BONES & JOINTS
CONGENITAL DISEASES OF BONE

Osteogenesis Imperfecta (OI) (Brittle bone diseases) is a group of hereditary disorders caused by gene mutations that eventuate in defective synthesis of and thus premature degradation of type I collagen. The fundamental abnormality in all forms of OI is too little bone, resulting in extreme susceptibility to fractures. The bones show marked cortical thinning and attenuation of trabeculae. Extraskeletal manifestations also occur because type I collagen is a major component of extracellular matrix in other parts of the body. The classic finding of blue sclerae is attributable to decreased scleral collagen content; this causes a relative transparency that allows the underlying choroid to be seen. Hearing loss can be related to conduction defects in the middle and inner ear bones, and small misshapen teeth are a result of dentin deficiency.

Achondroplasia is a major cause of dwarfism. The underlying etiology is a point mutation in the fibroblast growth factor receptor, which causes inhibition of chondrocyte proliferation, which is associated with suppression of the normal epiphyseal growth plate expansion. Thus, long bone growth is markedly shortened. The most conspicuous changes include disproportionate shortening of the proximal extremities, bowing of the legs, and a lordotic posture.
Achondroplasia is an autosomal dominant disorder.

**ACQUIRED DISEASES OF BONE DEVELOPMENT**

**Osteoporosis** is characterized by increased porosity of the skeleton resulting from reduced bone mass. The disorder may be localized to a certain bone (s), as in disuse osteoporosis of a limb, or generalized involving the entire skeleton. Generalized osteoporosis may be primary, or secondary.

**Primary generalized osteoporosis**
- **Postmenopausal**
- **Senile**

**Secondary generalized osteoporosis**

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Senile and postmenopausal osteoporosis are the most common forms. In the fourth decade in both sexes, bone resorption begins to overrun bone deposition. Such losses generally occur in areas containing abundant cancellous bone such as the vertebrae & femoral neck. The postmenopausal state accelerates the rate of loss; that is why females are more susceptible to osteoporosis and its complications.
**Gross features**
- Because of bone loss, the bony trabeculae are thinner and more widely separated than usual. This leads to obvious porosity of otherwise spongy cancellous bones.

**Microscopic features**
- There is thinning of the trabeculae and widening of Haversian canals.
- The mineral content of the thinned bone is normal, and thus there is no alteration in the ratio of minerals to protein matrix.

**Etiology & Pathogenesis**
- Osteoporosis involves an imbalance of bone formation, bone resorption, & regulation of osteoclast activation. It occurs when the balance tilts in favor of resorption.
- Osteoclasts (as macrophages) bear receptors (called RANK receptors) that when stimulated activate the nuclear factor (NFκB) transcriptional pathway. RANK ligand synthesized by bone stromal cells and osteoblasts activates RANK. **RANK activation converts macrophages into bone-crunching osteoclasts and is therefore a major stimulus for bone resorption.**
Osteoprotegerin (OPG) is a receptor secreted by osteoblasts and stromal cells, which can bind RANK ligand and by doing so makes the ligand unavailable to activate RANK, thus limiting osteoclast bone-resorbing activity.

Dysregulation of RANK, RANK ligand, and OPG interactions seems to be a major contributor in the pathogenesis of osteoporosis. Such dysregulation can occur for a variety of reasons, including aging and estrogen deficiency.

- **Influence of age**: with increasing age, osteoblasts synthetic activity of bone matrix progressively diminished in the face of fully active osteoclasts.

- **The hypoestrogenic effects**: the decline in estrogen levels associated with menopause correlates with an annual decline of as much as 2% of cortical bone and 9% of cancellous bone. *The hypoestrogenic effects are attributable in part to augmented cytokine production* (especially interleukin-1 and TNF). These translate into increased RANK-RANK ligand activity and diminished OPG.

- **Physical activity**: reduced physical activity increases bone loss. This effect is obvious in an immobilized limb, but also occurs diffusely with decreased physical activity in older individuals.

