MUSCULOSKELETAL PATHOLOGY-2 METABOLIC DISEASES

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OSTEOPENIA AND OSTEOPOROSIS

- Osteopenia: decreased bone mass
- Osteoporosis (OP): severe osteopenia that predisposes to fracture

Radiologically:

- Osteopenia: bone mass is 1-2.5 standard deviation below mean normal
- Osteoporosis: <2.5 SD of normal bone mass
- Normally, maximum bone density is reached in second decade of life, then an annual loss of 0.7% of mass takes place
- Maximum mass depends on genetic factors, diet and exercise

CLINICAL TYPES OF OSTEOPOROSIS

- Might be localized to certain bones (disuse of limbs)
- Generalized OP is mostly primary, seen is two settings:

A) Senile

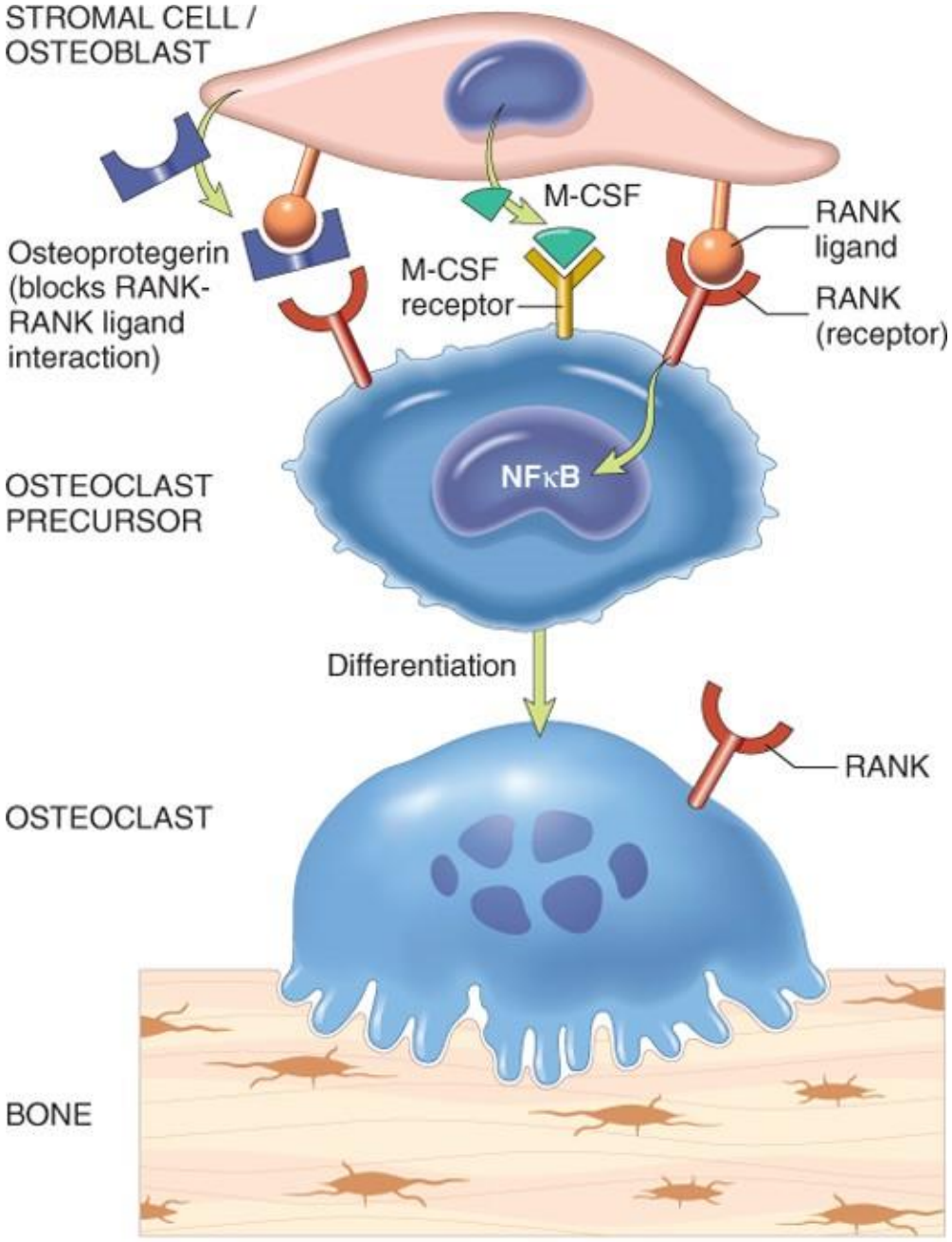
B) Post-menopausal

- Secondary OP is rare, associated with:

A) Endocrine diseases (hyperthyroidism)

B) Gastrointestinal diseases (malnutrition)

C) Exposure to drugs (corticosteroid, heparin)



- Paracrine mechanisms regulating osteoclast formation and function. Osteoclasts are derived from the same stem cells that produce macrophages. RANK (receptor activator for nuclear factor-κB) receptors on osteoclast precursors bind RANK ligand (RANKL) expressed by osteoblasts and marrow stromal cells. Along with macrophage colony-stimulating factor (M-CSF), the RANK-RANKL interaction drives the differentiation of functional osteoclasts. Stromal cells also secrete osteoprotegerin (OPG) that acts as a decoy receptor for RANKL, preventing it from binding the RANK receptor on osteoclast precursors. Consequently OPG prevents bone resorption by inhibiting osteoclast differentiation

SENILE OP

- Occurs due to:
- Age-related cellular changes (low replication rate of cells, less biosynthesis)
- Reduced physical activity (resistance training > endurance)
- Genetic factors: polymorphism in RANK, RANKL, OPG, HLA, estrogen receptors
- Calcium deficiency in adolescence (especially in girls) and vitamin D deficiency are risk factors for senile OP
- Called: low-turn over OP

POST MENOPAUSAL OP

- Under normal conditions, estrogen:

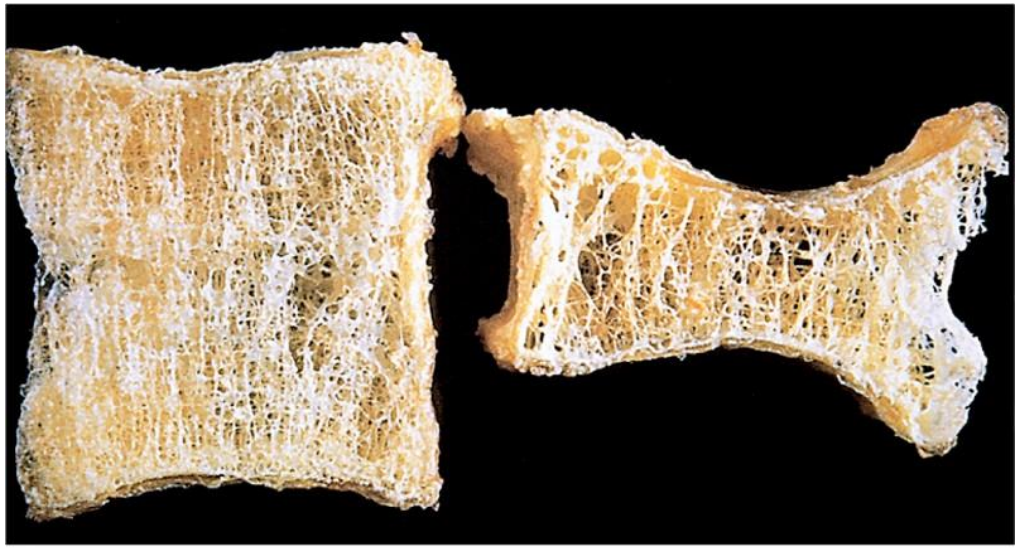
a) Inhibits apoptosis of osteoblasts

b) Increases apoptosis of osteoclasts

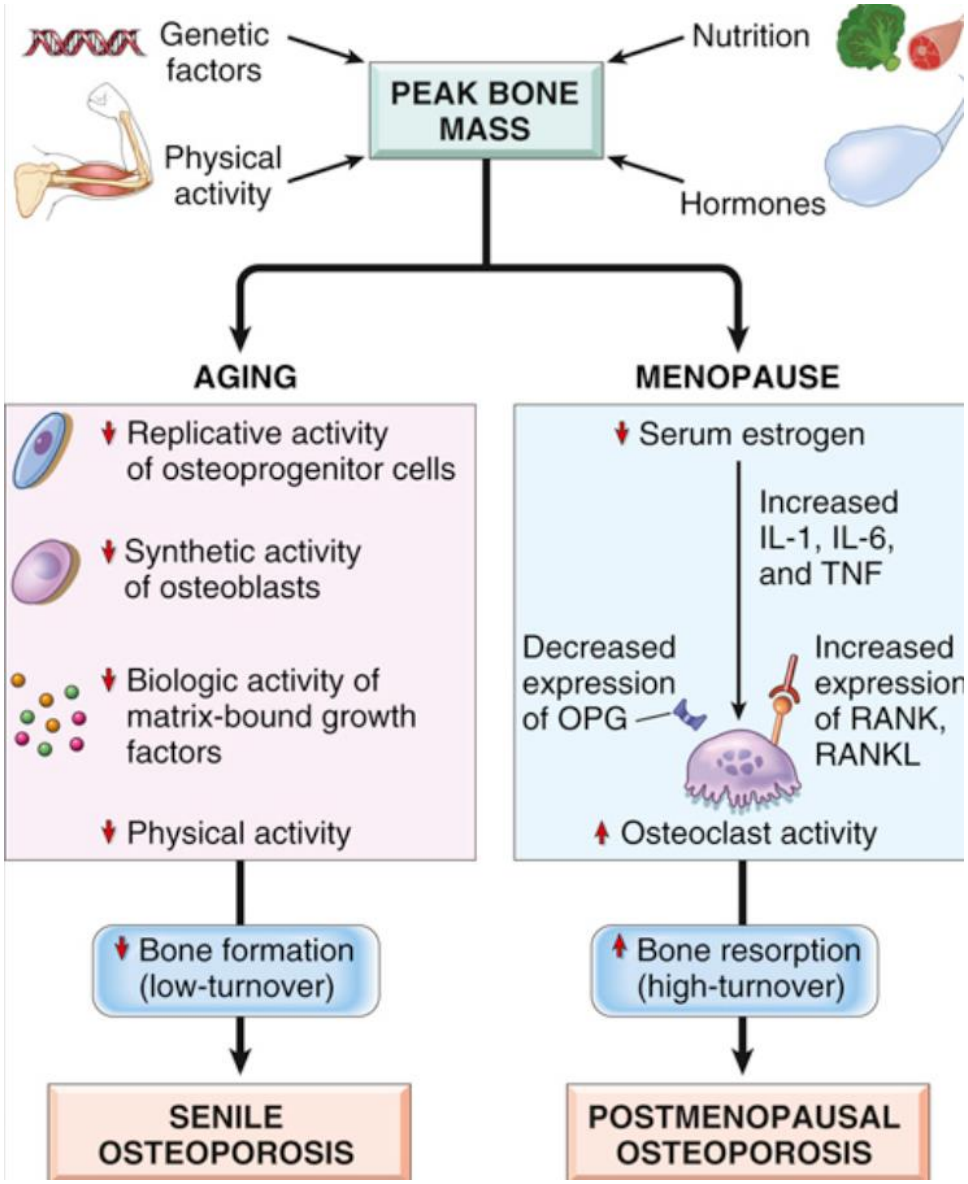
c) Inhibits RANKL (by suppressing cytokines)

- The rate of bone loss in postmenopausal women is 2% every year
- 40% of postmenopausal women suffer from osteoporosis
- For unknown reasons, estrogen deficiency causes increase in serum cytokines (IL-1, IL-6, TNF) which all activate RANKL
- Called: high-turn over OP

