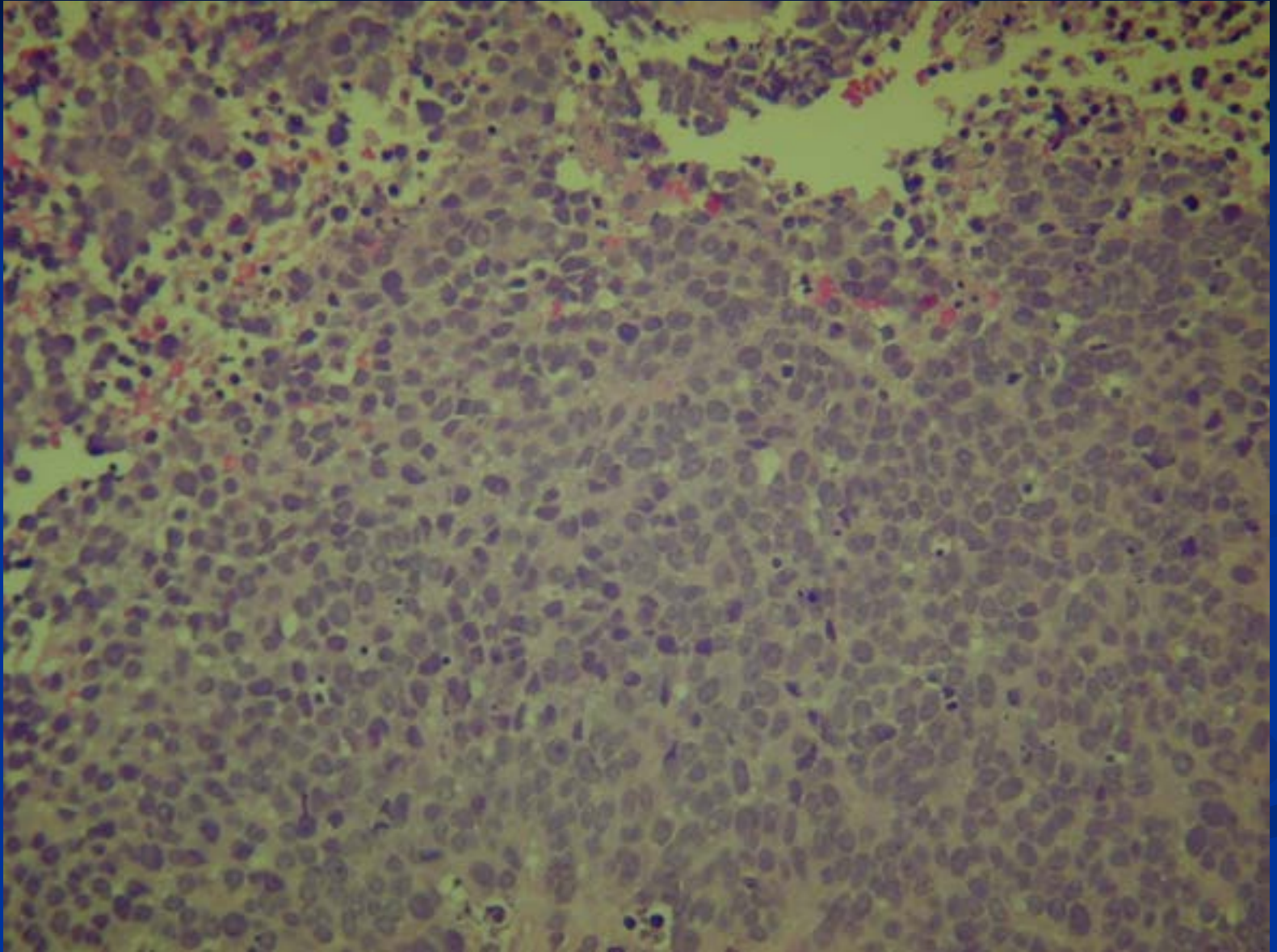
- Undifferentiated, small round, blue cells rich in glycogen
- Uniform cells with scanty pale cytoplasm and indistinct cell borders
- No Matrix
- Virtually no cytoplasm
- Cells are similar in appearance
- **Chromosomal Translocation t(11;22)(q24;q12)**
- PAS positive (glycogen positive); Reticulin stain 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