- **Genetic factors**: these influence vitamin D receptors efficiency, calcium uptake, or PTH synthesis and responses.

- **Calcium nutritional insufficiency**: the majority of adolescent girls (but not boys) have insufficient dietary intake of calcium. As a result, they do not achieve the maximal peak bone mass, and are therefore likely to develop clinically significant osteoporosis at an earlier age.

- **Secondary causes of osteoporosis**: these include prolonged glucocorticoid therapy (increases bone resorption and reduce bone synthesis.)

The clinical outcome of osteoporosis depends on which bones are involved. *Thoracic and lumbar vertebral fractures are extremely common, and produce loss of height and various deformities, including kyphoscoliosis* that can compromise respiratory function. Pulmonary embolism and pneumonia are common complications of fractures of the femoral neck, pelvis, or spine.

**Paget Disease (Osteitis Deformans)**
This unique bone disease is characterized by repetitive episodes of exaggerated, regional osteoclastic activity (osteolytic stage), followed by exuberant bone formation (mixed osteoclastic-osteoblastic stage), and finally by exhaustion of cellular activity (osteosclerotic stage). The net effect of this process is a gain in bone mass; however, the newly formed bone is disordered and lacks strength. Paget disease usually does not occur until mid-adulthood but becomes progressively more common thereafter. The axial skeleton and proximal femur are involved in the majority of cases. Complications include in patients with extensive disease, congestive heart failure (hypervascularity of marrow tissue), cranial nerves impingement and rarely bone sarcoma (usually osteogenic).

**Rickets and Osteomalacia:**

*raccel of unmineralized matrix.*

Rickets in growing children and osteomalacia in adults are skeletal diseases with worldwide distribution. They may result from

1. Diets deficient in calcium and vitamin D
2. Limited exposure to sunlight (in heavily veiled women, and inhabitants of northern climates with scant sunlight)
3. Renal disorders causing decreased synthesis of 1,25 (OH)2-D or phosphate depletition

Although rickets and osteomalacia rarely occur outside high-risk groups, milder forms of vitamin D deficiency (also called vitamin D insufficiency) leading to bone loss and hip fractures are quite common in the elderly. Whatever the basis, a deficiency of vitamin D tends to cause hypocalcemia. *When hypocalcemia occurs, PTH production is increased,* that ultimately leads to restoration of the serum level of calcium to near normal levels (through mobilization of Ca from bone & decreased renal calcium excretion; and increased renal excretion of phosphate (result in hypophosphetemia; so mineralization of bone is impaired or there is high bone turnover.

*The basic derangement in both rickets and osteomalacia is an excess of unmineralized matrix.* This complicated in rickets by derangement of endochondral bone growth.

The following sequence ensues in rickets:

1. Overgrowth of epiphyseal cartilage with distorted, irregular masses of cartilage
2. Deposition of osteoid matrix on inadequately mineralized cartilage
3. Disruption of the orderly replacement of cartilage by osteoid matrix, with enlargement and lateral expansion of the osteochondral junction
4. Microfractures and stresses of the inadequately mineralized, weak, poorly formed bone
5. Deformation of the skeleton due to the loss of structural rigidity of the developing bones

**Gross features**

- The gross skeletal changes depend on the severity of the disease; its duration, & the stresses to which individual bones are subjected.
- During the nonambulatory stage of infancy, the head and chest sustain the greatest stresses. The softened occipital bones may become flattened. An excess of osteoid produces *frontal bossing.* Deformation of the chest results from overgrowth of cartilage or osteoid tissue at the costochondral junction, producing the "rachitic rosary." The weakened metaphyseal areas of the ribs are subject to the pull of the
respiratory muscles and thus bend inward, creating anterior protrusion of the sternum (pigeon breast deformity). The pelvis may become deformed.

- When an ambulating child develops rickets, deformities are likely to affect the spine, pelvis, and long bones (e.g., tibia), causing, most notably, lumbar lordosis and bowing of the legs.

