Bone Pathology I and II

Fracture:
Fracture – defined as a discontinuity of bone. Fractures rank among the most common bone pathologies.

Classification:
Traumatic vs nontraumatic
Complete vs incomplete
Closed (overlying tissue is intact) vs compound (fracture extends into the overlying skin)
Comminuted (bone is splintered)
Displaced (fractured bone is not aligned)

The repair of a fracture is highly regulated. The trauma of the bone fracture ruptures associated blood vessels. The resulting blood coagulum creates a fibrin mesh scaffold to recruit inflammatory cells, fibroblasts and endothelium. A soft tissue matrix called a callus forms and is able to hold the ends of the fractured bone in apposition, but it is not calcified and cannot support weight bearing. Subsequently, bone progenitors deposit new foci of woven bone (define woven bone) which then act as a nidus for enchondral ossification (define enchondral ossification) recapitulating the process of bone formation in epiphyseal growth plates. This connects the trabeculae in adjacent bone. With ossification the fracture ends are bridged by a bony callus.

The healing of a fracture can be disrupted by many factors: displacement, comminuted bone, inadequate mobilization, infection, inadequate levels of calcium or phosphorous, vitamin deficiencies, systemic infection, diabetes, vascular insufficiency.

A stress fracture develops slowly over time as a collection of micro-fractures associated with increased physical activity ie repetitive weight on bone (jogging, military boot camp).

When a fracture occurs in a bone already altered by a disease process, it is called a pathologic fracture.
Causes of pathologic fractures include osteoporosis, vitamin D deficiency, hyperparathyroidism, Paget disease of bone, osteogenesis imperfecta and neoplasms. These entities are subsequently discussed.

Osteoporosis
Osteoporosis is the most common metabolic bone disease in the United States.

Pathology: Osteoporosis is a disease characterized by an absolute REDUCTION IN BONE MASS. MINERALIZATION IS NORMAL.
The critical loss of bone mass makes the skeleton structurally weak and vulnerable to fractures. The number and size of the trabeculae of cancellous bone are decreased. The thickness of the bone cortex is also decreased.
The greatest bone loss is seen in vertebrae, wrists, ribs, and pelvis/hips.
Etiology/Pathogenesis:
Generalized osteoporosis may be a primary skeletal disorder (senile, postmenopausal, idiopathic osteoporosis).
There are many hypotheses of the pathogenesis of senile/postmenopausal osteoporosis. Age-related changes in bone cells and matrix, physical activity, genetic factors, hormonal influences and the calcium nutritional state all play a role. Dysregulation of RANK, RANK ligand, and OPG interactions is a likely major contributor to the pathogenesis. (Refer to Robbins figure 20-2. Ultimately there is an imbalance between bone resorption and bone formation (Refer to Robbins figure 20-4)

Osteoporosis may be a secondary skeletal disorder (Refer to Robbins Table 20-1).

Clinico-pathologic correlation:
Bone fractures may be associated with minimal “trauma”
Vertebral fractures frequently occur in thoracic and lumbar region. Multiple level vertebral fractures result in loss of height, kyphoscoliosis, and chronic pain.
Femoral neck fractures, fractures of distal radius are also common.
Osteoporosis is not reliably detected in plain radiographs until 30-40% of bone mass is lost (x-ray will then reveal thin trabeculae).
Specialized radiographic techniques (DEXA scans) measure bone density.
Measurements of serum phosphorous, calcium, and alkaline phosphatase are NOT diagnostic.
Prevention is critical – need exercise, appropriate calcium and vitamin D intake.

Rickets/Osteomalacia
Rickets refers to a childhood disorder, osteomalacia to the adult counterpart.

