Pagets disease of bone

HISTORY OF PRESENTING ILLNESS:

- GRADUALLY WORSENING PAIN AND DEFORMITY:
  - Pelvis
  - Spine
  - Skull
  - Femur
  - Tibia

The pain is typically bony pain, i.e. dull and gnawing, worse at night

What kind of deformity?
- BOWING of the tibia
- Worsening KYPHOSIS
- FRONTAL BOSSING
- HEAD ENLARGEMENT (!)
- FACIAL DEFORMITY
- LOSS OF TEETH
- CRANIAL NERVE ENTRAPMENT especially CN 8- thus, HEARING LOSS

May cause secondary arthritis; walking on bowed tibias causes unnatural mechanical stresses on your joints

DIFFERENTIALS ACCORDING TO THE FACULTY

- Metabolic bone disease
  - osteoporosis +/- crush fractures, Paget's disease.
- Primary malignancy of bone or marrow
  - e.g. multiple myeloma, osteosarcoma
- Extra-vertebral disease effecting bone.
  - eg bony metastases from remote tumour.
- Infection
  - spinal osteomyelitis or epidural abscess.
- Degenerative spinal disease
  - facet joint OA, disc herniation, spinal canal stenosis,
- Referred pain
  - abdominal aortic aneurysm, carcinoma pancreas

INVESTIGATIONS

- Alkaline Phosphatase: Bone-specific AP is better; marker of bone formation
- Urinary Hydroxyproline levels, marker of bone resorption
  The degree of bone marker elevation reflects the extent and severity of the disease.
  Serum total ALP remains the test of choice for assessing response to treatment
- Calcium, Phosphorus
- Serum 25OH Vitamin D

RADIOLOGY

- "Blade of grass" lesion – first phase (its in someone's distal humerus)
- Diffuse radiodense enlargement of a vertebra is referred to as "ivory vertebra."

MANAGEMENT: must stop the osteoclasts!

CALCIUM SUPPLEMENTS + BISPHOSONATES: the “-dronates”; tiludronate, alendronate, and risedronate

FOSAMAX
- Is Alendronate

PAMIDRONATE is the only one used intravenously.!! BE SURE TO GET ENOUGH Ca++
synthetic analogues of pyrophosphate that bind to the hydroxyapatite found in bone. Fosamax (alendronate sodium) is a bisphosphonate that acts as a potent, specific inhibitor of osteoclast mediated bone resorption. Preferentially to sites of bone resorption, specifically under osteoclasts, and inhibits osteoclastic bone resorption with no direct effect on bone formation.

May result in hypocalcemia if bone formation proceeds at a ridiculous rate while bone resorption is inhibited.

ANALGESIA – NSAIDs +/- Opiates (try to stay out of the opiates)

Plus... SURGICAL MANAGEMENT of severe deformity + access devices eg canes, walkers...
RISK FACTORS:
Genetics
- positive family history in 5 to 25% of patients
- disease 7 or 10 times more prevalent in first degree relatives
- genes implicated include a receptor activator for a nuclear factor (RANK) involved in osteoclast differentiation.
- Other genes as well, far too many to list
Overall, a heterogenous multigenic inheritance pattern

EXACT AETIOLOGY IS UNKNOWN:
? does a virus (measles) alter the DNA of those osteoclasts? Maybe another virus?

Alkaline Phosphatase is released

The cells that come to replace the bone that is being destroyed are FUNCTIONALLY NORMAL OSTEOLASTS

Hypervascularity
Happens because woven bone is much more permeable to blood vessels

Second phase: Woven Bone Formation
replaces normal lamellar bone with haphazard (woven) bone. Not structurally sound, is it.
At the same time, fibrous connective tissue may replace normal bone marrow

The final Sclerotic Phase.
bone resorption declines progressively
Remaining behind from this process:
hard, dense, less vascular pagetic or mosaic bone, which represents the so-called burned-out phase of Paget disease.

WITH MASSIVE SKELETON INVOLVEMENT: the diversion of blood into the great volume of hypervascular bone may cause HIGH OUTPUT HEART FAILURE; PLUS so much calcium floating around causes AORTIC STENOSIS and diffuse VASCULAR CALCIFICATION

Over-recruitment of precursors by an increased level of IL-6

Increased NUMBER and ACTIVITY of Pagetic osteoclasts
- Large
  - Increased 10- to 100-fold in number,
  - A greater number of nuclei (as many as 100 compared to the normal 3 to 5 nuclei)
  - THUS: sevenfold increase in resorptive surfaces; and so
  - Erosion rate of 9 times the normal

Thus, the CHARACTERISTIC FEATURES:
increased bone resorption + accelerated bone formation

Initial osteolytic phase
- prominent bone resorption
- marked hypervascularization.
- warmth and swelling can be palpated
Radiographically, this looks like an advancing lytic wedge, or "blade of grass" lesion

OVER-Expression of the c-fos protooncogene in the osteoclast: (thus launching osteoclasts into relentless activity)

OVER-Expression of the anti-apoptotic bcl-2 gene: hence prolonged osteoclast survival

Hyper-responsiveness of the precursor (inactive) osteoclasts to active Vit D

Osteoclasts are hyper-responsive to the RANK ligand (genetic abnormality)
(RANK seems to mediate the effects of all other bone growth factors on the osteoclast)

OVER-Expression of the c-fos protooncogene in the osteoclast: (thus launching osteoclasts into relentless activity)