- In adults the lack of vitamin D deranges the normal bone remodeling that occurs throughout life. The newly formed osteoid matrix laid down by osteoblasts is inadequately mineralized, thus producing the excess of persistent osteoid that is characteristic of osteomalacia. Although the contours of the bone are not affected, the bone is weak and vulnerable to gross fractures or microfractures, which are most likely to affect vertebral bodies and femoral necks.

**Hyperparathyroidism**

Abnormally high levels of parathyroid hormone (PTH) cause hypercalcemia. This can result from either primary or secondary causes. **Primary hyperparathyroidism** is caused usually by a parathyroid adenoma, which is associated with autonomous PTH secretion. **Secondary hyperparathyroidism**, on the other hand, can occur in the setting of chronic renal failure. In either situation, the presence of excessive amounts of this hormone leads to significant skeletal changes related to a persistently exuberant osteoclast activity that is associated with increased bone resorption and calcium mobilization. The entire skeleton is affected. PTH is directly responsible for the bone changes seen in primary hyperparathyroidism, but in secondary hyperparathyroidism additional influences also contribute. In chronic renal failure there is inadequate 1,25-(OH)_{2}-D synthesis that ultimately affects gastrointestinal calcium absorption. The hyperphosphatemia of renal failure also suppresses renal α1-hydroxylase, which further impair vitamin D synthesis; all these eventuate in hypocalcemia, which stimulates excessive secretion of PTH by the parathyroid glands, & hence elevation in PTH serum levels.

**Bone changes include**

- Increased osteoclastic activity, with bone resorption. Cortical and trabecular bone are lost and replaced by loose connective tissue.

- Bone resorption is especially pronounced in the subperiosteal regions and produces characteristic radiographic changes, best seen along the radial aspect of the middle phalanges of the second and third fingers.

- Reduced bone mass, and hence are increasingly susceptible to fractures and bone deformities.
Osteonecrosis (Avascular Necrosis)
Ischemic necrosis with resultant bone infarction occurs mostly due to fracture or after corticosteroid use. **Microscopically**, dead bone trabeculae (characterized by empty lacunae) are interspersed with areas of fat necrosis. The cortex is usually not affected because of collateral blood supply; in subchondral infarcts, the overlying articular cartilage also remains viable because the synovial fluid can provide nutritional support. With time, osteoclasts can resorb many of the necrotic bony trabeculae; any dead bone fragments that remain act as scaffolds for new bone formation, a process called **creeping substitution**. Symptoms depend on the size and location of injury. Subchondral infarcts often collapse and can lead to severe osteoarthritis.

Osteomyelitis
This refers to **inflammation of the bone and related marrow cavity almost always due to infection**. Osteomyelitis can be acute or a chronic. The most common etiologic agents are pyogenic bacteria and *Mycobacterium tuberculosis*.

**Pyogenic Osteomyelitis**
The offending organisms reach the bone by one of three routes:
1. *Hematogenous dissemination* (most common)
2. *Extension from a nearby infection* (in adjacent joint or soft tissue)
3. *Traumatic implantation of bacteria* (as after compound fractures or orthopedic procedures).

*Staphylococcus aureus* is the most frequent cause. Mixed bacterial infections, including anaerobes, are responsible for osteomyelitis complicating bone trauma. In as many as 50% of cases, no organisms can be isolated.

