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
    - Every 6-12 months in asymptomatic patients, or in treated stable patients to follow serum alkaline phosphate levels
    - Lifetime follow up (rare chance of osteosarcoma)
    - Earlier follow up with recurrence of symptoms
2. Specialist referral
    - 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
    - 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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Author: Brandon Bryce, MD, *Penn State Hershey Medical Center, PA*

Editor: Melissa Stiles, MD, *Fox Valley FMR, University of WI*