Pathology of Bone & Joints

Extracted from chapters in Rubin’s Pathology & Robbin’s & Cotran Textbook of Pathology
The Normal Skeleton

- Essential for mechanical support and mineral homeostasis
- Houses hemopoietic tissue
- Determines body size & shape

206 bones of varying size and shape

<table>
<thead>
<tr>
<th>Organic</th>
<th>Inorganic</th>
</tr>
</thead>
<tbody>
<tr>
<td>35%</td>
<td>65%</td>
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</tbody>
</table>
The Normal Skeleton

*Inorganic Matrix*

- Calcium hydroxyapatite
  \[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2\]
  - Mineral homeostasis
    - 99% of calcium stores
    - 85% of phosphate stores
    - 65% of sodium and magnesium stores
  - Bone strength
Organic Components of Bone

• **Bone Cells**
  – Osteoprogenitor cells → Osteoblasts → Osteocytes
  – Hematopoietic progenitor cells → Osteoclastic precursors → Osteoclasts

• **Bone Matrix**
  – Type 1 Collagen (29%)
  – Non-collagenous proteins (3%)
  – Serum
Organic Component: Cells

Pluripotent Mesenchymal Stem Cell

Growth factors: BMP

CBFA1 (Core Binding Factor A1/RUNX2)
Organic Matrix: Growth Factors and Cytokines

**GROWTH FACTORS AND CYTOKINES**

- TGF-β
- IGF-I, II
- PDGF
- FGF
- PGE₂

Mesenchymal Stem Cell → Pre-Osteoblast → Osteoblast

**CBFA1/RUNX2** – ↑Osteoblast-specific gene expression
Organic Matrix

Osteoblasts

Hormone receptors:
- Estrogen
- PTH
- Thyroid
- Vit D
- Glucocorticoids

Proliferation

Differentiation of osteoblasts
Organic Matrix

**Osteoblasts**

- Synthesize proteins
- Initiate mineralization
- Bind hormones
- Make bone
- Regulate osteoclasts

**Osteoid (matrix)**

12-15 days

**Bone (mineralized matrix)**
Osteocytes
Organic Matrix

Osteoclasts

- Derived from HEMATOPOETIC progenitor
- Intimately related to bone surface
- Releases protelytic enzymes
- Role in bone resorption

Howship lacunae
Osteoclasts have a ruffled and a smooth surface
Organic Components of Bone

• Bone Cells

• Bone Matrix
  – Type 1 Collagen (29%) - 90% by weight of organic component
  – Non-collagenous proteins (3%)
  – Minerals 60%
  – Water 10%
Types of Bone

• Osteoid (unmineralized matrix)
• Woven bone
• Lamellar bone
  – Cortical
  – Cancellous
Types of Bone

Woven bone

First laid down in fetal skeleton and disease states – New Bone
Forms quickly
Resists force from all directions

Woven bone in adults is always pathologic – e.g. fractures
Types of Bone - Lamellar

Cortical & Cancellous (trabecular)

- Mature bone
- Resists unidirectional force
- Facilitates weight bearing
Normal Cancellous Bone
Trabecular lamellar bone
Metabolic Bone Disease
The Normal Skeleton

*Modeling and Remodeling*

- Coordinated activity of osteoblasts and osteoclasts (*basic multicellular unit*)
- Bone formation and resorption tightly coupled
Regulation of Bone Modeling

• The key cell is the Osteoblast
  – Responds to stimulation from osteocytes
  – Responds to stimulation from blood borne factors
  – Stimulates development of osteoclasts
  – Activates osteoclasts
Bone – Multicellular Unit

Bone resorption and formation are controlled by: Systemic factors and local cytokines, growth factors, signal-transducing molecules in the bone matrix.
Receptor Activator of NF-KappaB Ligand (RANKL)

- Expressed on Osteoblasts
- Upregulated by PTHRP, vitamin D3, some malignancies
- Binds to RANK (TNF family) on Osteoclasts and precursors to activate them
- Function inhibited by Osteoprotegrin (TNF family): binds to RANKL acting as a decoy preventing RANK-RANKL interaction
Regulation of Osteoclast

PTH, IL-11, vitamin D3

**Osteoblasts** (& marrow stromal cells) paracrine molecular mechanisms

**Osteoclasts** (activation, proliferation, fusion, differentiation, survival)

M-CSF $\rightarrow$ ↑ Osteoclasts

OPG (decoy) blocks RANKL and checks stimulation of osteoclasts
The Normal Skeleton
Modeling and Remodeling