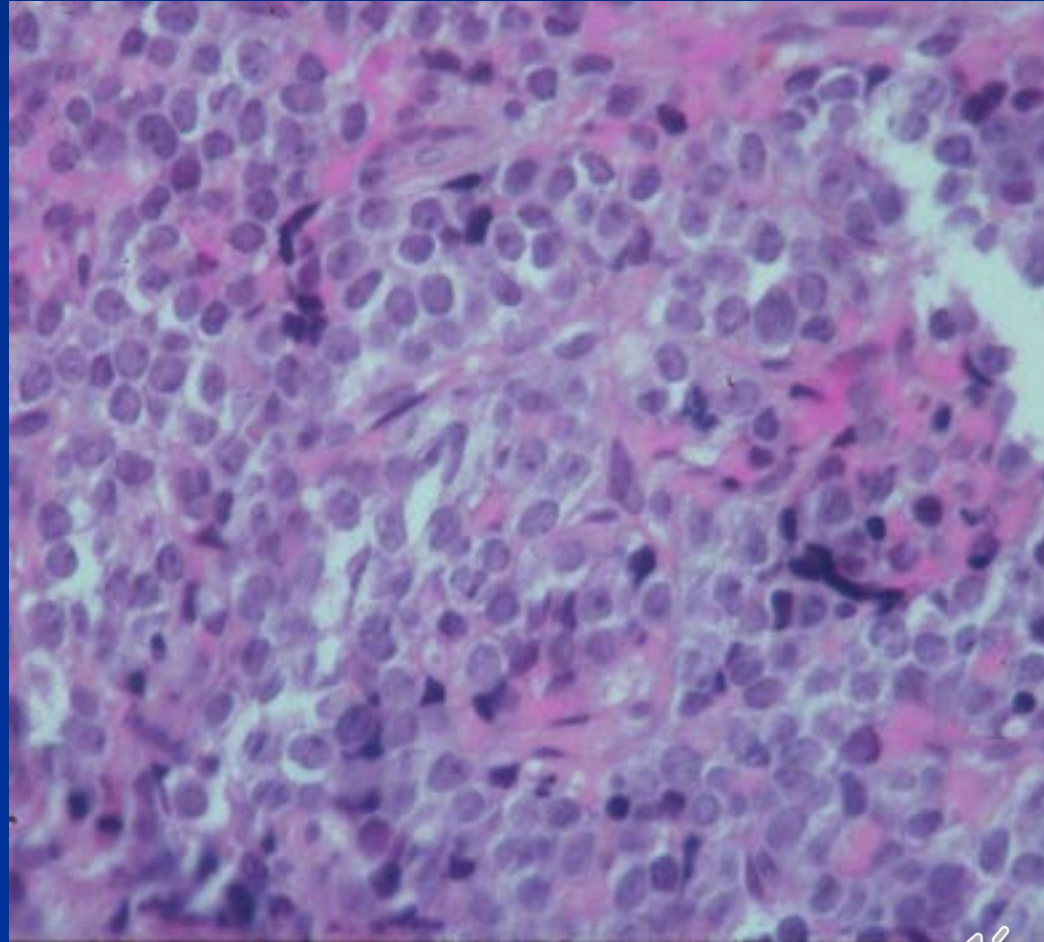


Microscopic Pathology: Ewing Sarcoma

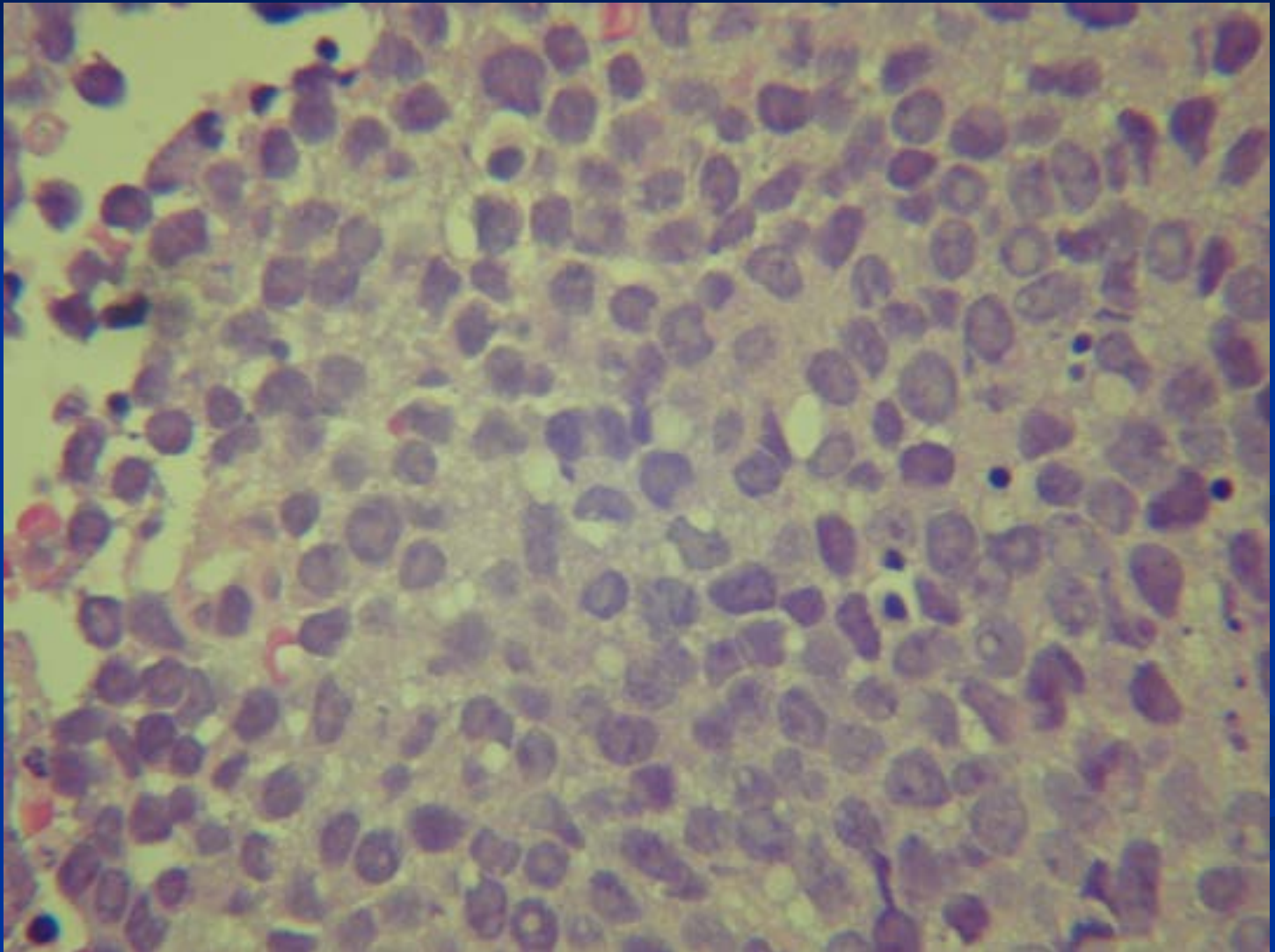


Microscopic Pathology: Ewing Sarcoma

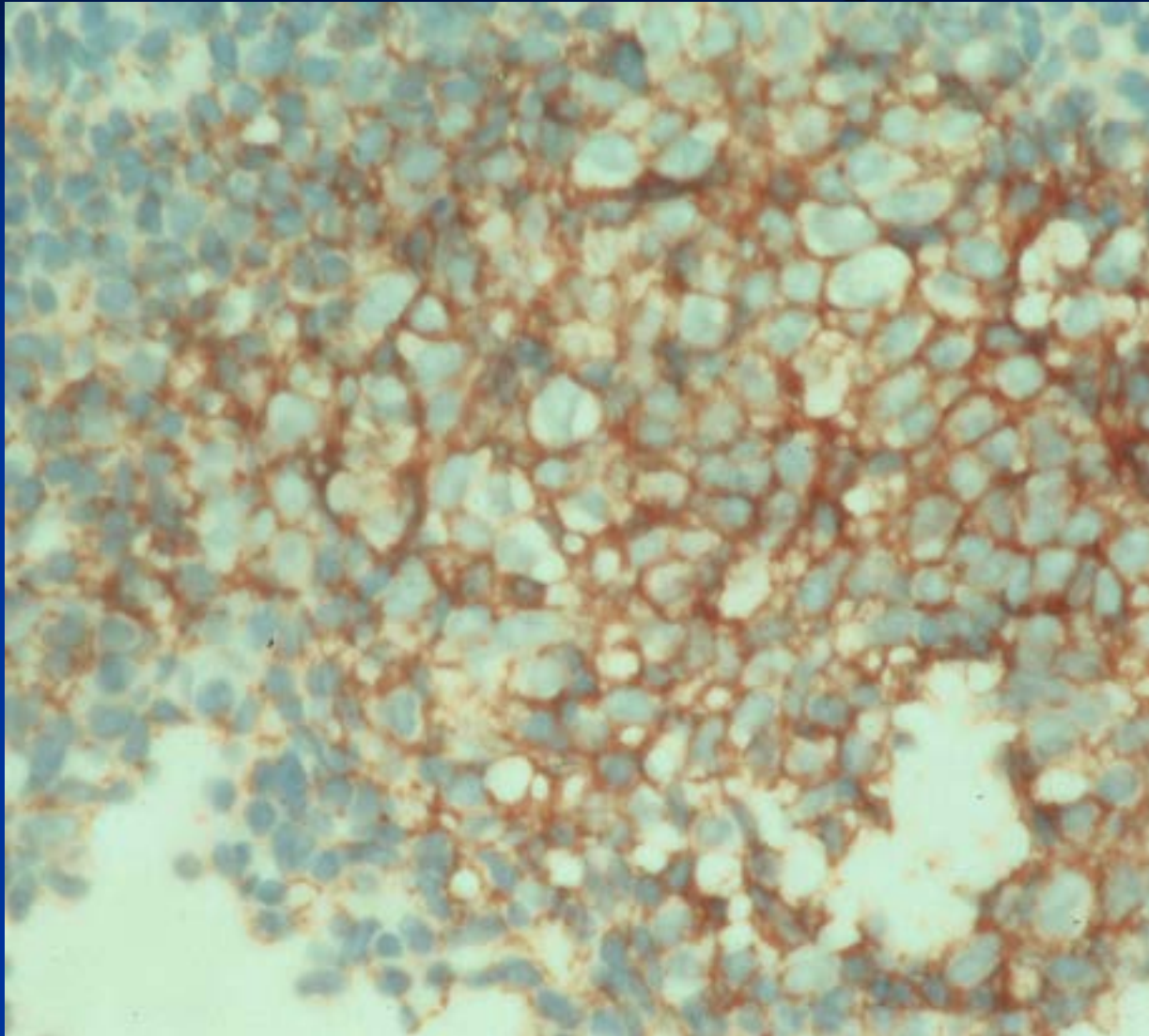
- Uniform small round blue cells
- Few mitoses
- Large nuclei and virtually no cytoplasm
- No matrix
- Pink staining filaments



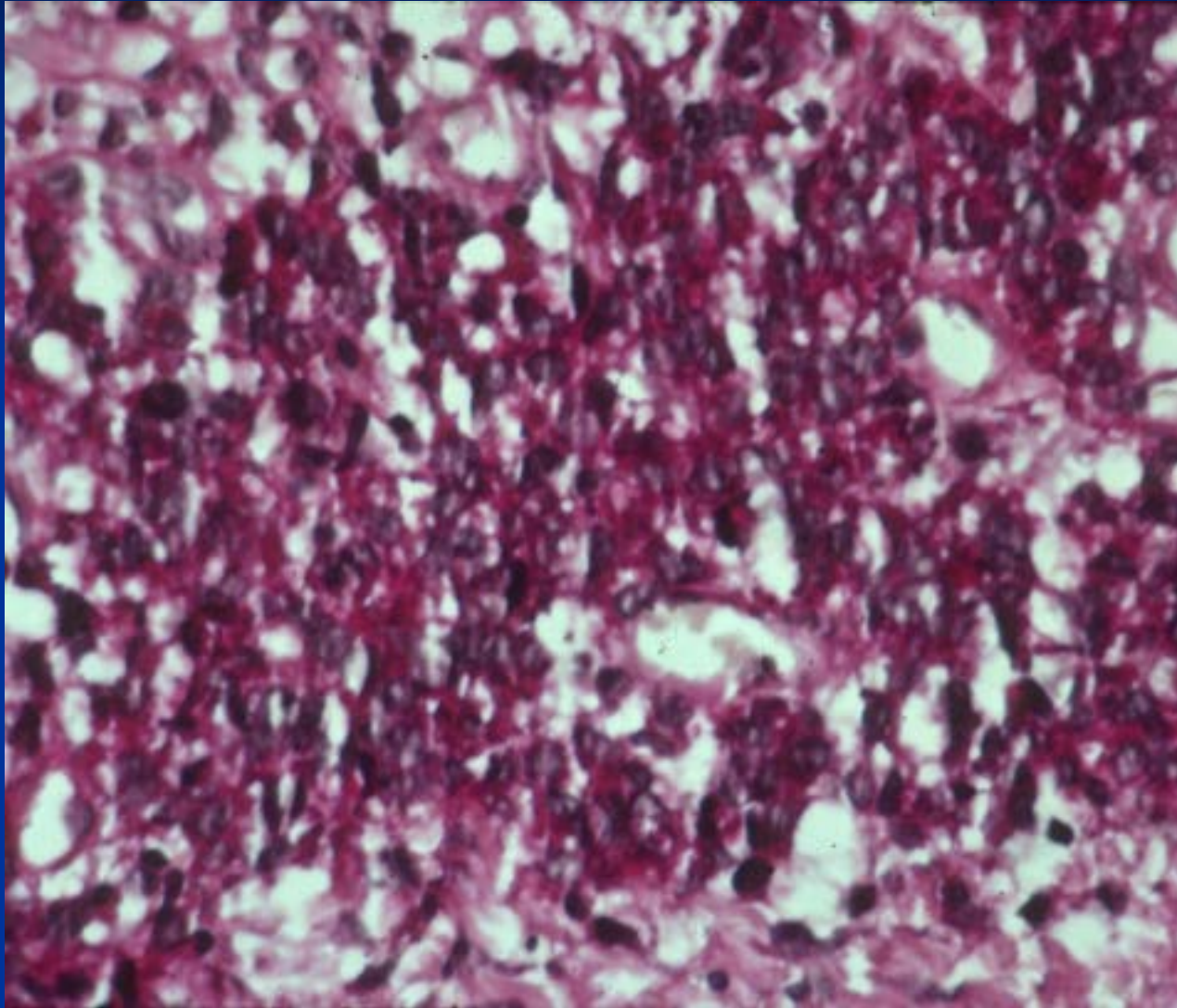
Microscopic Pathology: Ewing Sarcoma



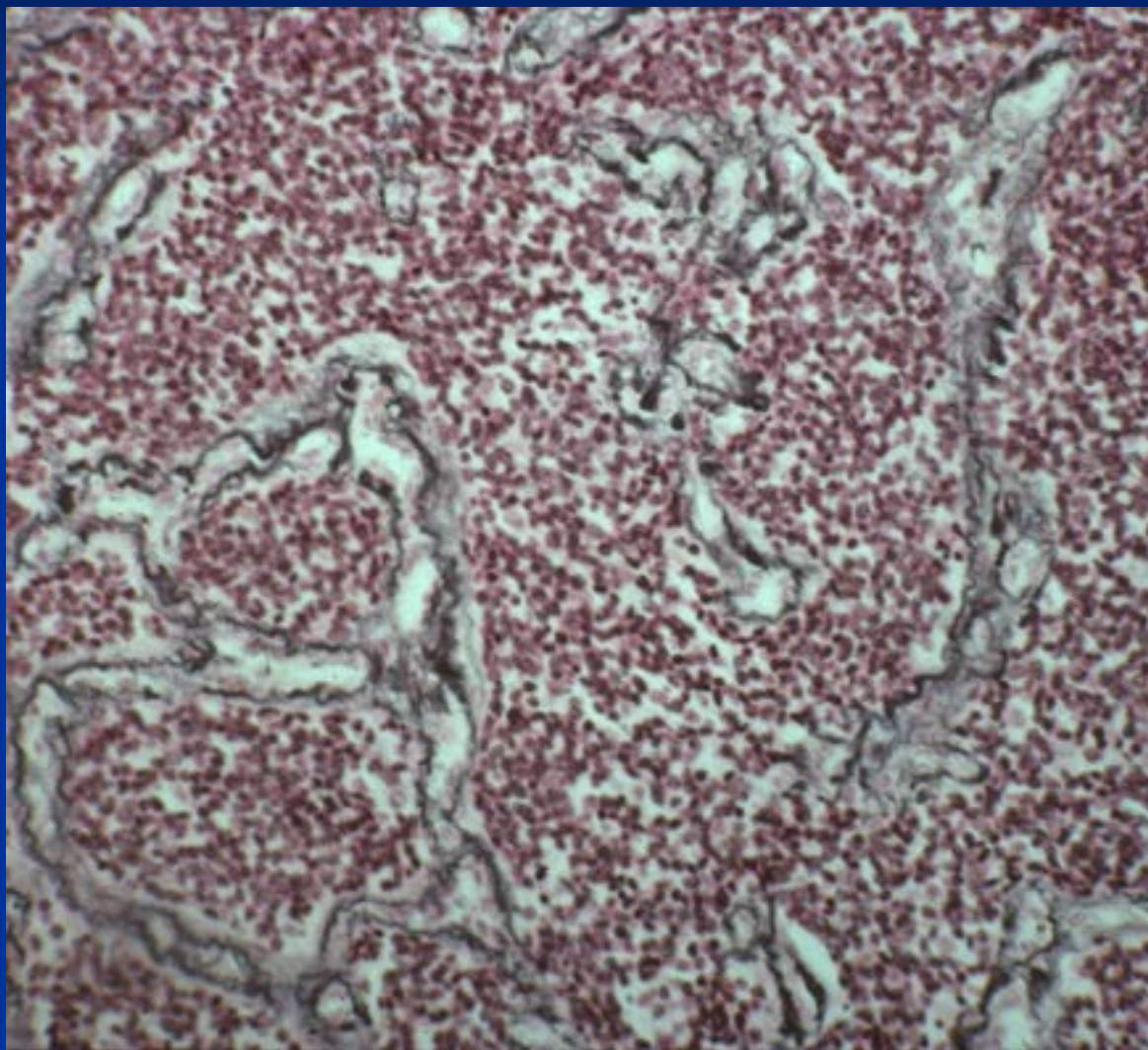
Ewing Sarcoma: CD 99 Identifies MIC2 Overexpression