Etiology:
Both rickets and osteomalacia are manifestations of vitamin D deficiency (Inadequate synthesis or dietary deficiency of vitamin D) or its abnormal metabolism (for example decreased absorption of fat-soluble vitamin, end organ resistance to 1,25 (OH)2D, Phosphate depletion) (refer to Robbins figure 7-20)

Pathology:
The deficiency of vitamin D leads to defective mineralization of bone, decreased mineral content of bone and a relative increase of osteoid. The bones are left “soft”.
Contrast this to osteoporosis where the total bone mass is decreased but the mineral content of the remaining bone is normal.

Clinico-pathologic correlation:
In children the deficiency of vitamin D causes extensive changes at the physeal plate which does not become adequately mineralized. Osteoclast activity does not resorb the cartilage growth plate leaving the growth plate thickened, irregular and lobulated. Endochondral ossification proceeds slowly. Therefore, in children with rickets many bones are potentially affected with a variety of deformities (frontal bossing, rachitic rosary, pigeon breast deformity, bowing of the legs). Fractures can occur as well.
In adults with osteomalacia bone is weak and vulnerable to fractures or microfractures with associated bone pain. Patients may also have nonspecific complaints such as muscle weakness or diffuse aches and pains. Changes are reversible when vitamin D is repleted.

**Hyperparathyroidism**

**Pathogenesis:**
Increased parathyroid hormone levels are detected by receptors on osteoblasts which then initiate the release of mediators that stimulate osteoclast activity.

**Pathology:**
Skeletal manifestations are caused by unabated osteoclastic bone resorption. Osteoclasts tunnel into trabeculae— a process termed “dissecting osteitis”. The marrow spaces around the affected surfaces are replaced by fibrovascular tissue. With continued microfractures and associated hemorrhages there is an influx of macrophages and ingrowth of reactive fibrous tissue which results in the development of mass lesions known as “brown tumors”. The hallmark of severe hyperparathyroidism is termed “osteitis fibrosa cystica” (von Recklinghausen disease of bone). It is fortunately rarely seen today because hyperparathyroidism is recognized and treated at earlier stages. It is the end result of increased bone cell activity, peritrabecular fibrosis and brown tumors which undergo cystic degeneration.

**Clinico-pathologic correlation:**
The overall decrease in bone mass predisposes to fractures. Skeletal deformities are caused by weight bearing stress. Bone changes may regress with control of hyperparathyroidism/reduction of PTH level.

**Paget Disease of the Bone**
Paget Disease is caused by osteoclast dysfunction
There are three associated stages: i) osteolytic; ii)mixed osteoclastic-osteoblastic; iii)burnt out quiescent osteosclerotic

**Pathology:**
Initially the disease is characterized by increased bone destruction (osteolysis) which is haphazard. As the disease progresses a phase of simultaneous osteolysis and osteogenesis occurs. There are numerous osteoclasts and osteoblasts in the involved bone. As the disease advances further, the original bone is replaced by vascular connective tissue and poorly organized bone. Although the thickness of the bone is overall increased, the bone is soft, composed of poorly mineralized matrix and vascular connective tissue. The bone therefore lacks structural strength. Eventually the disease “burns out” and the bone becomes sclerotic. The characteristic lesion is a “mosaic” pattern of bone formation with intertrabecular fibrosis. The disease may affect one or many bones. Commonly the tibia, pelvis, femur, skull, and spine are involved in decreasing order of frequency.
**Etiology/Pathogenesis:**
The precise etiology is unknown but evidence suggests an infection by a paramyxovirus. There is a genetic component: 15-40% of patients with Paget Disease have a family history. Data has shown that the hereditary forms are associated with mutations of the SQXTM gene lead to RANK mediated increased osteoclast activity.

**Clinico-pathologic correlation:**
The onset of Paget disease is in mid-adulthood and more common thereafter. Many patients may remain asymptomatic.
Associated symptoms:
- Pain localized to the affected bone(s) most common symptom.
- Bone overgrowth may cause deformities such as thickening of the skull and craniofacial bones (leontiasis ossea). (and hat size increases).
- Ossicles of the middle ear can be affected and result in hearing loss.
- Although thick, the affected bones are prone to micro-fractures and fractures.
- The hypervascularity of the pagetic bone may warm the overlying skin. Increased blood may behave as an arteriovenous shunt leading to high-output heart failure.

