Spot Diagnosis
Osteopetrosis

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Osteopetrosis

- First described in 1904 by a German scientist Albers-Schönberg.
- Osteopetrosis is a syndrome characterized by the failure of osteoclasts to resorb bone. As a consequence, bone modeling and remodeling are impaired resulting in skeletal fragility despite increased bone mass, and it may also cause hematopoietic insufficiency, disturbed tooth eruption, nerve entrapment syndromes, and growth impairment.
Osteoclast

- An osteoclast is a large cell that is characterized by multiple nuclei and a cytoplasm with a homogeneous, "foamy" appearance. This appearance is due to a high concentration of vesicles and vacuoles.
Osteoclastogenesis

- **RANKL** (Receptor Activator for Nuclear Factor κ B Ligand), also known as TNF-related activation-induced cytokine (TRANCE), osteoprotegerin ligand (OPGL), and ODF (osteoclast differentiation factor), is a surface-bound molecule found on osteoblasts serves to activate osteoclasts.
Osteoclastogenesis

- M-CSF acts through its receptor on the osteoclast, c-fms (colony stimulating factor 1 receptor), a transmembrane tyrosine kinase-receptor, leading to secondary messenger activation of tyrosine kinase Src.

- Osteoprotegerin (OPG), which binds to RANKL thereby preventing interaction with RANK, inhibits osteoclastogenesis.
At a site of active bone resorption, the osteoclast forms a specialized cell membrane, the "ruffled border," that touches the surface of the bone tissue. The ruffled border, which facilitates removal of the bony matrix, is a morphologic characteristic of an osteoclast that is actively resorbing bone.
Osteoclast

- Inside bone, osteoclasts lie in small cavities called Howship’s Lacunae.
- The sealing zone is the attachment of the osteoclast's plasmalemma to the underlying bone bounded by belts of specialized adhesion structures called podosomes.
- The osteoclast releases hydrogen ions through the action of carbonic anhydrase and avacoular ATPase acidifying and aiding dissolution of the mineralized bone matrix into Ca2+, H3PO4, H2CO3, water and other substances.
- In addition, several hydrolytic enzymes, such as members of the cathepsin and matrix metalloprotease (MMP) groups, are released to digest the organic components of the matrix.
Etiology

• 116-kD subunit of vacuolar proton pump
• Chloride channel 7
• Cathepsin K
• Carbonic anhydrase 2
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Infantile</th>
<th>Intermediate</th>
<th>Adult Onset</th>
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</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>AR</td>
<td>AR</td>
<td>AD</td>
</tr>
<tr>
<td>Bone marrow Failure</td>
<td>Severe</td>
<td>None</td>
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<tr>
<td>Prognosis</td>
<td>Poor</td>
<td>Poor</td>
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Clinical Features
Infantile Osteopetrosis

- Failure to thrive and growth retardation are symptoms.
- Bony defects occur.
  - Nasal stuffiness
  - Neuropathies deafness, proptosis, and hydrocephalus.
  - Delayed dentition
  - Osteomyelitis of the mandible
  - Bones are fragile and can fracture easily.
- Defective osseous tissue tends to replace bone marrow, which can cause bone marrow failure.
- Extramedullary hematopoiesis might occur with resultant hepatosplenomegaly, hypersplenism, and hemolysis.
- Other manifestations include sleep apnea and blindness due to retinal degeneration.
Investigations
Lab Findings

- Hypocalcemia
- Secondary hyperparathyroidism
- Acid phosphatase is increased
- Levels of creatinine kinase isoform BB (CK-BB) is increased
Radiologic Findings

- Generalized osteosclerosis.
- Alternating sclerotic and lucent bands may be noted in iliac wings and near ends of long bones.
- The bones might be clublike or appear like a bone within bone (endobone).
- The entire skull is thickened and dense, especially at the base. Sinuses are small and underpneumatized.
- Radiodense vertebrae may show alternating bands, known as the rugger-jersey sign.
- Fractures or osteomyelitis.
Histologic Findings

• Failure of osteoclasts to resorb skeletal tissue is the pathognomonic feature of true osteopetrosis. Remnants of mineralized primary spongiosa are seen as islands of calcified cartilage within mature bone. Woven bone is commonly seen. Osteoclasts can be increased, normal, or decreased in number.
Treatment & Medication
• Vitamin D (calcitriol)
• Gamma interferon
• Erythropoietin
• Corticosteroids
• Treatment of complications
• Bone Marrow Transplant
Questions!!