Modeling: Childhood and adolescence
Skeletal Growth
Osteoblastic Function Predominates
The Normal Skeleton

Modeling and Remodeling

Peak Bone Mass
Early adulthood
5-10% skeletal turn-over/year
The Normal Skeleton

*Modeling and Remodeling*

Resorption exceeds renewal in fourth decade
Progressive bone loss
Osteoporosis
Metabolic Bone Disease

Osteoporosis

- Diminished bone mass
- Localized or diffuse
- Primary or secondary
- Risk of fracture
- Severe disease of elderly
- Expensive to health care - > $ 14 BILLION/YR
GENETIC FACTORS

PHYSICAL ACTIVITY

PEAK BONE MASS

NUTRITION

MENOPAUSE
- Decreased serum estrogen
- Increased IL-1, IL-6, TNF levels
- Increased expression of RANK, RANKL
- Increased osteoclast activity

AGING
- Decreased replicative activity of osteoprogenitor cells
- Decreased synthetic activity of osteoblasts
- Decreased biologic activity of matrix-bound growth factors
- Reduced physical activity

OSTEOPOROSIS
Metabolic Bone Disease

Senile Osteoporosis
Metabolic Bone Disease

Post-Menopausal Osteoporosis
Complex Interplay of Factors That Regulate Bone Mass
Osteoporosis

Diffuse process involving all Bones

Normal Cortex

Osteoporosis
Resembles cancellous bone
Osteoporosis

-Thin bony trabeculae, Loss of apposition

Trabecular Bone

Cortical Bone

Widened Haversian canal
Secondary Osteoporosis

- Endocrine
  - Hyperparathyroidism
  - Hyperthyroidism, Diabetes, Addison’s disease, Pituitary tumors
- Neoplasia: Carcinomatosis, multiple myeloma, paraneoplastic disease
- Gastrointestinal: Malnutrition, hepatic insufficiency, vitamin D or C deficiency, malabsorption
- Drugs: Chemotherapy, corticosteroids, alcohol
- Immobilization
Regulation of Osteoclast

PTH, IL-11, vitamin D3

Pathogenesis

- ↑ PTH → Stimulation of osteoblasts (↑ RANKL) to activate osteoclasts
- ↑ Osteoclastic Activity → Massive bony resorption
Metabolic Bone Disease

Hypercparathyroidism: Pathology

Unabated Osteoclastic Activity
↓
Giant cell tumor-like mass
Neo-vascularization, Hemorrhage
(Brown tumor)
Renal Osteodystrophy

- Chronic renal failure → hyperphosphatemia → Hypocalcemia → Secondary $\uparrow$ PTH

- Reason for Hypocalcemia
  - Decreased vitamin D metabolism in kidney (inhibition of conversion of vitamin D to active metabolites by phosphate)
  - Diminished intestinal absorption of vitamin D

- Iron and aluminum accumulation in bone (from dialysate) prevents further bone deposition
Renal Osteodystrophy

- $\uparrow$PTH $\rightarrow$ $\uparrow$Osteoclastic activity $\rightarrow$ $\uparrow$Bone resorption
- $\downarrow$Matrix mineralization (osteomalacia)
- Osteoporosis
- Growth retardation
Metabolic Bone Disease  
**Vitamin D Deficiency**  
**Osteomalacia & Rickets**

- Abnormal mineralization
- Malnutrition, malabsorption, receptor abnormalities
- Under-mineralized matrix
  - Persistent hyaline cartilage
  - Fractures, skeletal deformity
- Rickets in children, osteomalacia in adults
Vitamin D Deficiency
Vitamin D Deficiency
Metabolic Bone Disease
Paget’s Disease
Paget’s Disease

Disease of Osteoclasts

- **Etiology**
  - Virally induced [Paramyxovirus (measles, RSV) - nucleocapsid antigens identified in osteoclasts]
  - (Paramyxovirus- slow virus disease)
  - Genetic predisposition – mutation – p62

- **Pathogenesis**
  - Virus stimulates IL-6
  - IL-6 & M-CSF → Activate osteoclasts
  - Osteoclasts hyperresponsive to RANKL & vit. D
  - p62 – ↑ RANK/RANKL SIGNALLING - ↑ Osteoclasts