Ewing Sarcoma: PAS Positive Glycogen Positivity

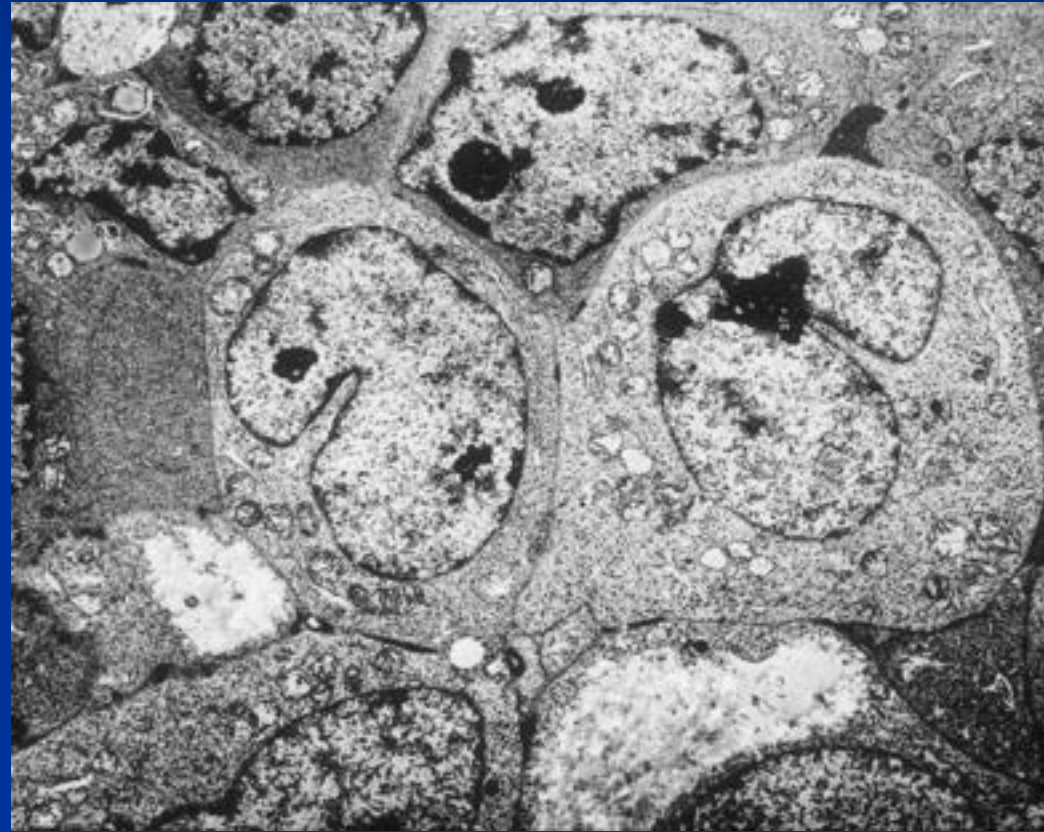


Ewing Sarcoma: Reticulin Poor



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 extraskkeletal 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



**Permeative Lesion with
Reactive Sclerosis**



Radiographic Presentation: Primary Lymphoma of Bone

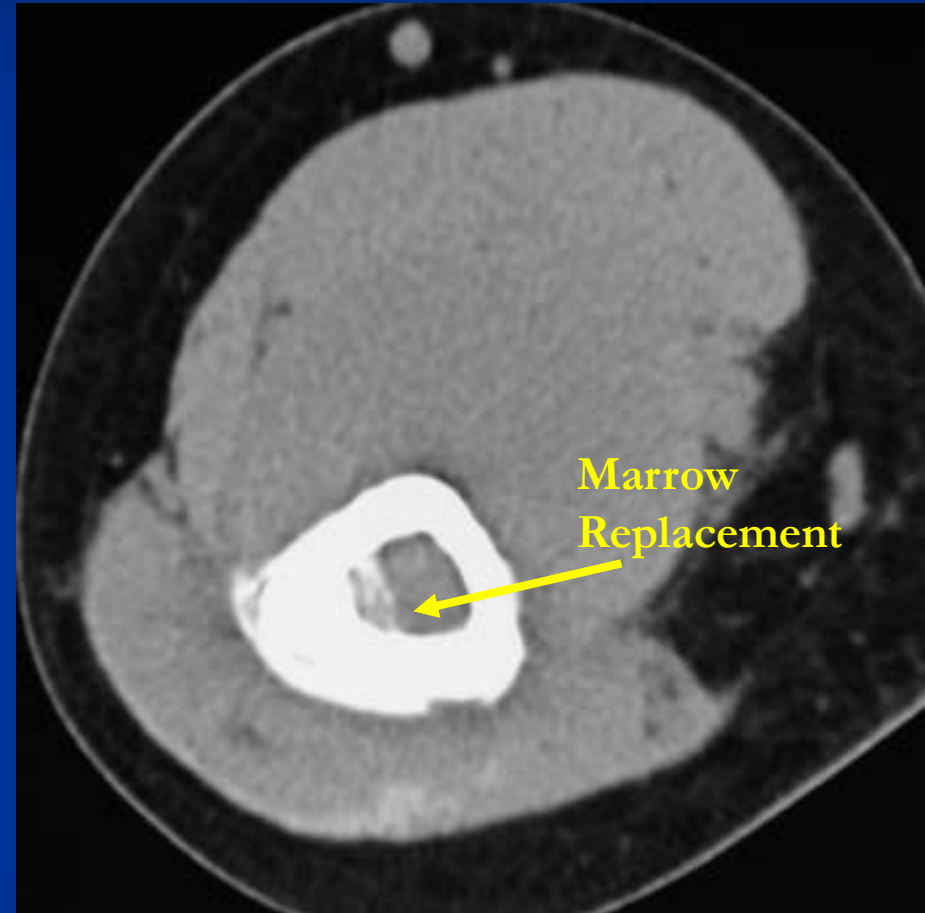
- 25% involve flat bones (pelvis, sacrum, ribs)
- Mixed lysis/sclerosis in 28%
- Aggressive or nonaggressive PR common

Permeative Lesion



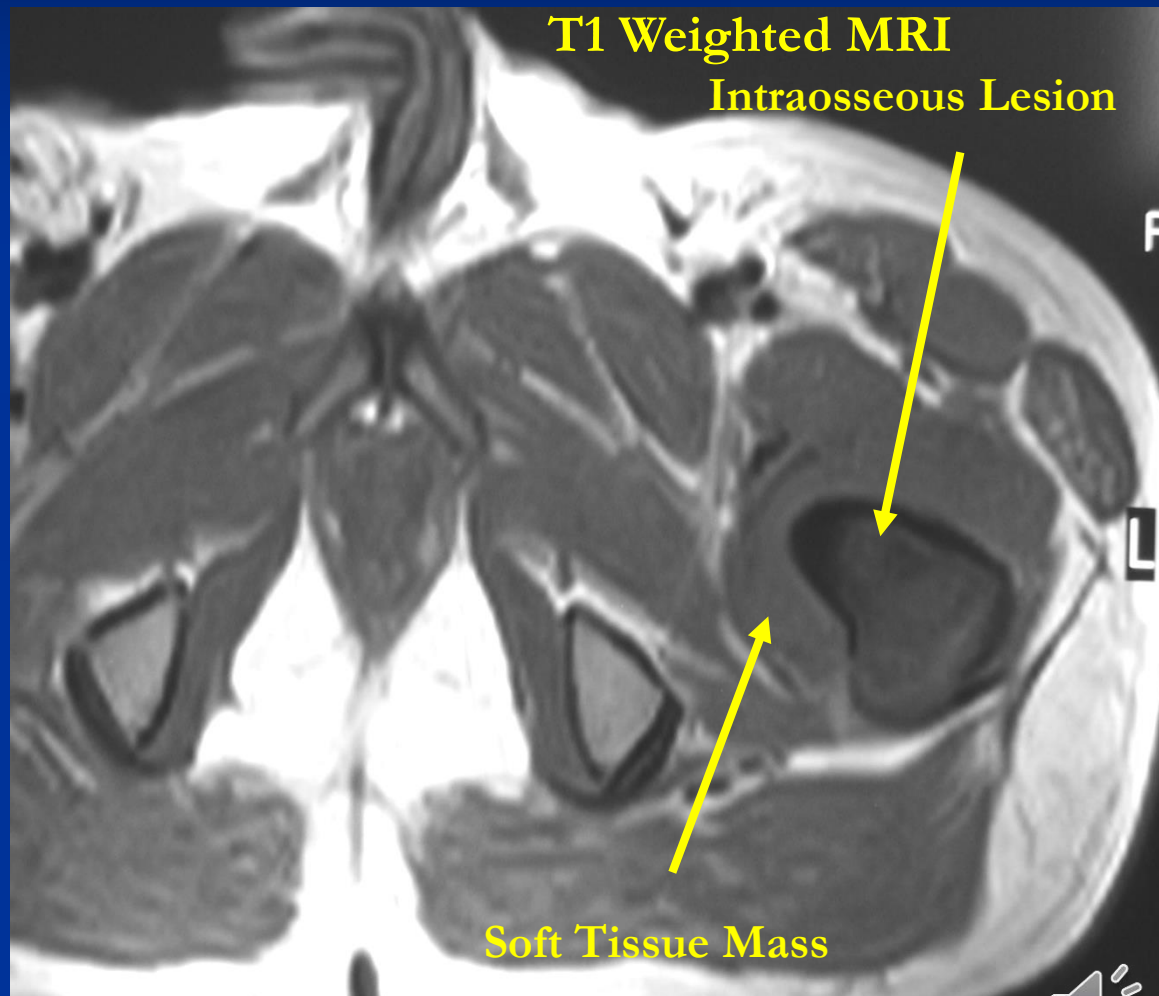
Radiographic Presentation: Primary Lymphoma of Bone