A key diagnostic finding is an isolated elevation of serum alkaline phosphatase (which reflects the increased osteoblastic bone activity)

The most dreaded complication is neoplastic change and the development of a bone sarcoma.

**Metabolic Summary:**
Be sure you can EXPLAIN why the following characteristic patterns occur:

<table>
<thead>
<tr>
<th></th>
<th>Serum Calcium</th>
<th>Serum Phosphate</th>
<th>Serum Bone Alkaline Phosphatase</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Osteoporosis</td>
<td>Normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>low or low</td>
<td>often low</td>
<td>usually elevated</td>
<td>elevated</td>
</tr>
<tr>
<td>(osteomalacia/rickets)</td>
<td>normal</td>
<td>normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Hyperparathyroidism</td>
<td>Elevated</td>
<td>low or low</td>
<td>usually normal (but could be</td>
<td>elevated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>normal</td>
<td>slightly elevated)</td>
<td></td>
</tr>
<tr>
<td>Paget Disease</td>
<td>Normal</td>
<td>normal</td>
<td>elevated</td>
<td>normal</td>
</tr>
</tbody>
</table>

**Genetic Bone Disease**

**Osteogenesis Imperfecta (OI)**
Also referred to as “brittle bone disease”, OI is a group of inherited disorders (or acquired mutations) in which defective type I collagen formation leads to fragility of bone and multiple fractures. It is a systemic disorder of connective tissue.
Pathogenesis:
Genetic defects reside in mutations in the genes that code for alpha1 and alpha2 chains of the collagen molecule.

Clinico-pathologic correlation:
OI represents a spectrum of disorders (4 major types) marked by extreme skeletal fragility and multiple fractures due to poorly formed osteoid matrix. Other organs are also affected because of the abnormality of type I collagen:
- Sclera are translucent blue
- Hearing impairments
- Dental abnormalities (small, misshapen, blue-yellow teeth)
- Hypermobility of joints

ACHONDROPLASIA
This disease is a major cause of dwarfism.

Pathogenesis
It is an autosomal dominant disorder; the majority of cases represent new mutations. It is caused by a defect in cell signaling resulting in a reduction in the proliferation of chondrocytes in the growth plate and enchondral bone formation. A mutation of FGF receptor 3, which normally inhibits cartilage proliferation, leads to constitutive activation and resultant suppressed growth. There is a failure of longitudinal bone growth (ie short limbs). Membranous ossification is not affected (ie head growth is not impaired.)

Clinico-pathologic correlation:
Patients have shortened proximal extremities. The trunk is of relatively normal length. The head is enlarged with a bulging forehead and conspicuous depression of root of nose. Skeletal abnormalities are usually not associated with changes in longevity, intelligence, or reproductive status.

Other:
OSTEONECROSIS (Avascular necrosis)
Osteonecrosis is a condition in which there is infarction of bone and bone marrow. It can occur in the medullary cavity of the metaphysis or diaphysis. The cortex is usually spared because of collateral blood flow. Osteonecrosis can also develop in the subchondral region of the epiphysis. The overlying articular cartilage is spared because of nutrient supply from synovial fluid.

Etiology/Pathogenesis:
All forms of bone necrosis result from ischemia. The mechanisms and disorders that result in ischemia vary and include trauma, corticosteroids, dysbarism, sickle cell disease and other hemoglobinopathies, and Gaucher disease.
Clinico-pathologic correlation:
Patients experience bone or joint pain. Subchondral infarcts may result in collapse of affected bone

BONE NEOPLASMS

General Comments
The majority of bone neoplasms are METASTATIC. Primary bone neoplasms are uncommon. They generally occur more often in children and adolescents, during years of bone growth, although specific types of tumors target certain age groups and anatomic sites. Primary bone neoplasms may arise from a variety of cellular elements. Most bone tumors are classified according to the normal cell or tissue type they recapitulate (Refer to Robbins Table 20-2).