(till date, no virus has been isolated from affected bone)
Paget’s Disease

Disease of stages

Osteolytic Stage:
- Osteoclastic activity—patchy, florid

Mixed Lytic and Blastic Stage:
- Predominently osteoblastic

Osteosclerotic (burnt-out) Stage:
- End stage: ↑ bone mass
Paget’s Disease

• More common in whites in England, France, Austria, US, Germany, New Zealand, Australia
• Less in Japan, China, Scandinavia, Africa
• 5-11% of whites, Adults, M = F
• Diagnosis:
  – X-ray
  – ↑Serum Alkaline Phosphatase
  – ↑Urinary Hydroxyproline
• May be monostotic or polyostotic
Paget’s Disease
Pathology - Osteolytic Stage

Resorption pit
Paget’s Disease

Mosaic pattern of lamellar Bones - Haphazard cement lines
Paget’s Disease

Mono-ostotic: 15% - Skull, tibia, femur, vertebra, humerus
Polyostotic: 85% - Pelvis, vertebra, skull
80% involve axial bones or femur
Paget’s Disease

Complications

• Deformities – Pain (compressed nerves)
• Fracture/Microfractures (chalk-stick #) → Pain
• Degenerative Joint Disease → Pain

Rarely:
• High-Output cardiac failure (osteoblastic phase)
• Tumors
  – Sarcoma- 5-10%, High grade, Lethal
  – Giant cell tumor
  – Extra-osseous hematopoiesis
Paget’s Disease

Complications

Secondary Sarcoma - MFH

Secondary Osteosarcoma
Skeletal development and disease states
Growth Plate - Enchondral ossification

- Reserve zone
- Zone of Proliferation
- Zone of Hypertrophy
- Zone of Mineralization
- Primary Spongiosa
Skeletal Development

• Any failed step in skeletal morphogenesis or modeling may cause disease
  – Mesenchyme condensations
  – Chondrocyte proliferation
  – Defective matrix production
  – Defective modeling/remodeling
Abnormal Chondrocyte Development

*Dwarfism - Achondroplasia*

↑FGFR3 → ↓Cartilage proliferation
Abnormal Chondrocyte Development

*Dwarfism - Achondroplasia*

- Autosomal Dominant
- Disordered proliferation of chondrocytes in cartilage anlage and growth plate
  - ↓ Proliferation
  - ↓ hypertrophy
  - Incomplete enchondral ossification
- Shortened limbs and ribs
Achondroplasia

- Normal head, IQ, reproductive system and life expectancy

Verne Troyer: 2'8"
Osteogenesis Imperfecta

- Group of phenotypically related disorders caused by deficiencies in type I collagen synthesis
- Most commonly recognized congenital disease affecting collagen production
- Involves bone matrix and other connective tissues with type 1 collagen: joints, eyes, skin, ears, teeth
Osteogenesis Imperfecta
Defective Osteoblasts and Matrix Production
Ehler-Danlos Syndrome

- Heterogenous group of connective-tissue disorders, recently classified in different types
- Hyperextensibility of skin, easy bruising, hypermobile joints, Aortic dissection; blue sclerae may be present
- Bone is osteopenic, kyphoscoliosis, spondololisthesis

“Indian Rubber Man”
Marfan’s Syndrome

• Heterogeneous group of inherited (AD) connective tissue disorder affecting bones, heart, aorta and eyes
• Mutation in locus of fibrillin gene on chromosome 15
• Usually tall with exceptionally long extremities, and long tapering fingers and toes
• Hyperflexible joints, kyphosis, scoliosis, pectus excavatum
• Eyes: subluxation of lens – ectopia lentis
• CVS: Mitral valve prolapse, Aortic dilatation due to cystic medionecrosis – AR; Aortic dissection
Marfan’s Syndrome
Metabolic Bone Disease

Scurvy

- Vitamin C deficiency
- Failed cross-linking of collagen
- Fragile capillaries and venules
  - Subperiosteal hemorrhages
- Defective osteoid synthesis
  - Microfractures
- Bony deformities
Metabolic Bone Disease

Scurvy
Abnormalities in Matrix Turnover

• Osteopetrosis
  – Brittle bone disease
  – Dysfunction of carbonic anhydrase
    • Inability of osteoclasts to degrade pre-existing cartilage and bone
    • Persistence of cartilage anlage (primary spongiosum) in medullary cavity
  – Progressive deposition of bone on pre-existing matrix
Osteopetrosis

Dysfunction of Osteoclasts
Osteopetrosis
Osteopetrosis
Osteopetrosis

*Diffuse symmetrical Sclerosis*

Brittle (marble) bone disease - break like chalk
Osteopetrosis

Small neural foramina - nerve compression & paresis
Abnormal Skeletal Development

Summary

Any failed step in skeletal morphogenesis may cause disease.