**Pathologic features**:
- The offending bacteria proliferate & induce an acute inflammatory reaction.
- Entrapped bone undergoes early necrosis; the dead bone is called sequestrum.
- The inflammation with its bacteria can permeate the Haversian systems to reach the periosteum. In children, the periosteum is loosely attached to the cortex; therefore, sizable subperiosteal abscesses can form and extend for long distances along the bone surface.
- Lifting of the periosteum further impairs the blood supply to the affected region, and both suppurative and ischemic injury can cause segmental bone necrosis.
- Rupture of the periosteum can lead to an abscess in the surrounding soft tissue and eventually the formation of cutaneous draining sinus. Sometimes the sequestrum crumbles and passes through the sinus tract.
- In infants (uncommonly in adults), epiphyseal infection can spread into the adjoining joint to produce suppurative arthritis, sometimes with extensive destruction of the articular cartilage and permanent disability.
- After the first week of infection chronic inflammatory cells become more numerous. Leukocyte cytokine release stimulates osteoclastic bone resorption, fibrous tissue ingrowth, and bone formation in the periphery, this occurs as a shell of living tissue (*involucrum*) around a segment of dead bone. Viable organisms can persist in the sequestrum for years after the original infection. Chronicity may develop when there is delay in diagnosis, extensive bone necrosis, and improper management.
Complications of chronic osteomyelitis include
1. A source of acute exacerbations
2. Pathologic fracture
3. Secondary amyloidosis
4. Endocarditis
5. Development of squamous cell carcinoma in the sinus tract (rarely osteosarcoma).

Tuberculous Osteomyelitis
Bone infection complicates up to 3% of those with pulmonary tuberculosis. Young adults or children are usually affected. The organisms usually reach the bone hematogenously. *The long bones and vertebrae are favored sites.* The lesions are often solitary (multifocal in AIDS patients). The infection often spreads from the initial site of bacterial deposition (the synovium of the vertebrae, hip, knee, ankle, elbow, wrist, etc) into the adjacent epiphysis, where it causes typical *granulomatous inflammation with caseous necrosis and extensive bone destruction.* Tuberculosis of the vertebral bodies (*Pott disease*), is an important form of osteomyelitis. Infection at this site causes vertebral deformity and collapse, with secondary neurologic deficits. Extension of the infection to the adjacent soft tissues with the development of *psoas muscle abscesses* is fairly common in Pott disease. Advanced cases are associated with cutaneous sinuses, which cause secondary bacterial infections. Diagnosis is established by synovial fluid direct examination, culture or PCR.
BONE TUMORS
Primary bone tumors are classified according to their normal cell of origin or line of differentiation. Among the benign mass lesions, osteochondroma and fibrous cortical defect occur most frequently. Osteosarcoma is the most common primary bone cancer, followed by chondrosarcoma and Ewing sarcoma. Benign tumors markedly outnumber their malignant counterparts, particularly before age 40; bone tumors in the elderly are much more likely to be malignant.

Most bone tumors develop during the first few decades of life and tend to originate in the long bones of the extremities. Nevertheless, specific tumor types target certain age groups and anatomic sites; such clinical information is often critical for the appropriate diagnosis. For instance, most osteosarcomas occur during adolescence, with half arising around the knee, either in the distal femur or proximal tibia. In contrast, chondrosarcomas tend to develop during mid- to late adulthood and involve the trunk, limb girdles, and proximal long bones.

Benign lesions are frequently asymptomatic and are detected as incidental findings. Others produce pain or a slowly growing mass. Occasionally, a sudden pathologic fracture is the first manifestation. Radiologic imaging is important in the evaluation of bone tumors; however, biopsy and microscopic evaluations are necessary for the final diagnosis.

Bone-Forming Tumors
1. Osteoma is a benign lesion of bone that in many cases represent a developmental abnormality or reactive growth rather than true neoplasms. They are most common in the head, including the paranasal sinuses. Microscopically, there is a mixture of woven and lamellar bone. They may cause local mechanical problems (e.g., obstruction of a sinus cavity) and cosmetic deformities.

2. Osteoid Osteoma and Osteoblastoma are benign neoplasms with very similar histologic features. Both lesions typically arise during the 2nd & 3rd decades. They are well-circumscribed lesions, usually involving the cortex. The central area of the tumor, termed the nidus, is characteristically radiolucent. Osteoid osteomas arise most often in the proximal femur and tibia, and are by definition less than 2 cm, whereas osteoblastomas are larger. Localized pain is an almost universal complaint with osteoid osteomas, and is usually relieved by aspirin. Osteoblastomas arise most often
in the vertebral column; they also cause pain, which is not responsive to aspirin. *Malignant transformation is rare unless the lesion is treated with radiation.*

**Gross features**
- Both lesions are round-to-oval masses of hemorrhagic gritty tan tissue.
- A rim of sclerotic bone is present at the edge of both types of tumors.