Primary bone tumors range in their biologic potential from innocuous to fatal.

The evaluation of bone tumors (diagnosis) depends not only on tissue examination but also requires knowledge of the age of the patient, location, and radiographic appearance of the tumor.

Bone Forming Neoplasms
2 neoplasms are presented – one benign, one malignant

Osteoid Osteoma
An osteoid osteoma is a benign neoplasm composed of a center of haphazardly arranged trabeculae of woven bone rimmed by osteoblasts. The stroma surrounding the tumor bone consists of loose connective tissue with many dilated and congested capillaries. These lesions frequently arise in the cortex of the femur or tibia.

Etiology/Pathogenesis:
Unknown

Clinico-pathologic correlation:
Osteoid osteoma predominantly affect men less than 25 years old. A key clinic feature is the development of nocturnal pain relieved by aspirin because of the high prostaglandin content of the tumor and nerve fibers within the tumor. Excision of the tumor is curative.

OSTEOSARCOMA (Osteogenic sarcoma)
Osteosarcoma is the most common primary malignant tumor of bone (excluding multiple myeloma and lymphoma). An osteosarcoma is a malignant neoplasm of mesenchymal cells which forms osteoid and bone. Most osteosarcomas arise in the medullary cavity of the metaphysis of long bones. 60% arise close to the knee: distal femur and proximal tibia.
**Gross Pathology:** These are bulky tumors which frequently destroy the overlying bone cortex and produce a soft tissue mass. The cancer spreads widely in medullary cavity.

**Histology:** The tumor is composed of anaplastic mesenchymal cells intermixed with osteoid (and sometimes cartilage).

**Etiology/Pathogenesis:**
70% of tumors have genetic abnormalities which include nonspecific ploidy changes and chromosomal aberrations.
Two of the most common gene mutations are of the tumor suppressor genes Rb and p53.
Patients with germline mutations of the Rb gene have 1000x risk of developing osteosarcoma.
Patients with germline p53 mutations (Li-Fraumeni syndrome) also have a markedly increased risk of osteosarcoma development.

**Clinico-pathologic correlation:**
It is an aggressive neoplasm with bloodstream metastases. The lung is the most common site of metastases.
Osteosarcomas occur in men greater than women, most commonly between the ages of 10 and 20 years. They most commonly present as a painful, enlarging mass.
Radiographs show a destructive mass; the tumor breaks through the bone cortex lifting the periosteum. The irregular radiographic shadow between cortex and raised ends of periosteum = “Codman triangle”

**Chondromatous Neoplasms**
2 neoplasms are presented – one benign, one malignant

**OSTEOCHONDROMA**
An osteochondroma is a **benign** neoplasm.

**Pathology:**
It is a cartilage capped tumor attached to the underlying skeleton by a bony stalk. (ie mature bone with a cartilage cap). It arises in bones of enchondral origin, most commonly at the metaphysis near the growth plate of long tubular bones.

**Clinico-pathologic correlation:**
The tumor is usually a slow growing mass detected as an incidental finding. It may cause pain if it impinges on a nerve or if the tumor stalk fractures.

**CHONDROSARCOMA**
A chondrosarcoma is a **malignant** neoplasm.

**Pathologies:** The tumors are composed of malignant hyaline and myxoid cartilage. Malignant cartilage cells vary in degree of differentiation (tumor grade); the higher the grade (less
differentiation) the worse the prognosis. This neoplasm is generally bulky, lobulated, gray-white and translucent. It frequently arises in central portions of skeleton (pelvis, shoulder, ribs).