MORPHOLOGY: GROSS

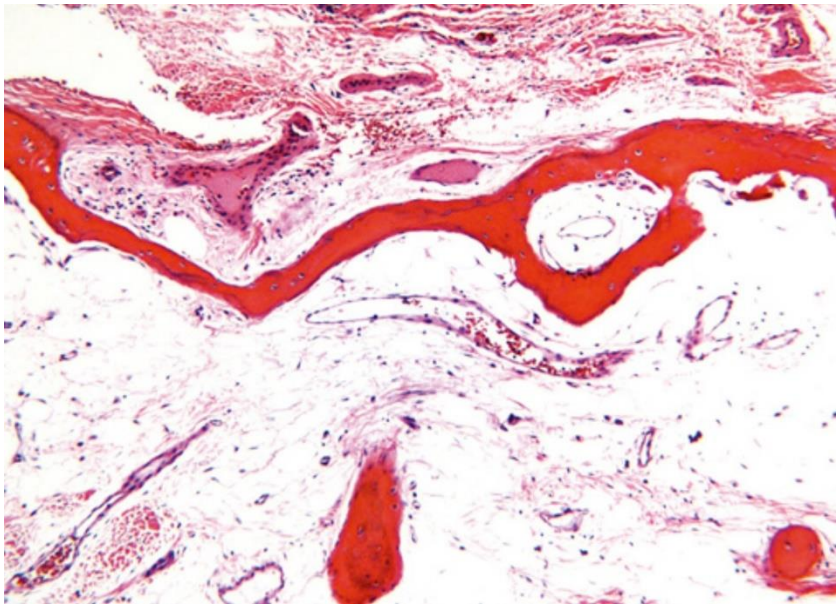


- Grossly: decreased interconnections, more porous
- Most prominent regions: cancellous bones of vertebrae, femur neck



- IL, Interleukin;
- OPG, osteoprotegerin;
- RANK, receptor activator of nuclear factor kappa-B;
- RANKL, receptor activator of nuclear factor kappa-B ligand;
- TNF, tumor necrosis factor

MORPHOLOGY: MICROSCOPIC



- Normal morphology, but less tissue
- Bone trabeculae becomes thin

CLINICAL COMPLICATIONS

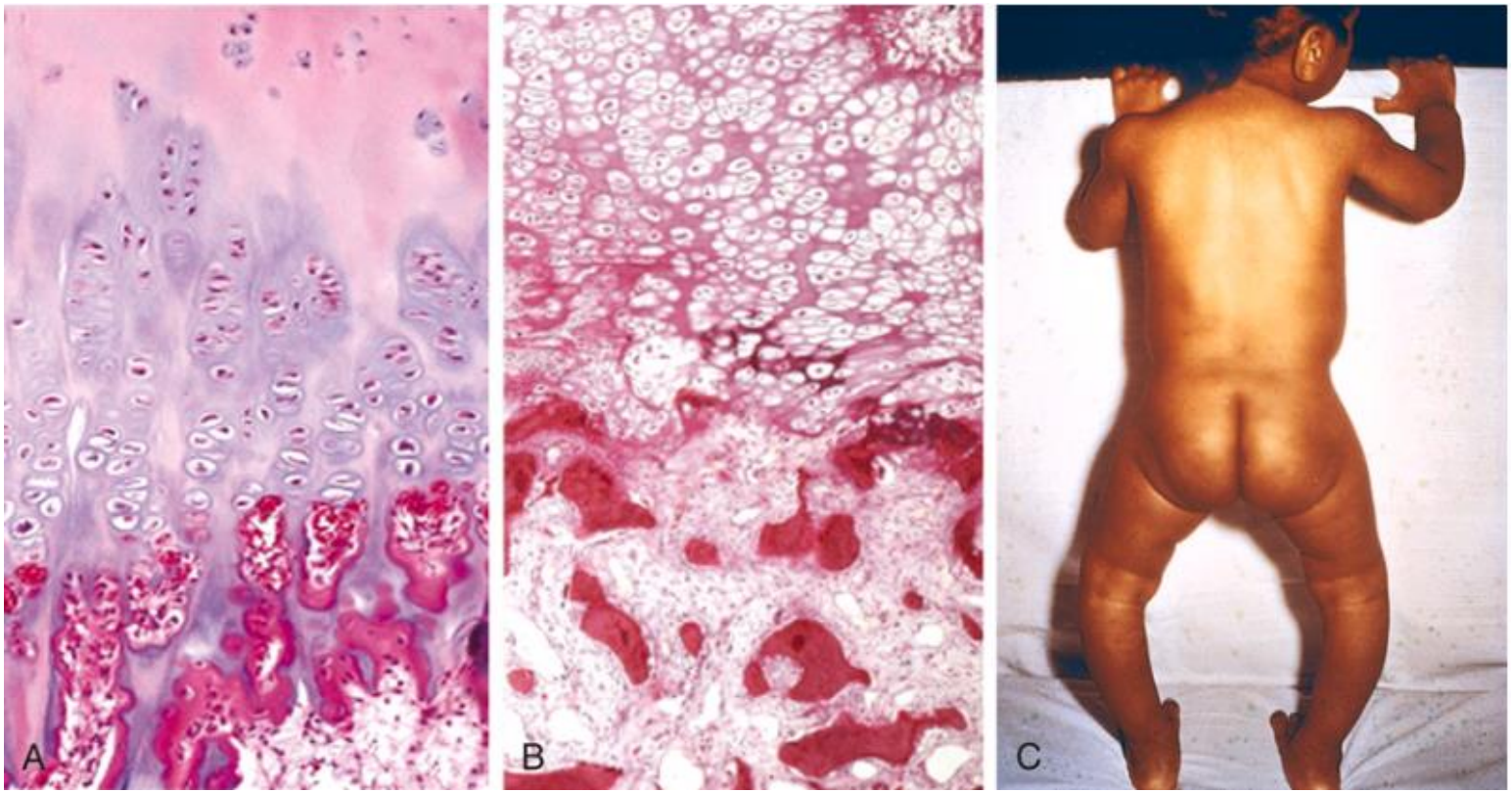
- Fracture is painful, causes significant morbidity
- Fracture of spine causes deformity, lordosis, kyphoscoliosis
- Fracture of femur neck or pelvis may cause fat embolism, pneumonia
- A few patients are asymptomatic