- Abnormal Mesenchymal Condensations
  - Syndactyly
- Abnormal Chondrocyte Proliferation/Cartilage Development
  - Dwarfism
- Abnormal Matrix Production
  - Osteogenesis imperfecta
- Abnormal Modelling/Remodelling
  - Osteopetrosis
Summary

• Abnormal bone modeling/remodeling
  – Osteoporosis
  – Osteopetrosis

• Abnormal mineral metabolism
  – Rickets, osteomalacia
  – Hyperparathyroidism

• Abnormal matrix production
  – Scurvy
  – Osteogenesis imperfecta
Pathology of Joint Diseases
The Normal Joint

Components – Synovium & Cartilage

**Synovial cells:** Mesenchymal – cuboid or fibroblast like cells – 1-4 cell thick

Produce:
- Hyaluronic acid
- Proteins
- Secrete fluid into joint space

**Articular cartilage:** Shock absorber

Chondrocytes regulate matrix turn over:

Synthesis:
- Type II collagen
- Proteoglycans

Breakdown: Matrix degrading enzymes

Devoid of vessels, nerves

1-4 mm thick

Nourished by synovial fluid
Articular Cartilage

Type II Collagen

Maintains friction free movement
Organized arrays of type II collagen - arches - transmit vertical stress, resist tensile forces, spread the load across the joint surface to allow the underlying bone to absorb shock
Arthritis

- Osteoarthritis
- Rheumatoid arthritis
- Other: gout, pseudogout (covered earlier)
- Seronegative arthritis
- Infectious
Arthritis
Multiple Etiologies

- Infection
- Immune-mediated Injury
- Crystal deposition
- Degenerative

Inflammation of the Joint
Osteoarthritis

Degenerative Joint Disease

• Most common form of arthritis
• Progressive destruction of articular cartilage
• Not true inflammatory arthritis
• Billions of health care dollars/lost work days
Osteoarthritis
*Degenerative Joint Disease*

- **Primary**
  - Aging phenomenon
  - Oligoarticular
  - 80-95% of people over 65 years

- **Secondary**
  - Younger patients
  - Predisposition
    - Diabetes
    - Hemachromatosis
    - Ochronosis
    - Obesity
    - Congenital deformity
  - Polyarticular
  - Severe
Osteoarthritis

• Changes in components of articular cartilage
  – Altered proteoglycans
  – Diminished pliability of collagen

• Changes in chondrocytes
  – IL-1 and TNF-a break down matrix
  – Inhibit type II collagen synthesis

• Other changes
  – Proinflammatory cytokines
  – Inflammatory cells
Osteoarthritis

Pathogenesis

• Degenerative disease of cartilage (chondrocytes and matrix)
  – Direct injury
  – ↓Synthesis
  – ↑Enzymatic breakdown:
    • Metalloproteinases breakdown PG (stromelysins) & collagen (collagenases)
    • Metalloproteinases are regulated by cytokines (IL-1 and TNF)
    • Genetic predisposition (cartilage abnormalities) -?collagen genes mutations
• Injury & repair of the subchondral bone
• Injury & repair of the Synovium (secondary to cartilage degeneration)
Primary OA

• Most common form of arthritis
• Primary OA typically involves variable number of joints in characteristic locations, as shown*
• Age: 75% of persons over age 70 have OA
• Female sex
• Obesity
• Hereditary
• Secondary:
  – Trauma
  – Neuromuscular dysfunction
  – Metabolic disorders

*Exceptions to these locations should trigger consideration of secondary causes of OA.
Haberden’s nodes - DIP
Bouchard’s nodes – PIP
1st Carpometacarpal joint – most commonly affected joint in hand (subluxation, ”squaring”)

Hands OA
Pathology of Osteoarthritis

Fibrillation & Vertical Cracking

Injury ↓
Chondrocyte proliferation - “cloning”

- Altered water (↑)/ proteoglycan (↓) content (chondromalacia-softening)