Opportunity to review the concepts of cancer “stage” vs “grade” previously discussed in MHD

**Etiology/pathogenesis:** Unknown.

**Clinico-pathologic correlation:**
This tumor usually develops in patients in the fourth to sixth decades. It presents as a painful, enlarging mass. The prognosis and biologic behavior generally correlates to the grade of tumor

**Miscellaneous Tumors – SELF STUDY**

**Ewing Sarcoma/Primitive Neuroectodermal Tumor (PNET)**
Primary *malignant* bone tumors of bone and soft tissue.
Most commonly develop in 10-15 year olds, boys > girls, black and Asian individuals rarely affected.
Arise in diaphysis of long tubular bones, particularly femur and flat bones of the pelvis.
Both Ewing and PNET are characterized by gene location involving EWS gene (chromosome 22) and ETS gene (a transcription factor). Most common translocation (11:22)(q24;q12). Translocation results in expression of target genes which leads to abnormal cell proliferation and survival.
X-ray appearance – destructive, lytic tumor that extends into the surrounding soft tissues. Has an “onion skin” appearance as the periosteal reaction produces layers of reactive bone.
Histologically these tumors are composed of *uniform* small round cells with scant cytoplasm rich in glycogen (cytoplasm may appear therefore clear).
Ewing and PNET are identical with respect to their behavior, chromosomal translocations – only difference (which is clinically not significant) is that PNETs have neural differentiation and histologically have the presence of “Homer-Wright Rosettes (tumor cells arranged in a circle about a central fibrillary space).
Clinically these tumors may mimic infection – patients may have fever; tenderness, warmth and swelling over tumor; leukocytosis; elevated ESR.
Clinically aggressive - surgical excision, chemotherapy, +- radiation therapy has improved prognosis with ~50% patients having long-term cures.

**METASTASES TO BONE**
Although any cancer can metastasize to bone, the most common skeletal metastases originate from cancer of the prostate, breast, kidney and lung.
The radiographic manifestations of metastases may be purely lytic, purely blastic, or mixed lytic and blastic.
Carcinomas of the breast, kidney, lung, and gastrointestinal tract and multiple myeloma induce a Lytic reaction. Prostatic adenocarcinoma is most commonly osteoblastic.
REVIEW of BONE TUMORS via a Jeopardy Format
Questions
(answers to follow)

**Real Estate (age, location, demographics)**
Most common benign bone tumor. Arises only in bone of enchondral origin from the metaphyses.

Major site of osteosarcomas in persons less than 25 years of age.

Most common form of skeletal malignancy.

Cell of origin of a primary bone neoplasm of patients in their 40s and older which most commonly arise in the central portions of the skeletal, including pelvis, shoulder and ribs.

The most common primary malignant tumor of human bone, excluding those of hematopoetic origin, also has a high incidence in which dog breed?

**That’s gross (gross and histologic pathology)**
Neoplasm composed of sheets of uniform, small round cells with scant cytoplasm that are slightly larger than lymphocytes.

Underlying condition which leads to the development of brown tumors of bone.

This condition which has an appearance of a mosaic pattern of lamellar bone is a risk factor for the development of osteosarcoma in the elderly

Unlike other bone neoplasms there is a direct correlation between this and the biologic behavior of this chondrosarcomas.

**See-thru (radiographic findings)**
Radiographic term describing an aggressive bone tumor breaking through the cortex, lifting the periosteum of bone and resulting in reactive periosteal bone formation.

The characteristic periosteal reaction of this bone neoplasm produces layers of reactive bone deposited in an “onion-skin fashion
Metastatic tumor to bone which most often elicits a sclerotic response and a blastic appearance on x-ray.

Multiple myeloma characteristically produces this finding on skeletal imaging.

**How’m I doing? (symptoms, prognosis)**

Benign bone neoplasm which characteristically causes nocturnal pain at tumor site relieved by aspirin.