- 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%

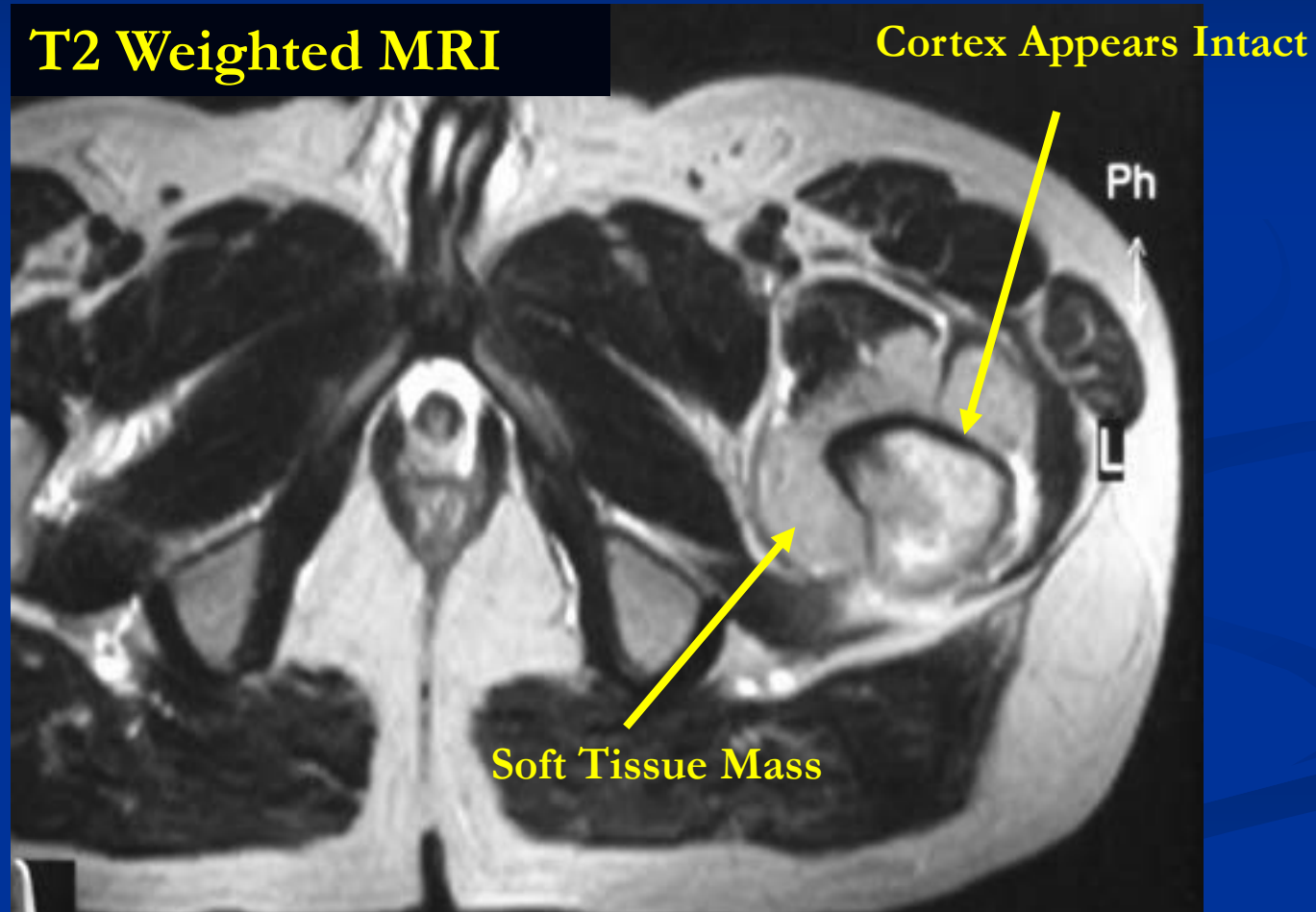


Radiographic Presentation: Primary Lymphoma of Bone

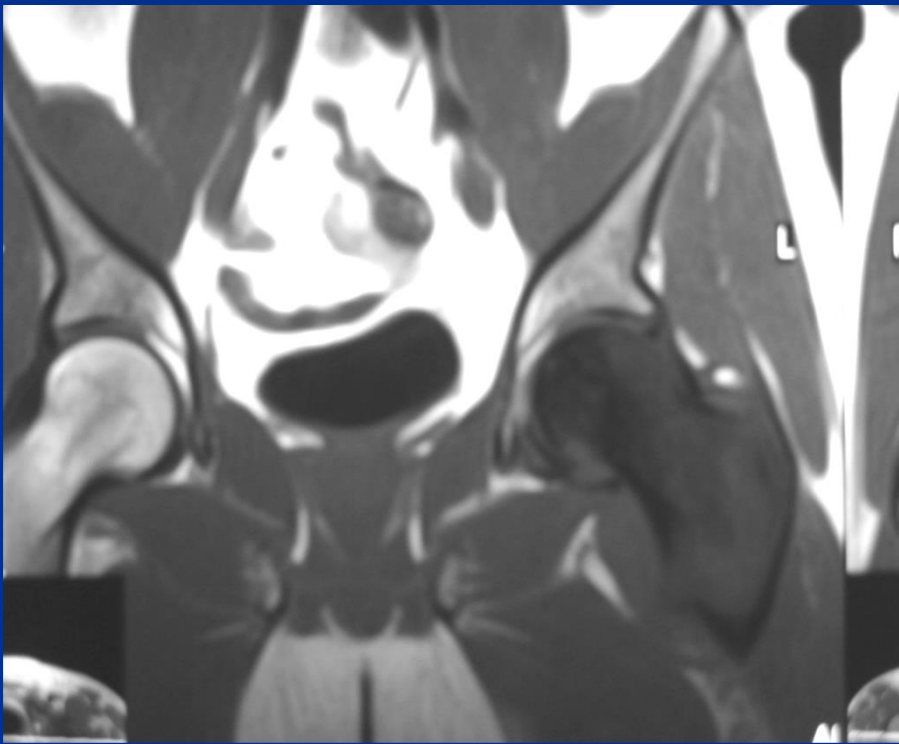
- Variable SI MR
 - Intermediate on T1
 - High on T2
- ST mass common (permeation of tumor cells through small vascular channels in the cortical bone without frank cortical breakthrough (also seen with Ewing/PNET))



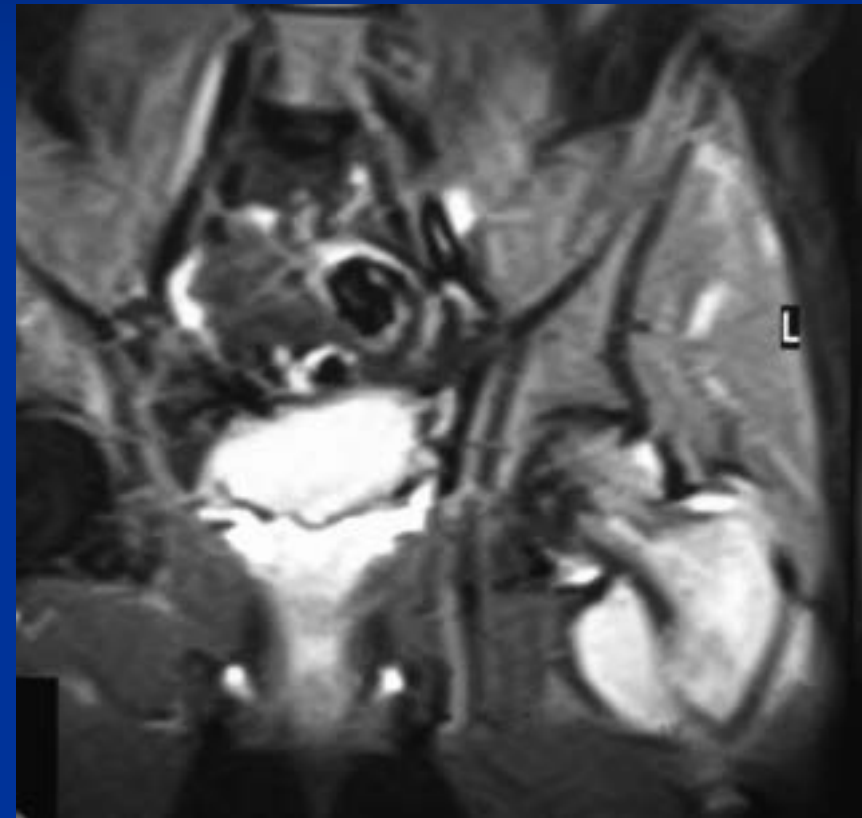
Radiographic Presentation: Primary Lymphoma of Bone



