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
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

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

Wittig Orthopedic Oncology
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
- Granulommatous 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 (coli 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

Permeative Bone Destruction
Soft Tissue Mass
X-ray/MRI: Ewing Sarcoma of Diaphysis of Left Femur

- Permeative Tumor
- Large Soft Tissue Mass
- Soft Tissue Mass
- No Mineralization
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 X-ray
- 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*
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

- Metadiaphyseal Origin
- Large Soft Tissue Mass
- Extensive Permeation of Marrow
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

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))

T1 Weighted MRI Intraosseous Lesion

Soft Tissue Mass
Radiographic Presentation: Primary Lymphoma of Bone

T2 Weighted MRI

Cortex Appears Intact

Soft Tissue Mass
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

Permeative

Motheaten Lesion
X-ray: Primary Lymphoma of Humerus

Permeative/Motheaten 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
  • 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

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

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
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!

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