- Type II collagen: ↓ synthesis, ↑ breakdown
Osteoarthritis

Erosion & Eburnation

Cartilage thinning; Exposure of subchondral bone; bone density correlates with applied load; OA- Irregular distribution of load → Subchondral bone remodeling - sclerosis
Repair response:
Fibrocartilage grows over articular cartilage From periphery → Osteophytes
Injury & repair of the subchondral bone

Subchondral cyst: Synovial fluid forced into subchondral microfractures in a ball-valve manner - Fluid collection walled off

Fibrocartilage repair arising in the subchondral bone
Osteoarthritis

Synovial changes may be present but are secondary to cartilage degeneration

Synovial proliferation, hyperplasia, inflammation (*pannus, if severe*) → Fibrosis → Ankylosis
Osteoarthritis

Pathology - Joint Mice

Microfractures
↓
chunks of dislodged bone and cartilage
↓
loose bodies (joint mice)
Osteoarthritis

Pathology of Spine

Narrowing of IV space

Osteophytes

nerve impingement

pain
Rheumatoid Arthritis
Rheumatoid arthritis

Systemic disease manifested by polyarthritis: pain, inflammation, swelling, destruction

- Prevalence estimated at ~0.5 - 1%
- Female:male ratio = 2.5:1
- Genetic predisposition
- Symmetrical arthritis, typically of the hands and feet, also often involving ankles, knees, wrists, elbows and shoulders
- Joint destruction occurs early and is a marker for disease progression

Rheumatoid Arthritis

Pathology

Papillary Synovial Hyperplasia
Bulbous fronds
Lymphocytes + plasma cell infiltrate, perivascular lymphoid aggregates, vascular congestion
Pathology of RA

Organizing fibrin over synovium and in joint space

Rice bodies
Pathology of RA

- Joint space - narrowed with pannus (fibrosing ankylosis)
- Eventually ossifies (bony ankylosis)
- Inflammation of adjacent tendons, ligaments, and muscle
- Rheumatoid nodules
Pathology of RA

Subarticular Osteoporosis

↑ Osteoclastic activity (due to ↑ RANKL produced by activated T cells and synovial fibroblasts)
→ Subchondral cysts,
Osteoporosis (localized and systemic)
Systemic Pathology in RA

- Soft tissue- Rheumatoid nodules
- Lung involvement
- Vasculitis
- Uveitis
  - Usually in juvenile RA
Rheumatoid Nodule

Necrosis with palisading macrophages and chronic inflammatory cells
Rheumatoid Nodule

- 25% of patients
- Skin subject to pressure - ulnar aspect of forearm, occiput, lumbosacral area
- Non-tender firm nodule in subcutaneous fat
- Also develop in Joints, Tendons, Soft Tissue, Lung, Heart (peri-, myo-, endocardium), Aorta, Spleen, Viscera
Complications in RA

- RA is a systemic disease
- End-stage lung disease
- Vasculitis & its complications
  - Myocardial infarction, cerebrovascular disease, renal failure, mesenteric and intestinal infarction, gangrene
- Systemic amyloidosis
- Iatrogenic effects of Tx- Immunosuppression
- Life Expectancy ↓ by 3-7 yrs
Differences: OA vs. RA

- **AM stiffness:**
  - OA < 30 minutes,
  - RA > 1 hour
- **Sxs:**
  - OA worse with activity
  - RA better with activity
- **Joint distribution:**
  - OA: weight bearing joints and PIP & DIP
  - RA: wrist / MCP / PIP
- **RA is systemic disease - fever, weight loss**
- **OA is non-inflammatory, RA is inflammatory**
- **OA has reparative activity and new bone formation – osteophytes, subchondral sclerosis**
- **RA - No reparative bone formation - periarticular osteopenia**
Normal joint

Osteoarthritis

Rheumatoid arthritis

NORMAL and ARTHRITIC JOINTS
Crystal Deposition Disease

**Gout**

- **Acute gouty arthritis**
  - Red, painful, swollen

- **Chronic tophaceous gout**
  - Fibrosis, crystal deposits, joint destruction

- **Gouty tophus**
  - Large crystalline masses with associated tissue reaction
Crystal Deposition Disease

Gout

• Epidemiology
  – Hyperuricemia
    • Primary (genetic predisposition)
    • Secondary (increased nucleic acid turnover: leukemia, alcohol, obesity, drugs, renal disease, purine rich diet)
  – Peak in 5th decade
  – Linked to duration of hyperuricemia (20-30 years)
Gout