MRI: Primary Lymphoma of Bone



T1 Weighted MRI



T2 Weighted MRI

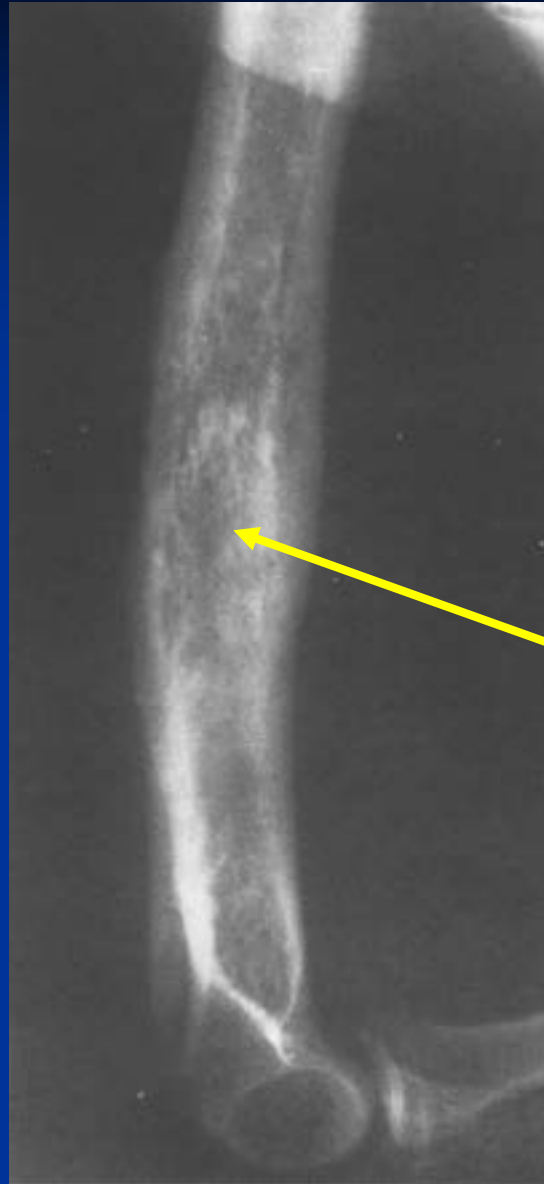


X-ray: Primary Lymphoma of Femur

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



X-ray: Primary Lymphoma of Distal Humerus



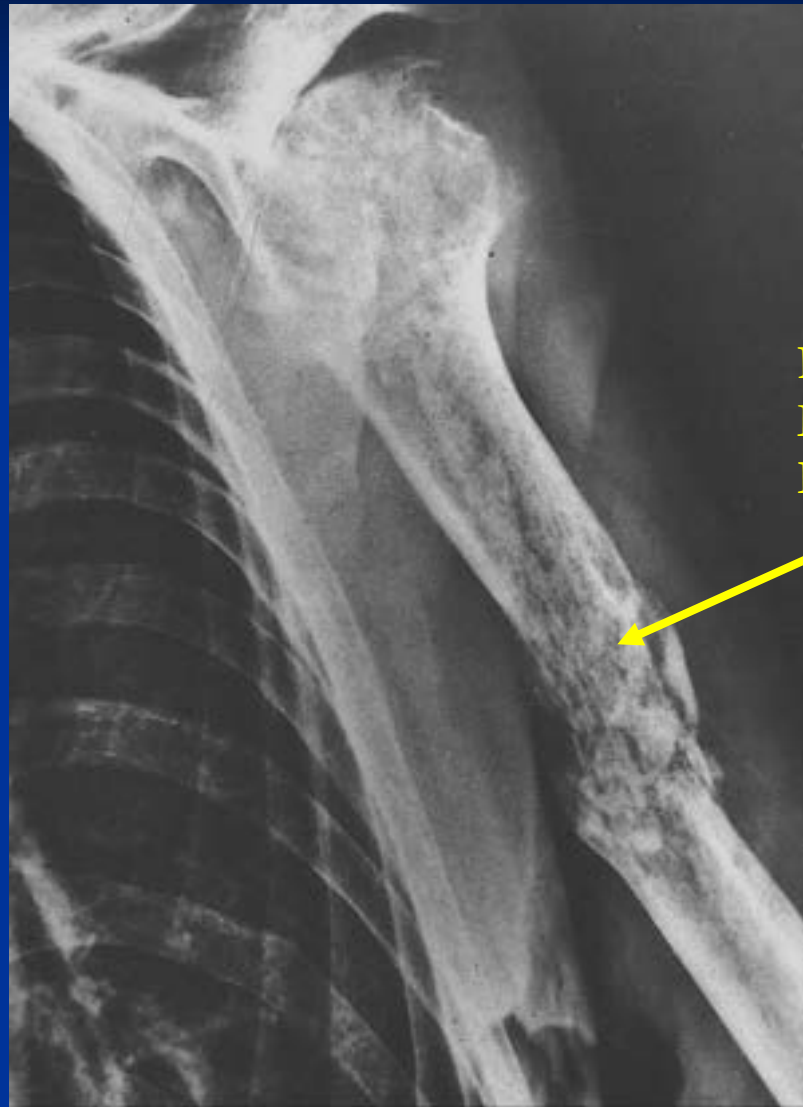
Permeative Lesion



X-ray: Primary Lymphoma of Tibia



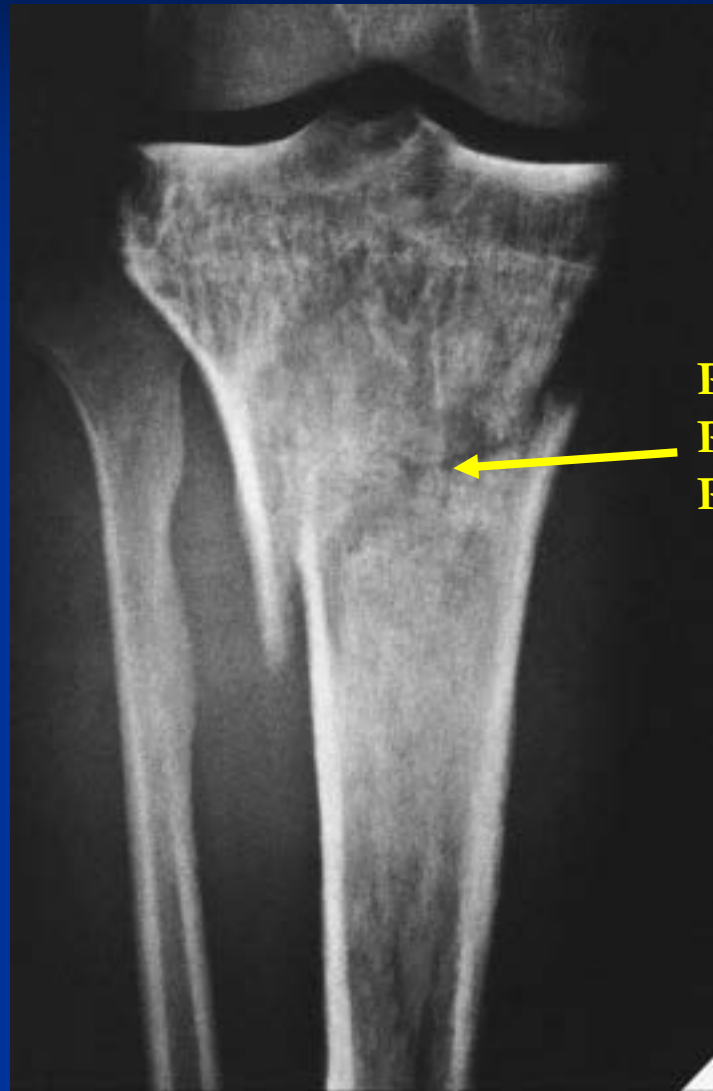
X-ray: Primary Lymphoma of Humerus



Permeative/Moth-eaten
Lesion with Pathologic
Fracture



X-Ray: Primary Lymphoma of Proximal Tibia



Permeative Lesion of
Proximal Tibia with
Pathological Fracture

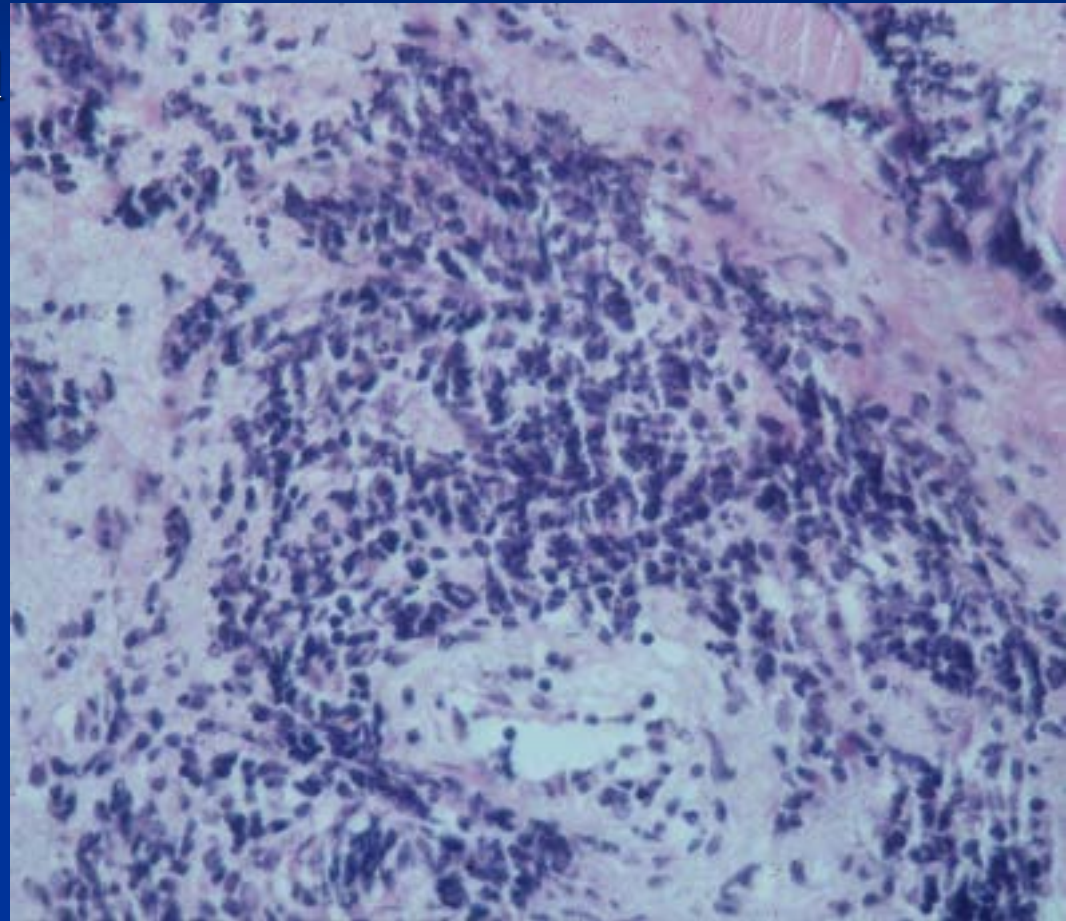


Microscopic Pathology

- 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
 - Prominent 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