**Microscopic features**
- There are interlacing trabeculae of woven bone surrounded by osteoblasts.
- The intervening connective tissue is loose, vascular & contains variable numbers of giant cells.

3. Osteosarcoma
This is “a bone-producing malignant mesenchymal tumor.” Excluding myeloma and lymphoma, osteosarcoma is the most common primary malignant tumor of bone (20%). The peak age of incidence is 10-25 years with 75% of the affected patients are *younger than age 20 years*; there is a second peak that occurs in the elderly, usually secondary to other conditions, e.g. Paget disease, bone infarcts, and prior irradiation. Most tumors arise in the metaphysis of the long bones of the extremities, with 60% occurring about the knee, 15% around the hip, & 10% at the shoulder. The most common type of osteosarcoma is primary, solitary, intramedullary, and poorly differentiated, producing a predominantly bony matrix.

**Gross features**
- The tumor is gritty, gray-white, often with foci of hemorrhage and cystic degeneration.
- It frequently destroys the surrounding cortex to extend into the soft tissue.
- There is extensive spread within the medullary canal, with replacement of the marrow. However, penetration of the epiphyseal plate or the joint space is infrequent.

**Microscopic features**
- Tumor cells are pleomorphic with large hyperchromatic nuclei; bizarre tumor giant cells are common, as are mitoses.
The direct production of mineralized or unmineralized bone (osteoid) by malignant cells is essential for diagnosis of osteosarcoma. The neoplastic bone is typically fine, lace-like but can also be deposited in broad sheets.

Cartilage can be present in varying amounts. When malignant cartilage is abundant, the tumor is called a chondroblastic osteosarcoma.

Pathogenesis

Several genetic mutations are closely associated with the development of osteosarcoma. In particular, RB gene mutations that occur in both sporadic tumors, and in individuals with hereditary retinoblastomas. In the latter there are germ-line mutations in the RB gene (inherited).

Spontaneous osteosarcomas also frequently exhibit mutations in genes that regulate the cell cycle including p53, cyclins, etc.

Osteosarcomas typically present as painful enlarging masses. Radiographs usually show a large, destructive, mixed lytic and blastic mass with infiltrating margins. The tumor frequently breaks the cortex and lifts the periosteum. The latter results in a reactive periosteal bone formation; a triangular shadow on x-ray between the cortex and raised periosteum (Codman triangle) is characteristic but not specific of osteosarcomas. Osteosarcomas typically spread hematogenously; 10% to 20% of patients have demonstrable pulmonary metastases at the time of diagnosis.

Cartilage-Forming Tumors

1. Osteochondroma (Exostosis) is a relatively common benign cartilage-capped outgrowth attached by a bony stalk to the underlying skeleton. Solitary osteochondromas are usually first diagnosed in late adolescence and early adulthood (male-to-female ratio of 3:1); multiple osteochondromas become apparent during childhood, occurring as multiple hereditary exostosis, an autosomal dominant disorder. Inactivation of both copies of the EXT gene (a tumor suppressor gene) in chondrocytes is implicated in both sporadic and hereditary osteochondromas. Osteochondromas develop only in bones of endochondral origin arising at the metaphysis near the growth plate of long tubular bones, especially about the knee. They tend to stop growing once the normal growth of the skeleton is completed. Occasionally they develop from flat bones (pelvis, scapula, and ribs). Rarely, exostoses involve the short tubular bones of hands and feet.

Pathological features
Osteochondromas vary from 1-20cm in size.
- The cap is benign hyaline cartilage.
- Newly formed bone forms the inner portion of the head and stalk, with the stalk cortex merging with the cortex of the host bone.