Affected individuals with this bone neoplasm may have systemic findings including fever, elevated ESR, anemia and leukocytosis.

This benign bone neoplasm may rarely transform to chondrosarcoma.

Estimated 5 year survival for patients with overtly metastatic osteosarcoma or recurrent osteosarcoma

**Science (syndromes, genetics, mutations)**

Bone neoplasm with a characteristic (11;22) translocation resulting in fusion genes producing transcription factors that alter expression of target genes resulting in abnormal cell proliferation and survival.

Patients with germline mutations in this gene have ~1000X increased risk of developing osteosarcoma.

Germline loss-of-function mutations in this gene results in the development of multiple hereditary exostosis syndrome.

A woman with a history of ovarian cancer and a family history of male cancer develops a pathologic fracture attributed to metastasis from breast cancer most likely has a mutation in this gene.
Answers

Real Estate (age, location, demographics)
Major site of osteosarcomas in persons less than 25 years of age.
What is the knee (or metaphyseal region of long bones)?

Most common form of skeletal malignancy.
What are metastatic tumors?

Cell of origin of a primary bone neoplasm of patients in their 40s and older which most commonly arise in the central portions of the skeletal, including pelvis, shoulder and ribs.
What is chondroblast? (chondrosarcoma)

The most common primary malignant tumor of human bone, excluding those of hematopoetic origin, also has a high incidence in which dog breed?
What is Great Dane or St Bernard?

That’s gross (gross and histologic pathology)
Neoplasm composed of sheets of uniform, small round cells with scant cytoplasm that are slightly larger than lymphocytes.
What is Ewing Sarcoma (or Primitive neuroectodermal tumor?)

Underlying condition which leads to the development of brown tumors of bone.
What is hyperparathyroidism?

This condition which has an appearance of a mosaic pattern of lamellar bone is a risk factor for the development of osteosarcoma in the elderly
What is Paget Disease of Bone?

Unlike other bone neoplasms there is a direct correlation between this and the biologic behavior of this chondrosarcomas.
What is tumor grade?

See-thru (radiographinc findings)
Radiographic term describing an aggressive bone tumor breaking through the cortex, lifting the periosteum of bone and resulting in reactive periosteal bone formation.
What is Codman Triangle?

The characteristic periosteal reaction of this bone neoplasm produces layers of reactive bone deposited in an “onion-skin fashion”.

11
What is Ewing Sarcoma (or Primitive neuroectodermal tumor?)

Metastatic tumor to bone which most often elicits a sclerotic response and a blastic appearance on x-ray.

What is prostate cancer?

Multiple myeloma characteristically produces this findings on skeletal imaging.

What are/is lytic lesions?

How’m I doing? (symptoms, prognosis)

Benign bone neoplasm which characteristically causes nocturnal pain at tumor site relieved by aspirin.

What is Osteid Osteoma?

Affected individuals with this bone neoplasm may have systemic findings including fever, elevated ESR, anemia and leukocytosis.

What is Ewing Sarcoma/Primitive Neuroectodermal Tumor?

This benign bone neoplasm may rarely transform to chondrosarcoma.

What is osteochondroma (or enchondroma)?

Estimated 5 year survival for patients with overtly metastatic osteosarcoma or recurrent osteosarcoma

What is 20%?

Science (syndromes, genetics, mutations)

Bone neoplasm with a characteristic (11;22) translocation resulting in fusion genes producing transcription factors that alter expression of target genes resulting in abnormal cell proliferation and survival.

What is Ewing Sarcoma (or primitive neuroectodermal tumor)?

Patients with germline mutations in this gene have ~1000X increased risk of developing osteosarcoma.

What is RB (retinoblastoma gene)? An alternate answer is what is germline p53 mutations.
A woman with a history of ovarian cancer and a family history of male cancer develops a pathologic fracture attributed to metastasis from breast cancer most likely has a mutation in this gene.

What is BRCA 2?