RICKETS AND OSTEOMALACIA

- Bone disease secondary to vitamin D deficiency or its abnormal metabolism
- Rickets: occurs in children, abnormal deposition of bone in the growth plates
- Osteomalacia: occurs in adults, bone has less minerals, prone to fractures
- Vitamin D deficiency is caused by limited sun exposure, inadequate dietary vitamin D, malabsorption disease, renal disease (no conversion to the active form: 1,25-dihydroxyvitamin D)
- Vitamin D deficiency results in hypocalcemia, which activates secretion of parathyroid hormone, aggravating bone resorption

RICKETS

- Growth of long tubular bones occur through endochondral ossification
- The cartilage of epiphysial plate is provisionally mineralized, then reabsorbed and replaced by osteoid matrix, which undergo mineralization to create bone.
- In rickets, epiphyseal cartilage appears large and distorted due to inadequate calcification and failure of maturation, may protrude into bone marrow cavity
- There is deposition of osteoid matrix on this cartilage, but the replacement is disordered, and show lateral expansion of the osteochondral junction



- Rickets. (A) Normal costochondral junction of a young child. Note cartilage palisade formation and orderly transition from cartilage to new bone. (B) Rachitic costochondral junction in which the palisade of cartilage is absent. Darker trabeculae are well-formed bone; paler trabeculae consist of uncalcified osteoid. (C) Note bowing of legs as a consequence of the formation of poorly mineralized bone in a child with rickets.

MORPHOLOGIC CHANGES OF RICKETS

Infants:

- Craniotabes: flattened soft skull bone
- Frontal bossing
- Chest deformity: large costochondral junction appears as nodules. Inward bending of ribs due to pull of respiratory muscles and diaphragm (Harrison groove)

Toddlers

- Deformity of pelvis, spines (lordosis)
- Bowing of lower limbs

MORPHOLOGY OF OSTEOMALACIA

- Grossly, bone has normal contour, but fragile
- Histologically: abundant osteoid matrix deposition, but appears eosinophilic (not mineralized), in contrast to normal basophilic osteoid (well-mineralized)