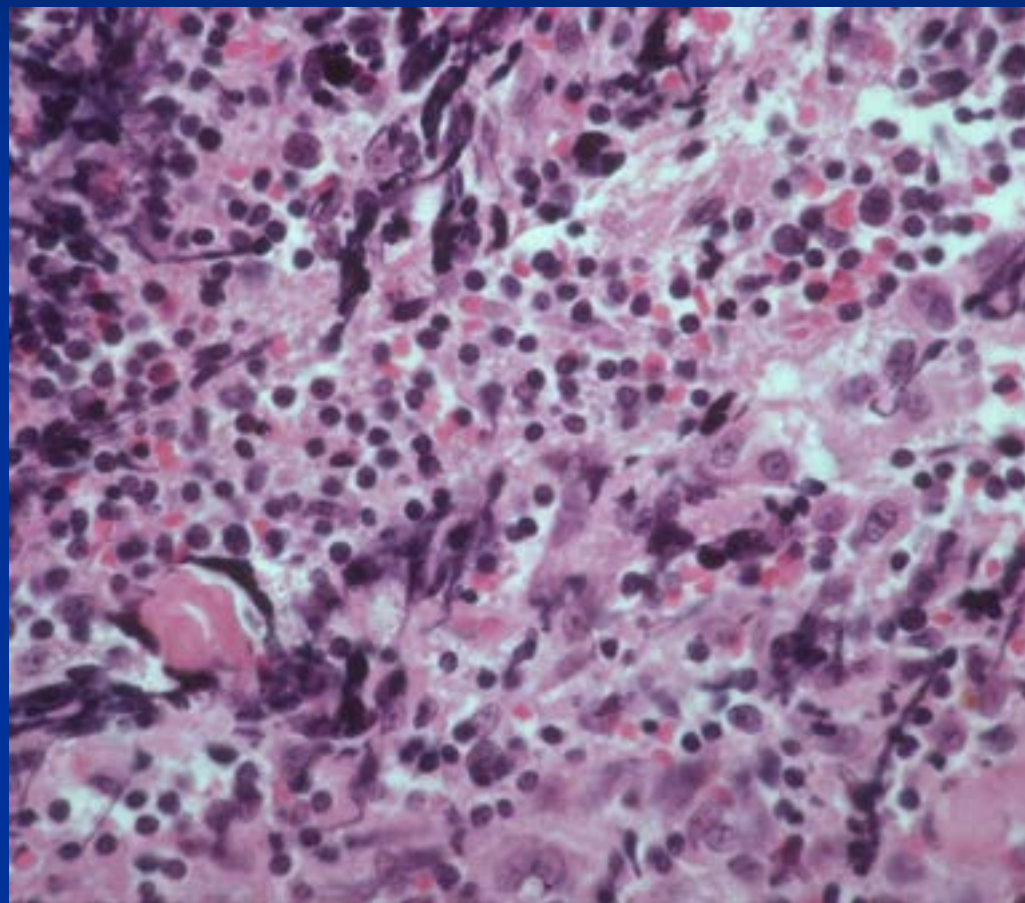
Microscopic Pathology: Lymphoma

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



Microscopic Pathology: Lymphoma

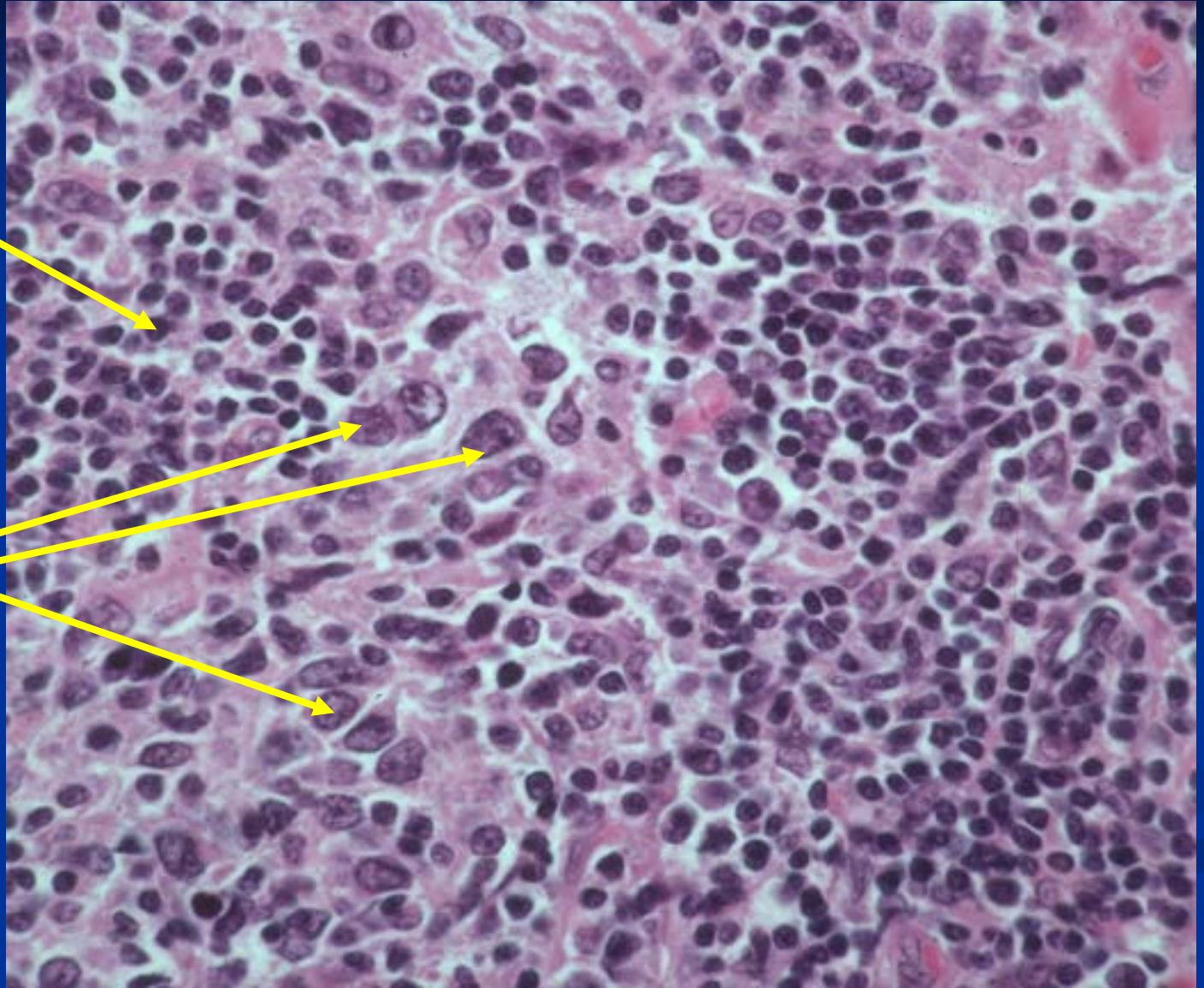
- Mixture of small round blue cells of different sizes and shapes
- No Matrix production
- Large B-Cells mixed with reactive inflammatory infiltrate leads to different cell types



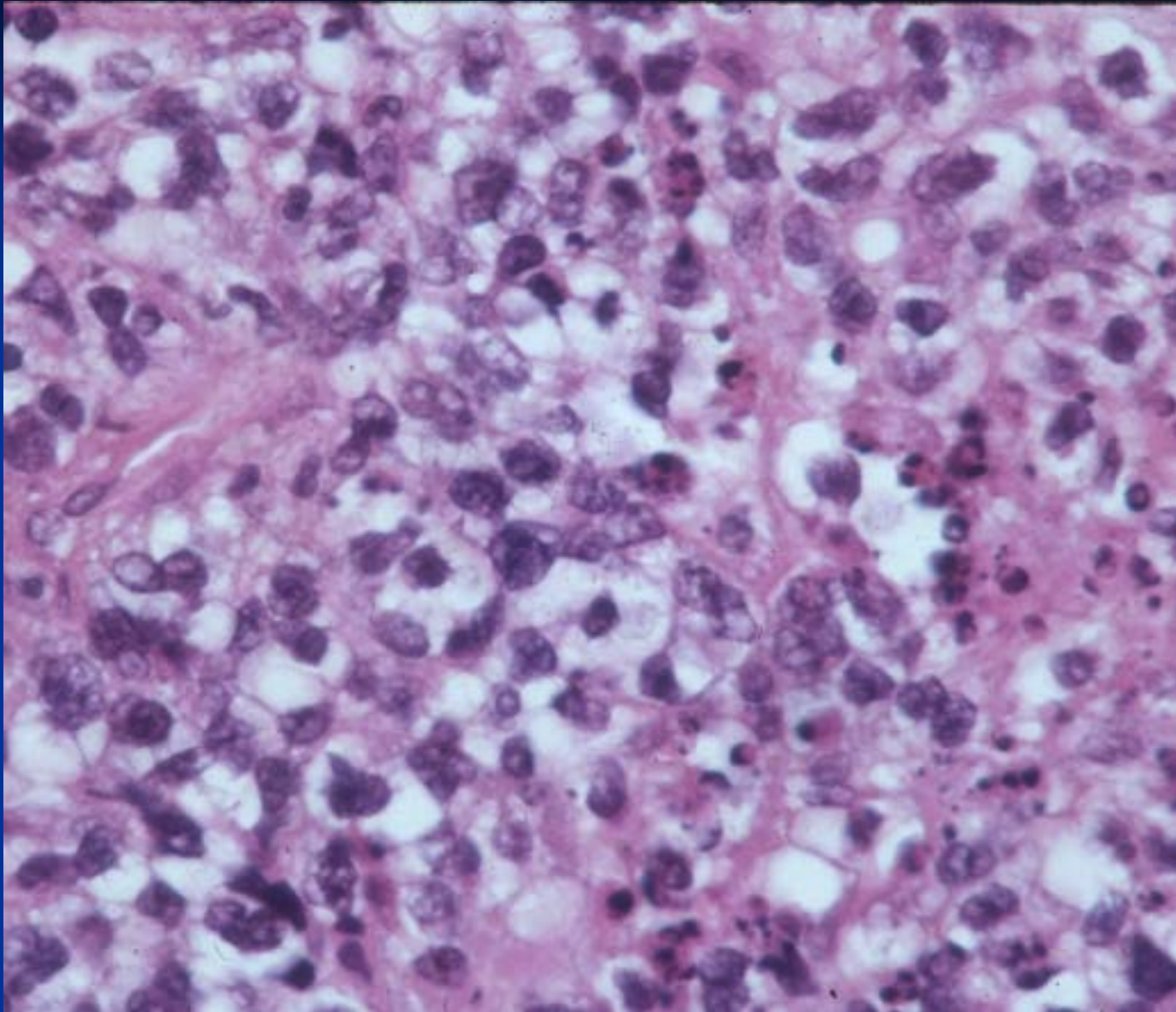
Microscopic Pathology: Lymphoma

Reactive
Inflammatory
Infiltrate of
Plasma Cells and
Lymphocytes

Large
Malignant
B-Cells



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

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

Prevalence:

- Most common primary neoplasm of bone
- Slight male predominance

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%)

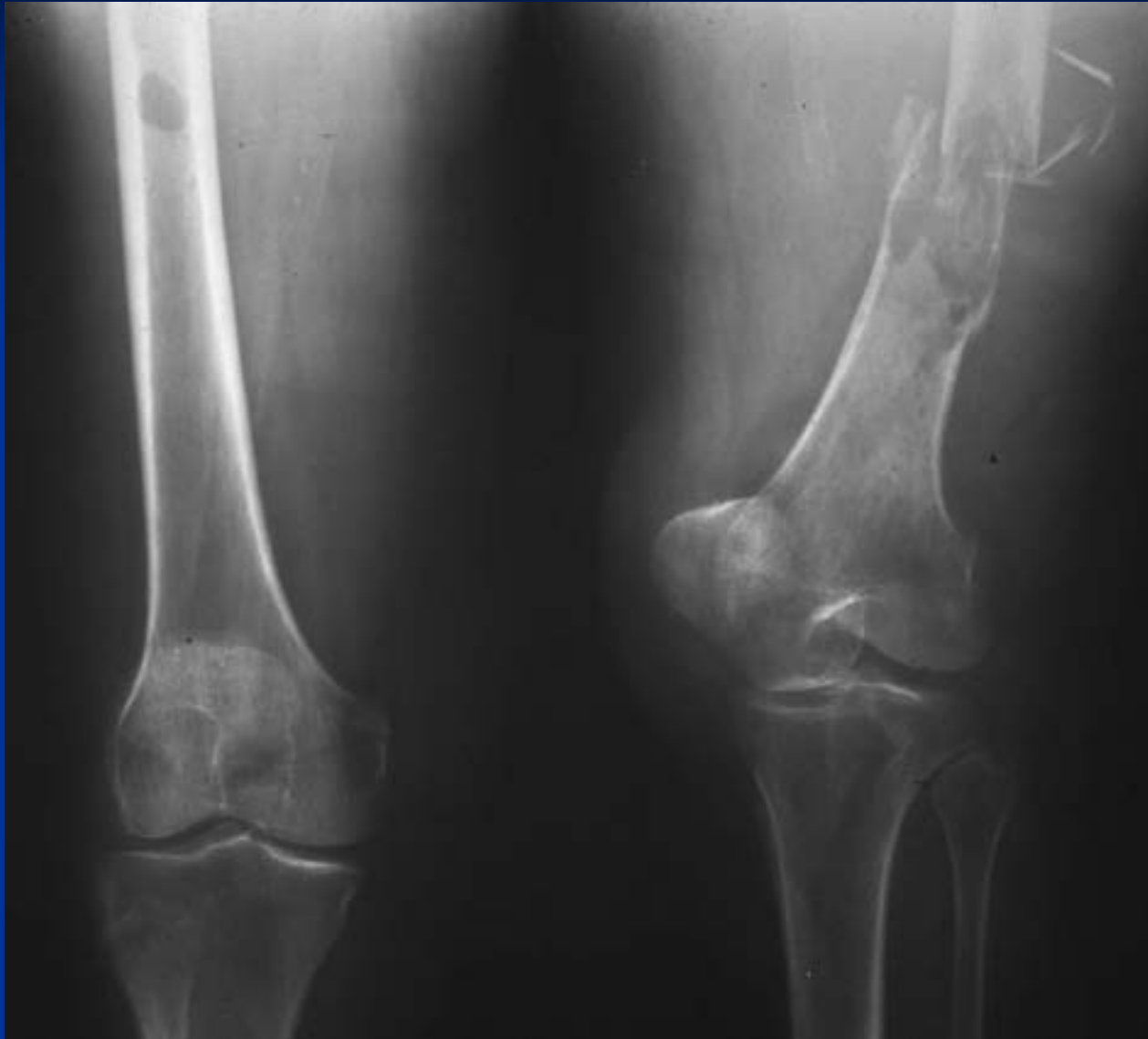
Myeloma

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

Myeloma



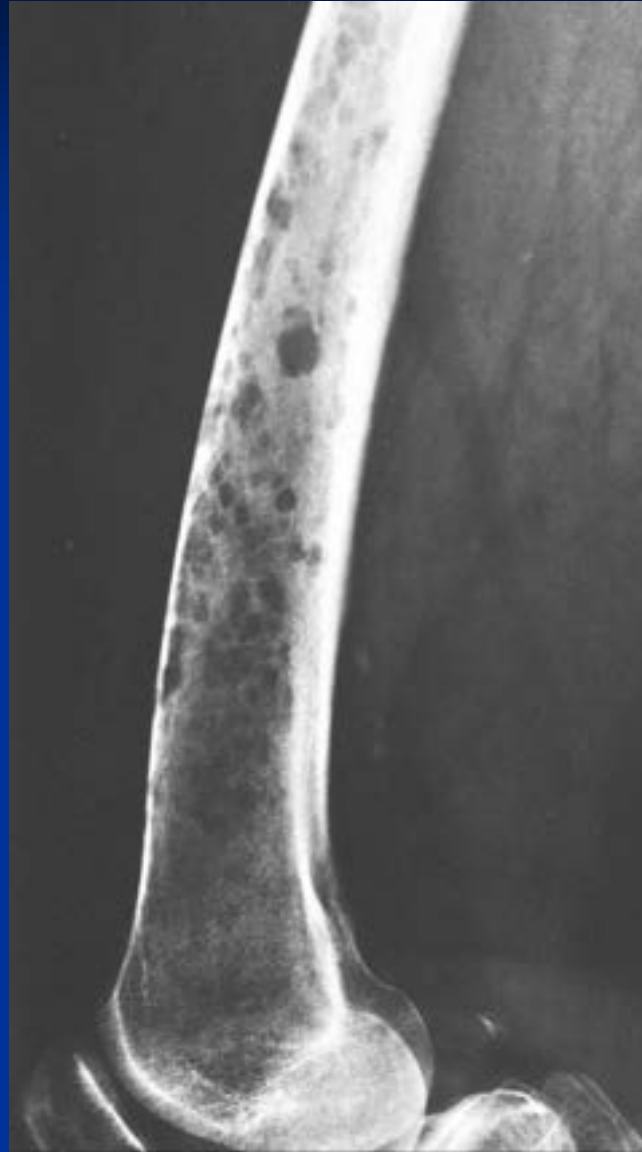
Myeloma



Myeloma



Myeloma



Myeloma



Myeloma



Osteosclerotic Myeloma



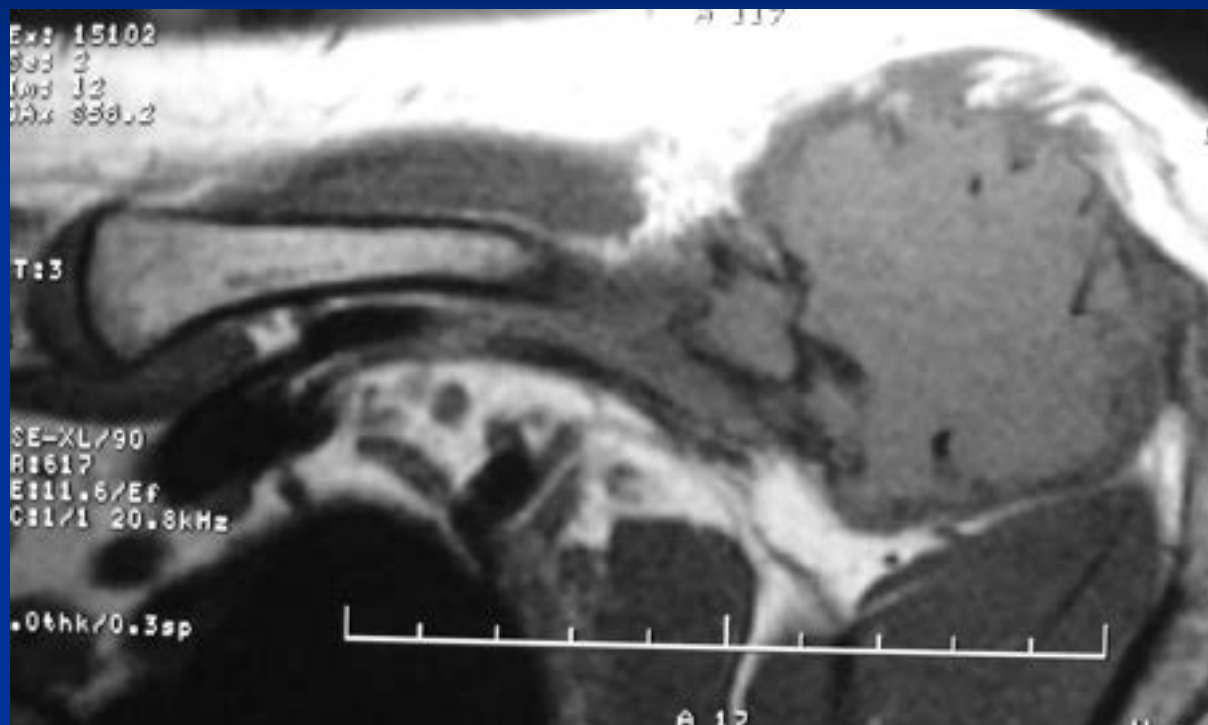
Osteosclerotic Myeloma



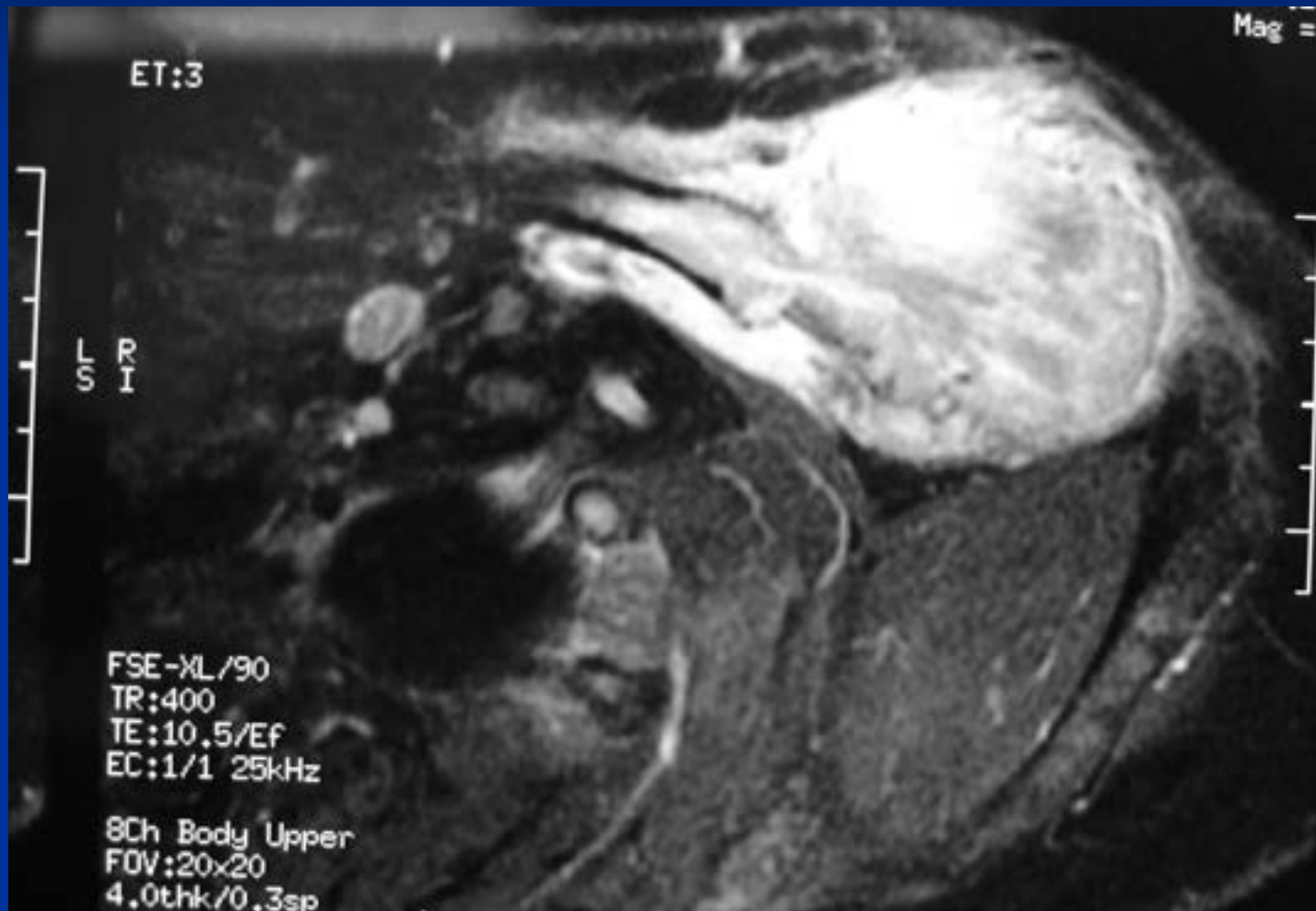
Osteosclerotic Myeloma



