Paget's Disease (Osteitis Deformans)

Background
1. Definition
   - Metabolic bone disease characterized by accelerated bone resorption and formation, resulting in bone that is less organized and more susceptible to deformity and fracture
2. General info
   - Unknown etiology
   - Viral and genetic factors have been implied

Pathophysiology
1. Pathology of disease
   - Affected osteoclasts increase in both size and number causing increased rate of bone resorption
   - In response, osteoblasts form bone in a more rapid and less organized manner, resulting in a mosaic pattern
2. Incidence/prevalence
   - 1-3% of adults >40 yo
   - Incidence increases with age
3. Risk factors
   - Higher prevalence in western Europe (UK, Germany and France) and populations that have immigrated to Australia, North and South America, New Zealand, and South Africa
4. Morbidity/mortality
   - 70% asymptomatic (most cases discovered incidentally)
   - Fractures are most common
   - Deafness
   - Tumors
   - Bone deformities

Diagnostics
1. History
   - Symptomatic patients will often present with deep, aching bone pain, even at rest
   - Paget's in the skull can cause narrowing of foramina, resulting in hearing loss, cranial nerve palsies, and risk of brainstem compression
2. Physical examination
   - Skeletal deformities
     - Bowing of lower extremities
     - Frontal bossing
   - Increased warmth over affected area
3. Diagnostic testing
   - Labs
     - Elevated total serum alkaline phosphatase
     - Vitamin D levels to rule out deficiency
- Serum calcium to rule out hyperparathyroidism
  - Normal in Paget's
- Urinary deoxypyridinoline and N-telopeptide of type I collagen are less reliable and more expensive
  - Imaging
    - Radiographs
      - Active sites often have an osteolytic front (classically 'blade of grass' lesion)
      - Long bones will show cortical thickening and sclerotic changes
    - Bone Scans
      - Most sensitive in detecting sites of active lesions, but are less specific
      - CT and MRI can help differentiate between malignant and Paget's bone
      - Biopsy is definitive

**Differential Diagnosis**

1. Osteosarcoma
   - Tendency to be located in metaphysis of long bones
   - Imaging
     - X-ray: sunburst sign (spiculated periosteal reaction)
     - X-ray: periosteal formation at edge of soft tissue
   - Core needle Bx for definitive Dx

2. Hyperparathyroidism (Osteitis fibrosa cystica)
   - PE
     - Proximal muscle weakness
     - Bone pain
     - Brisk stretch reflexes of muscles
   - Labs
     - Elevated serum Ca/ alkaline phosphatase
     - Elevated PTH (severe)
   - Imaging
     - "Salt-and-pepper" appearance of calvarium
     - Brown's "tumors" (collections of osteoclasts, causing lytic lesions in long bones and pelvis)
     - Resorption of terminal phalanges, distal clavicles

3. Osteomalacia (Vitamin D deficiency)
   - Low serum 25(OH)2D or low 1,25(OH)2D levels
   - Hypophosphatemia
   - Increase in alkaline phosphatase
   - Pathologic fracture
     - Fracture associated with abnormalities as stated herein

4. Traumatic fracture
   - History of trauma
   - Absence of serum markers
   - Absence of characteristics on X-ray for classic Paget's or cancer
5. Osteoporosis
   - Testing to r/o secondary osteoporosis
     - PTHrP (parathyroid hormone related protein) – associated with humoral malignancy
     - Elevated PTH (parathyroid hormone) – hyperparathyroid, associated with hypercalcemia
     - Malignancy (bone mets) – depressed PTH
   - Bone density scanning for classifying severity of disease

**Therapeutics**

1. Initiation of treatment
   - Literature suggests treating the following patients (SOR:B)
     - Symptomatic
     - Asymptomatic with biochemical markers suggestive of bone remodeling (Serum Alkaline Phosphatase or SALP 125-150% above normal)
   - Patients with active lesions in weight bearing limbs or near major joints

2. Bisphosphonates
   - Mainstay of treatment of Paget's is to normalize SALP (serum alkaline phosphatase) (SOR:A)
     - Oral
       - Alendronate 40 mg/d for 6 months
         - Normalization of SALP in 63% of patients in US trial
         - Retreatment when normal or nadir levels rise >25%
       - Risedronate 30 mg/d for 2 months
         - Normalization of SALP in 73% in US trial
         - Retreatment indications same as for Alendronate
       - Etidronate 400 mg/d for 6 months, with at least 6 month interval before retreatment
         - Normalization of SALP in 15%
       - Tiludronate 400 mg/d for 3 months
         - Normalization of SALP in 35% of patients
     - IV
       - Pamidronate 30-90 mg given over 2-3 hour infusion
         - For mild disease, single 60-90 mg dose is commonly used
         - For more advanced disease, 1-2 infusions per week on nonconsecutive days of 90 mg can be given up to 180-360 mg
           - Normal SALP in approximately 50% of patients
           - Fever, flu-like symptoms are most common adverse affects, seen after the first dose
       - Zoledronic acid
         - Currently in consideration for FDA approval
         - 5 mg, 15 minute infusion
         - Normal SALP in up to 89% 6 months after treatment
         - Adverse effects similar to pamidronate

3. Calcitonin
   - Salmon calcitonin given 100 U daily for several months
     - Normalization of SALP in approximately 50% of patients
     - Use of calcitonin has decreased due to efficacy of bisphosphonates
Follow up
1. Office
   o Every 6-12 months in asymptomatic patients, or in treated stable patients to follow serum alkaline phosphate levels
   o Lifetime follow up (rare chance of osteosarcoma)
   o Earlier follow up with recurrence of symptoms
2. Specialist referral
   o Complex or non-union fractures should be referred to orthopedics

Prognosis (SOR:B)
1. Paget's disease is a relatively benign condition with the majority of patients asymptomatic
   o Exceptions are bone pain, deformity, and possible fracture in weight bearing bones
2. The majority of patients treated for elevated SALP achieve a normal level, but this has not been shown to change prognosis
3. Left untreated, osteolytic changes can extend and bone deformities are more likely

References

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