HYPERPARATHYROIDISM

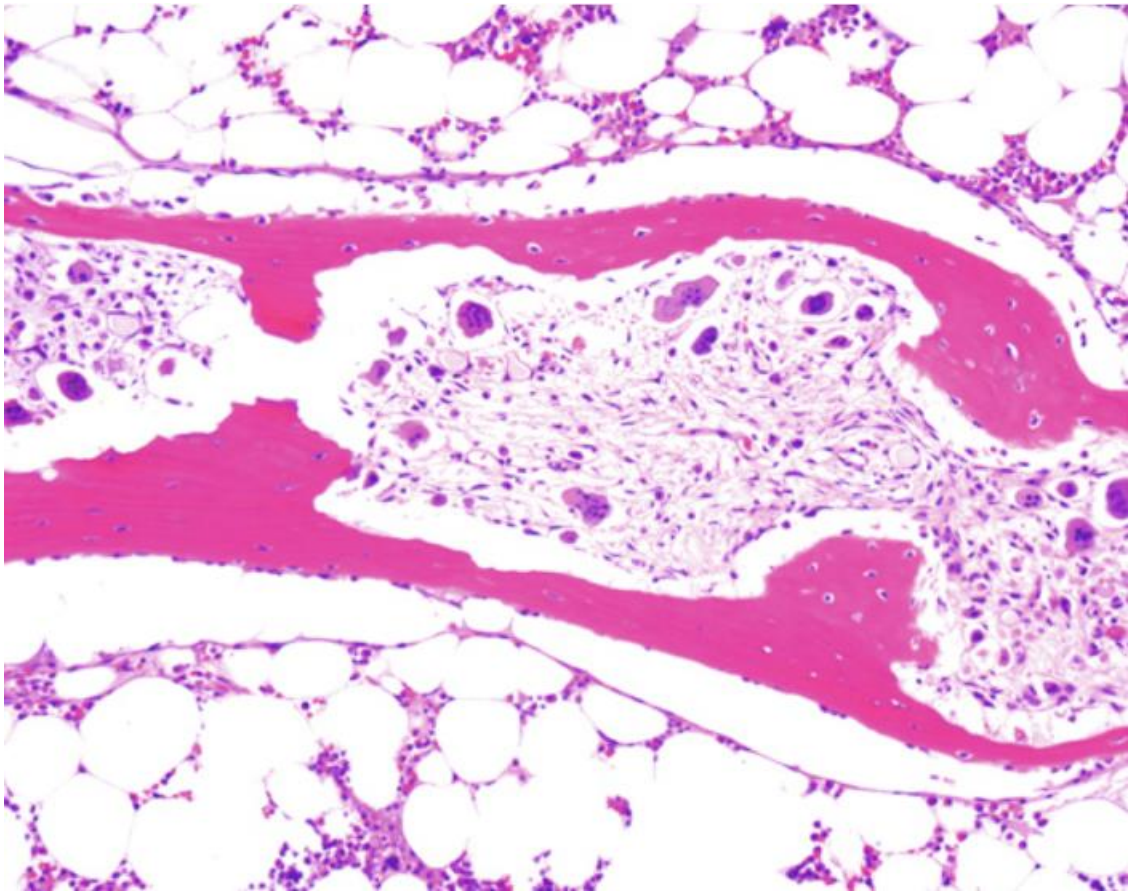
- PTH causes osteoclast activation, through increased RANKL expression on osteoblasts
- Increased reabsorption of calcium by renal tubules
- Increased urinary excretion of phosphates
- Increased synthesis of active vitamin D
- End result: generalized bone osteopenia, hypercalcemia and hypophosphatemia
- Small bones of phalanges, vertebra and proximal femur show the most prominent changes

ETIOLOGY

- Mostly secondary to parathyroid gland adenoma, called "primary hyperparathyroidism"
- Most cases are sporadic (middle age adults)
- Sometimes syndromic (multiple endocrine neoplasia syndrome), appears early in life
- Secondary hyperparathyroidism: seen patients with renal failure (no active vitamin D → hypocalcemia → increased PTH)

MICROSCOPIC CHANGES

- Thin bone trabeculae (similar to **osteoporosis**)
- **Dissecting osteitis** (railroad appearance of bone trabeculae)
- **Brown tumor**: due to repeated microfractures, the bone marrow is replaced by macrophages, fibroblasts, blood vessels and hemorrhage. Hemosiderin appears brown in color.
- In advanced stage, cysts and cavities develop, a condition called: **osteitis fibrosa cystica**



- Hyperparathyroidism with osteoclasts boring into the center of the trabecula (dissecting osteitis)