Plasmacytoma

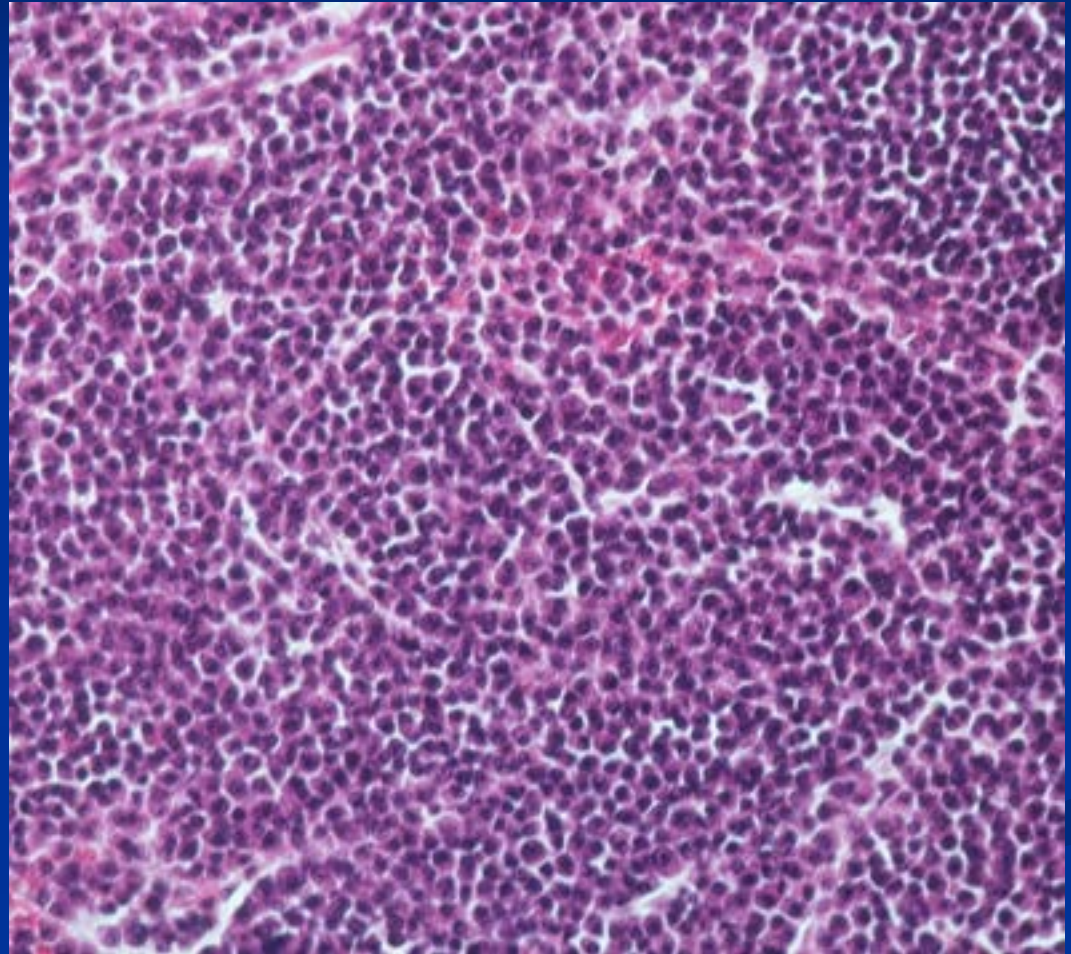


Plasmacytoma



Microscopic Pathology: Myeloma

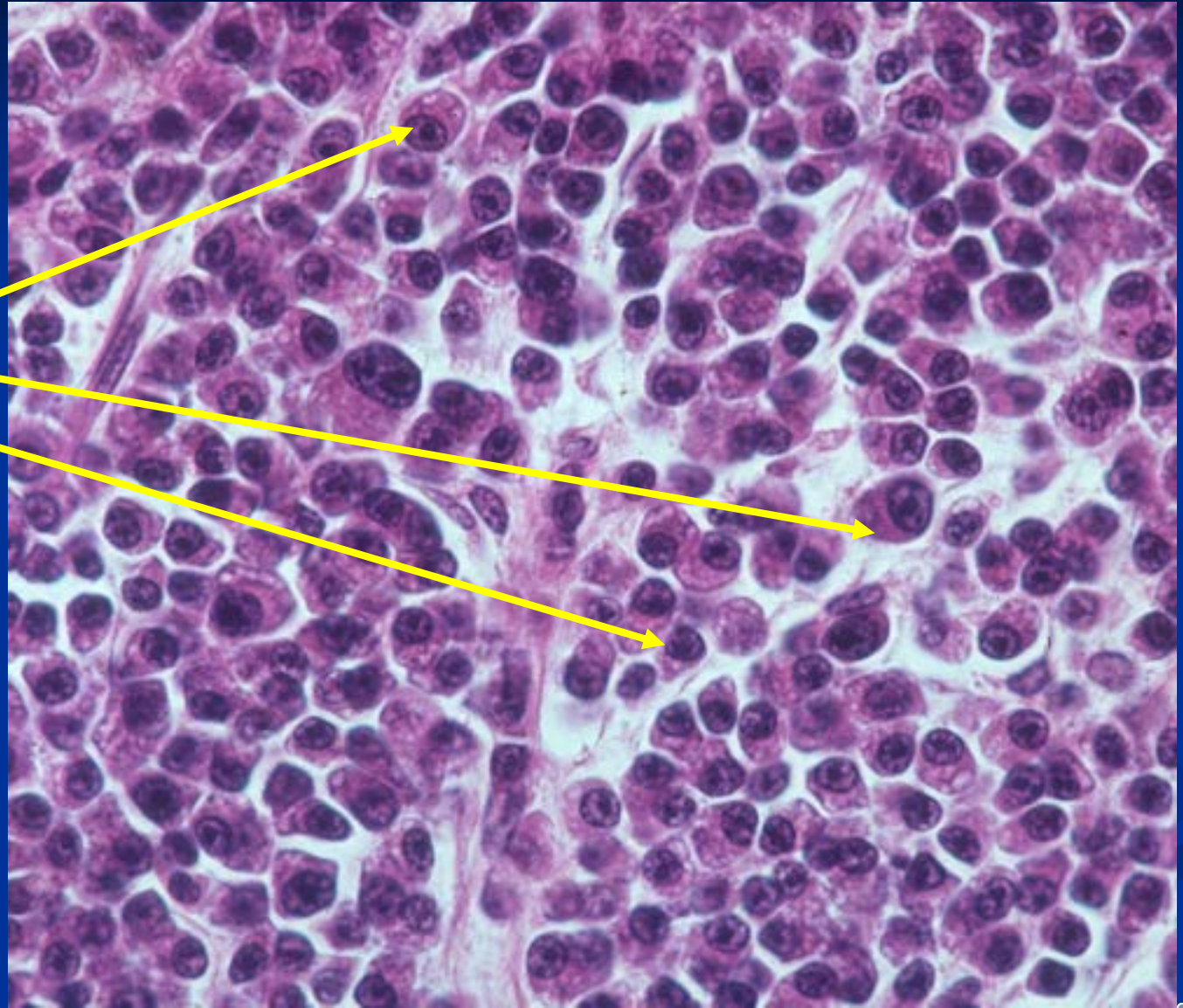
- Uniform small round blue cells
- No matrix
- Plasma cells with eccentric clock face nucleus and perinuclear halo
- Sheets of cohesive cells similar size and shape



Microscopic Pathology: Myeloma

Eccentric
Nuclei with
Perinuclear
Halo

Clockface
Nuclei



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!

www.TumorSurgery.org