- Acute gout
- Chronic tophaceous gout
Crystal Deposition Disease

Gout
Crystal Deposition Disease

Gout
Crystal Deposition Disease

Tophaceous Gout

- Deposition in areas of low temperature
- Incite inflammatory response
- Bone and joint destruction
- May ulcerate skin
Crystal Deposition Disease

Tophaceous Gout
Seronegative Spondyloarthropathies

- Heterogeneous group of diseases
- Arthritis one of several manifestations
- Associated with identified infectious agents
- In part, immune mediated
- Similar, but milder disease than rheumatoid arthritis
- HLA-B27 associated
Seronegative Spondyloarthropathy

Pathology

- Chronic synovitis
- Destruction of articular cartilage
- Fibrosis and narrowing of joint space (fibrosing ankylosis)*
- Ossification of fibrous tissue (bony ankylosis)*
- Joint immobility*

*Most common is ankylosing spondylitis
Seronegative Spondyloarthropathy

Pathology
Ankylosing Spondylitis

Pathology
Ankylosing Spondylitis
Pathology
Infectious Arthritis

• Extension from osteomyelitis
• Hematogenous seeding
• Organisms
  – Bacteria: Rapid joint destruction
    • S. Aureus (children)
    • N. Gonnococcus (adults)
    • Mycobacteria
    • Borrelia (Lyme disease)
  – Viral
    • Parvovirus B19
Infectious Arthritis

Infant

Child

Adult
Infectious Arthritis

Pathology
Arthritis

Summary

• Multiple etiologies lead to inflammation of joint
• Progressive inflammation leads to synovial proliferation and cytokine induced injury
• Direct toxicity to cartilage as well as diminished nutrition
• Result is destruction of articular cartilage and joint destruction
BONE TUMORS
Bone Tumors

General Principles

• Incidence
  – Most common malignant tumor is a METASTASIS
  – 2,500 new primary bone tumors/year U.S.
  – True incidence unknown, most asymptomatic, not biopsied
  – Sarcomas result in 1,300 deaths/year in U.S.
<table>
<thead>
<tr>
<th>Normal Tissue</th>
<th>Benign Tumor</th>
<th>Malignant Tumor</th>
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<tbody>
<tr>
<td>Bone</td>
<td>Osteoma</td>
<td>Osteosarcoma</td>
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<tr>
<td></td>
<td>Osteoid Osteoma</td>
<td>Osteoblastic</td>
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<td>Osteoblastoma</td>
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<td>No Normal Counterpart</td>
<td>Giant cell tumor</td>
<td>Malignant giant cell tumor</td>
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<tr>
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<td>Aneurysmal bone cyst</td>
<td>Ewing’s sarcoma</td>
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</table>
Bone Tumors

- **Diaphysis**
  - Ewing’s Sarcoma
- **Metaphysis**
  - Osteosarcoma
  - Chondrosarcoma
  - Osteochondroma
- **Epiphysis**
  - Chondroblastoma
  - Giant Cell Tumor
- Adamantinoma
- Aneurysmal Bone Cyst
- Enchondroma
Bone Tumors

**Clinical Symptoms**

- Benign tumors usually asymptomatic
- Malignant tumors are aggressive
- Symptoms
  - Pain
  - Pathologic fracture
  - Metastases
- Radiology
  - Site and appearance clues to diagnosis
Bone Tumors

Benign

- Well-circumscribed
- “Scalloped border”
- No destructive growth
- No invasion of other tissues or joint
- Usually small
- Typical in younger patients
Malignant Bone Tumor
Malignant Bone Tumors

Pathologic Features

• Histologic grade: Usually high grade, poor prognosis
  – Important predictor of behavior
  – Determines likelihood of adjuvant therapy

• Tumor stage
  – Predicts clinical outcome
Benign Bone Forming Tumors

Osteoid Osteoma

- Tumor of young adults
- Male predilection
- Predilection for appendicular skeleton
- Classic clinical presentation:
  Nocturnal pain alleviated by aspirin
Osteoid Osteoma
Osteoid Osteoma
Benign Bone Forming Tumors

Osteoma (Bone Island)

- Benign
- Mature bone
- Predilection for craniofacial bones
- Gardner’s Syndrome
Osteosarcoma