PAGET DISEASE

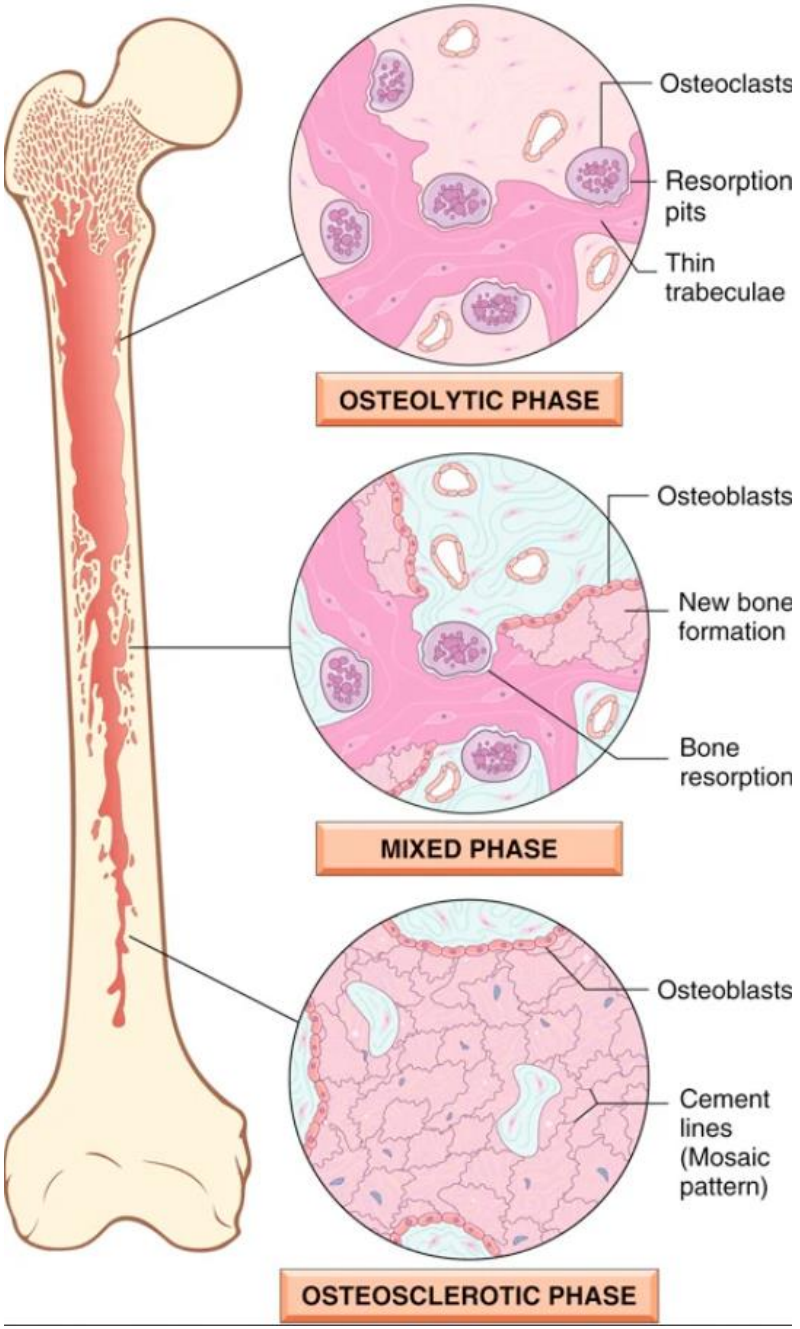
- Also called Osteitis Deformans
- Characterized by increased bone formation, that is disordered and abnormal
- Repetitive episodes of severe, regional osteoclastic activity and bone resorption *(osteolytic stage),* followed by exuberant bone formation *(mixed osteoclastic-osteoblastic stage),* and finally by an apparent exhaustion of cellular activity *(osteosclerotic stage)*
- The net effect of this process is *gain in bone mass;* however, the newly formed bone is disordered and lacks strength
- Does not occur until mid-adulthood but becomes progressively more common thereafter
- White population