Osteochondromas are slow-growing masses that may be painful. Osteochondromas rarely progress to chondrosarcoma or other sarcoma, although patients with the multiple hereditary exostoses are at increased risk of malignant transformation.

2. **Chondroma** is a benign tumor of hyaline cartilage. When it arises within the medullary cavity, it is termed *enchondroma*; when on the bone surface it is called *juxtacortical chondroma*. Enchondromas are usually diagnosed in persons between ages 20 and 50 years; they are typically solitary and located in the metaphyseal region of tubular bones, *the favored sites being the short tubular bones of the hands and feet*. **Ollier disease** is characterized by multiple chondromas preferentially involving one
side of the body. Chondromas probably develop from slowly proliferating rests of growth plate cartilage.

**Pathological features**

- Enchondromas are gray-blue, translucent nodules usually smaller than 3 cm.
- *Microscopically*, there is well-circumscribed hyaline matrix and cytologically benign chondrocytes.

Most enchondromas are detected as incidental findings; occasionally they are painful or cause pathologic fractures. Solitary chondromas rarely undergo malignant transformation, but those associated with enchondromatosis are at increased risk.

3. **Chondrosarcomas** are malignant tumors of cartilage forming tissues. They are divided into conventional chondrosarcomas and chondrosarcoma variants. Each of these categories comprises several distinct types, some defined on microscopic grounds & others on the basis of location within the affected bone, for e.g. they are divided into central (medullary), peripheral (cortical), and juxtacortical (periosteal).

*The common denominator of chondrosarcoma is the production of a cartilaginous matrix and the lack of direct bone formation by the tumor cells (cf osteosarcoma).* Chondrosarcomas occur roughly half as frequently as osteosarcomas; most patients age 40 years or more, with men affected twice as frequently as women.

**Pathological features**
Conventional chondrosarcomas arise within the medullary cavity of the bone to form an expansile glistening mass that often erodes the cortex. They exhibit malignant hyaline or myxoid stroma. **Spotty calcifications** are typically present. The tumor grows with broad pushing fronts into marrow spaces and the surrounding soft tissue. Tumor grade is determined by cellularity, cytologic atypia, and mitotic activity. Low-grade tumors resemble normal cartilage. Higher grade lesions contain pleomorphic chondrocytes with frequent mitotic figures with multinucleate cells and lacunae containing two or more chondrocytes. **Dedifferentiated chondrosarcomas** refers to the presence of a poorly differentiated sarcomatous component at the periphery of an otherwise typical low-grade chondrosarcoma. Other histologic variants include
myxoid, clear-cell and mesenchymal chondrosarcomas. Chondrosarcomas commonly arise in the pelvis, shoulder, and ribs. A slowly growing low-grade tumor causes reactive thickening of the cortex, whereas a more aggressive high-grade neoplasm destroys the cortex and forms a soft tissue mass. There is also a direct correlation between grade and biologic behavior. Size is another prognostic feature, with tumors larger than 10 cm being significantly more aggressive than smaller tumors. High-grade Chondrosarcomas metastasize hematogenously, preferentially to the lungs and skeleton.

**Fibrous and Fibro-Osseous Tumors**

Fibrous tumors of bone are common and comprise several morphological variants.

1. **Fibrous Cortical Defect and Nonossifying Fibroma**

   *Fibrous cortical defects* occur in 30% to 50% of all children older than 2 years of age; they are probably developmental rather than true neoplasms. The vast majority are smaller than 0.5 cm and arise in the metaphysis of the distal femur or proximal tibia; almost half are bilateral or multiple. They may enlarge in size (5-6 cm) to form *nonossifying fibromas*. Both lesions present as sharply demarcated radiolucencies surrounded by a thin zone of sclerosis. *Microscopically* they are cellular and composed of benign fibroblasts and macrophages, including multinucleated forms. The fibroblasts classically exhibit a storiform pattern. Fibrous cortical defects are asymptomatic and are usually only detected as incidental radiographic lesions. Most undergo spontaneous differentiation into normal cortical bone. *The few that enlarge into nonossifying fibromas can present with pathologic fracture; in such cases biopsy is necessary to rule out other tumors.*