- **Epidemiology**
  - Most common bone sarcoma (20%)
  - Bimodal age distribution
    - Elderly (Paget’s, radiation)
    - Children, young adults
  - Location
    - Metaphyseal (long bones) in youth
    - Flat bones in elderly
Osteosarcoma

Genetic Alterations

• Hereditary tumors
  – p53 mutations (LiFraumeni)
  – Retinoblastoma gene (hereditary Rb)

• Sporadic
  – P53 mutations
  – MDM2 (inactivates apoptotic capacity of p53)
  – Rb mutations are rare
Osteosarcoma

Pathology

• Anatomic location
  – Intramedullary (usually low grade)
  – Intracortical (high grade)
  – Juxtacortical (low or high grade)

• Grade
  – Grade 1: mild cytologic atypia
  – Grade 2: intermediate
  – Grade 3: high grade, pleomorphic
Osteoblastic Osteosarcoma
Cartilage Tumors

General Features

• Most are benign

• Types of cartilage:
  – Hyaline (found in tumors and normal)
  – Myxoid (found only in tumors)
  – Fibrocartilage (rare in tumors)
  – Elastic (extremely rare in tumors)
Osteochondroma

- Benign cartilage tumor of metaphysis
- Young adults
- Occur only in bones with enchondral ossification
Osteochondroma

Etiology unclear
Assumed to arise from displaced fragments of growth plate
New evidence suggests clonal proliferation (neoplasm)
Osteochondroma
Enchondroma

- Benign
  - Hyaline and myxoid cartilage
- Metaphyseal and diaphyseal
- Medullary cavity
- May erode (but not invade) cortex
- Present with pathologic fracture
- Solitary or syndromic (Ollier’s or Mafucci’s disease)
- May give rise to chondrosarcoma
Enchondroma
Enchondroma
Multiple Enchondromatosis

- Ollier’s Disease
  - Disfiguring
  - 20% develop chondrosarcoma

- Mafucci’s Disease
  - Enchondromas and soft tissue vascular tumors
  - 20% develop chondrosarcoma
  - 100% develop another extraskeletal malignancy
Ollier’s Disease

Multiple Enchondromas
Ollier’s Disease
Multiple Enchondromas
Ollier’s Disease

Multiple Enchondromas
Chondrosarcoma

- Typically occurs in older adults
- Pelvis, humerus, proximal femur
- May arise in enchondroma (low grade)
- Low grade (1/3) do not metastasize, but may recur and dedifferentiate
- High grade metastasize
Pubic bone: Chondrosarcoma
Chondrosarcoma
Chondrosarcoma
Conventional Chondrosarcoma
Conventional Chondrosarcoma
Giant Cell Tumor of Bone

- Benign locally aggressive tumor
- 4-5% of all primary bone tumors
- Age 20-40 yrs
- Epiphysis
- End of long bones
- X-ray: expanding lytic lesion “soap bubble appearance”
Giant Cell Tumor of Bone

Tumor cells mark as Macrophage-Histiocyte lineage

Pleomorphism and mitoses in mononuclear cells determines grade of tumor and biology
Ewing’s Sarcoma & Primitive Neuroectodermal Tumor (PNET)

- Family of small blue cell tumors with a characteristic $t(11;22)$ and $t(21;22)$
- 6-10% of all primary malignant bone tumors
- Age: youngest among malignant bone tumors
- Diaphysis of long bones
- Prognosis: dismal, improves by chemo
Ewing’s Sarcoma & PNET
Tibia:

Multiple Myeloma
Metastatic Tumors to Bone

• Metastatic carcinoma, most common malignant tumor of bone
• May be blastic or lytic
• Multifocal or solitary
• Common Primary sites:
  – **B** (breast)
  – **L** (lung)
  – **T** (thyroid)
  – **A**nd **a** (adrenal)
  – **K**osher (kidney)
  – **P**ickle (prostate)
Metastatic Tumors to Bone

• Should consider
  – Multifocal disease
  – Location (vertebrae, diaphysis)
  – Older patient
  – Pertinent history
Pathology of Bone Tumors

Summary

- Primary bone tumors classified according to matrix production
- Tumor site key to differential diagnosis
- Benign tumors are well-circumscribed, do not infiltrate bone
- Malignant tumors are radiographically and histologically infiltrative
- Metastatic disease most common, may mimic primary bone tumors