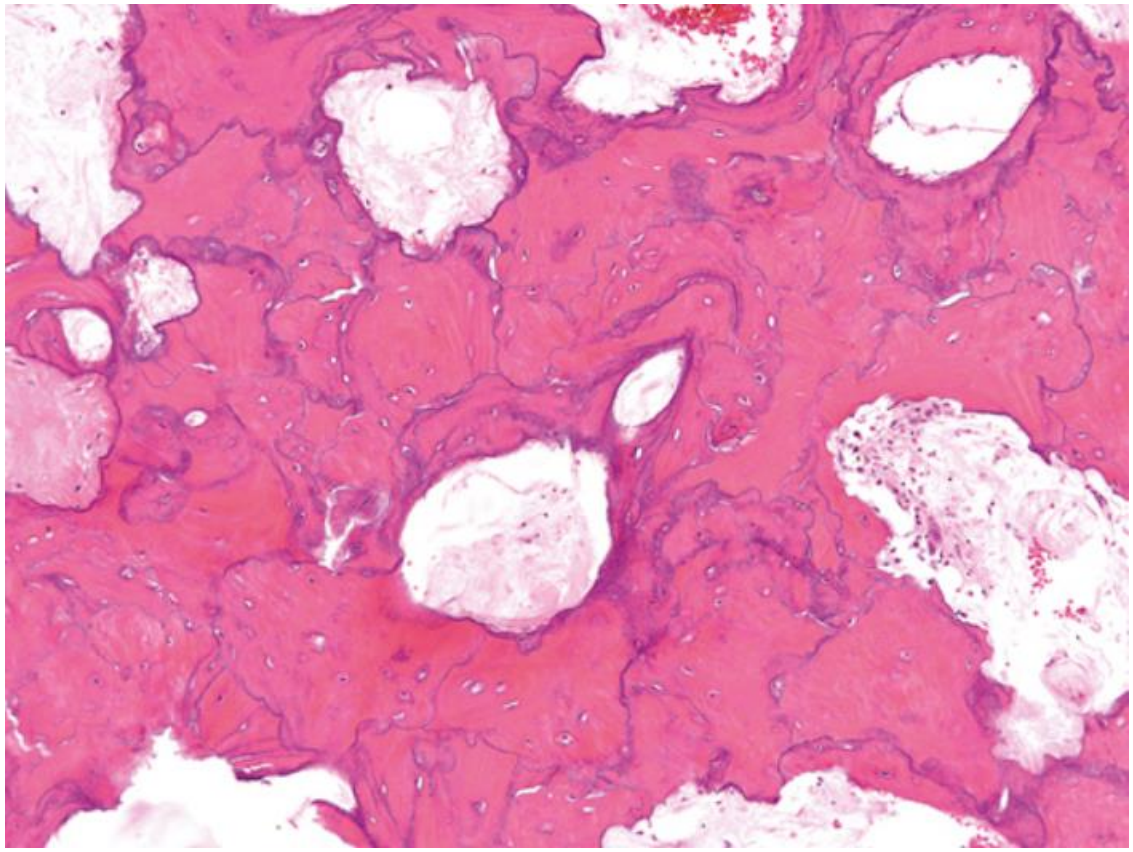
PATHOGENESIS

- Familial cases of Paget disease are present
- Sequestosome-1 mutation (SQSTM1) occurs in 50% of familial cases and 10% of sporadic cases
- It activates NF-kB, which activates osteoclasts
- Activating mutations in RANK gene and inactivating mutations in OPG result in juvenile-onset Paget disease
- Environmental factors: osteoclasts precursors are infected by measles, paramyxovirus

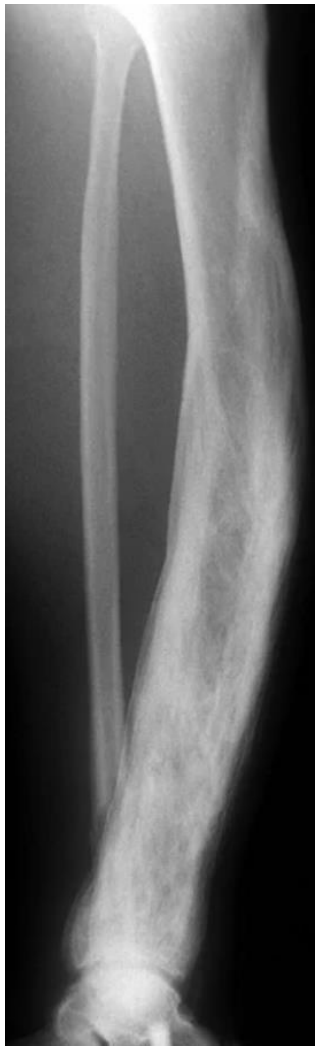
MICROSCOPIC FINDINGS

- Initial lytic phase: numerous large osteoclasts, some have >100 nuclei
- Mixed phase: osteoclasts persist, osteoblasts increase in number
- Sclerotic phase: mosaic pattern and jigsaw-puzzle of lamellar bone





- Mosaic pattern of lamellar bone pathognomonic of Paget disease



- Severe Paget disease. The tibia is bowed. The affected portion is enlarged and sclerotic, and it exhibits irregular thickening of both cortical and cancellous bone

CLINICAL FINDINGS

- 85% are polyostotic, 15% monostotic
- Spine and proximal femur are involved in 80% of cases
- Most cases are asymptomatic
- Localized pain is the most common symptom (microfracture, nerve compression)
- Leontiasis ossea (lion face): enlargement of craniofacial bones, heavy skull
- Platybasia: base of skull is flattened and compress against posterior fossa.
- Bowing of femur and tibia, Secondary osteoarthritis
- Kyphosis, spinal cord injury
- Increased vascularity in bone: warm skin, heart failure
- Secondary osteosarcoma