2. **Fibrous Dysplasia** is a benign mass lesion in which *all components of normal bone are present, but they fail to differentiate into mature structures*. Fibrous dysplasia occurs as one of three clinical patterns:
   A. Involvement of a single bone (monostotic)
   B. Involvement of multiple bones (polyostotic)
   C. Polyostotic disease, associated with café au lait skin pigmentation and endocrine abnormalities, especially precocious puberty (*Albright syndrome*).

   Fibrous dysplasia can be:
   - **Monostotic fibrous dysplasia** accounts for 70% of cases
   - **Polyostotic fibrous dysplasia without endocrine dysfunction** accounts for the majority of the remaining cases.
   - **Albright syndrome** accounts for 3% of all cases.

**Gross features**

- The lesion is well-circumscribed, intramedullary; large masses expand and distort the bone.

On section it is tan-white and gritty.

**Microscopic features**

- There are *curved trabeculae of woven bone* (mimicking Chinese characters), *without osteoblastic rimming*
- The above are set within fibroblastic proliferation

*Rarely, polyostotic disease can transform into osteosarcoma, especially following radiotherapy.*

**Other Bone Tumors**
1. Ewing Sarcoma & Primitive Neuroectodermal Tumor (PNET) are primary malignant small round-cell tumors of bone and soft tissue. They are viewed as the same tumor because they share an identical chromosome translocation; they differ only in degree of differentiation. PNETs demonstrate neural differentiation whereas Ewing sarcomas are undifferentiated. After osteosarcomas, they are the second most common pediatric bone sarcomas. Most patients are 10 to 15 years old. The common chromosomal abnormality is a translocation that causes fusion of the EWS gene with a member of the ETS family of transcription factors. The resulting hybrid protein functions as an active transcription factor to stimulate cell proliferation. These translocations are of diagnostic importance since almost all patients with Ewing tumor have t(11;22).

**Pathological features**
- Ewing sarcoma and PNETs arise in the medullary cavity but eventually invade the cortex and periosteum to produce a soft tissue mass.
- The tumor is tan-white, frequently with foci of hemorrhage and necrosis.

**Microscopic features**
- There are sheets of uniform small, round cells that are slightly larger than lymphocytes with few mitoses and little intervening stroma.
- The cells have scant glycogen-rich cytoplasm.
- The presence of Homer-Wright rosettes (tumor cells circled about a central fibrillary space) indicates neural differentiation, and hence indicates by definition PNET.

Ewing sarcoma and PNETs typically present as painful enlarging masses in the diaphyses of long tubular bones (especially the femur) and the pelvic flat bones. The tumor may be confused with osteomyelitis because of its association with systemic signs & symptoms of infection. X-rays show a destructive lytic tumor with infiltrative margins and extension into surrounding soft tissues. There is a characteristic periosteal reaction depositing bone in an onionskin fashion.
1. **Giant-Cell Tumor of Bone (GCT):**
   is dominated by multinucleated osteoclast-type giant cells, hence the synonym *osteoclastoma*. GCT is locally aggressive, usually arising in individuals in their 20s to 40s. Current opinion suggests that the giant cell component is likely a reactive macrophage population and the mononuclear cells are neoplastic. Tumors are large and red-brown with frequent cystic degeneration. They are composed of uniform oval mononuclear cells with frequent mitoses, with scattered osteoclast-type giant cells that may contain 30 or more nuclei.

The majority of GCTs arise in the epiphysis of long bones around the knee (distal femur and proximal tibia). Radiographically, GCTs are large, purely lytic, and eccentric; the overlying cortex is frequently destroyed, producing a bulging soft tissue mass with a thin shell of reactive bone. Although GCTs are benign, roughly 50% recur after simple curettage; some malignant examples (5%) metastasize to the lungs.