

Paget's Disease of Bone

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Significance of the clinical problem:

Paget's disease of bone is not rare, occurring in perhaps 1% of the older U.S. population. It is a cause of pain and disability, and causes laboratory abnormalities that can be confused with other conditions. It is important to correctly recognize and treat Paget's disease in order to provide relief of symptoms, and to prevent complications, as well as to ensure that other disorders are recognized and properly treated.

Barriers to optimal practice:

- Paget's disease, while not rare, is sufficiently uncommon that many clinicians are not familiar with its laboratory, clinical and radiographic characteristics, and thus may over- or under-diagnose, or may not recognize the complications.
- Due to unfamiliarity, clinicians may not be familiar with optimal treatment strategies.

Learning objectives:

As a result of participating in this session, learners should be able to:

- Understand the pathogenesis of Pagetic lesions.
- Recognize the laboratory and radiographic indicators of Paget's disease.
- Choose appropriate tests for the characterization of disease extent and activity.
- Recognize the major complications of Paget's disease.
- Choose appropriate treatment for Paget's disease and its complications.
- Recognize when highly specialized consultation may be needed.

Pathogenesis and Strategies for Diagnosis and Treatment:

As recently reviewed in the Endocrine Society Guidelines for Paget's Disease of Bone, patients usually come to attention as a result of symptoms or complications, as a result of an abnormal laboratory test result (typically serum alkaline phosphatase) or a radiographic finding. The Guidelines document contains an up to date review and references pertinent to the material in this presentation. A copy of the Guidelines is available at <http://www.endocrine.org/education-and-practice-management/clinical-practice-guidelines>.

The following briefly summarizes the essential points:

- Pathogenesis: Paget's disease is characterized by unusually large, hyperactive osteoclasts that resorb bone in an apparently incoherent manner in focal areas of involvement. Osteoblasts react by forming bone in disorderly patterns, resulting in bone that is often expanded but structurally compromised, resulting in deformity, pain, fracture and adverse effects on adjacent structures. Rarely, sarcomas may arise from areas of Paget's disease. There appear to be roles for both genetic and environmental factors, possibly including paramyxovirus exposure, in the pathogenesis, but the focal nature of the disease is unexplained.
- Paget's disease is usually a radiologic diagnosis. When patients present with pain and/or deformity, the initial step is usually plain radiography of the affected area. Characteristic changes include cortical thickening, a mixture of sclerotic and lytic changes in a coarse pattern, etc. If the skull base is involved, CT is preferred. Once Paget's disease is identified radiographically, total body scintigraphy with correlated radiographs is recommended to determine the extent and location of involvement.
- In most cases, the total serum alkaline phosphatase level is elevated. Other sources of elevated alkaline phosphatase should be excluded. The bone-specific alkaline phosphatase level is somewhat more specific and may be elevated when the total level is not. However, if the total SAP is high due to hepatic or other sources, the cross-reactivity in the BSAP assay may be problematic. The P1NP level correlates well with disease activity and is unaffected by SAP levels. Markers of bone resorption, such as second-morning urinary N-telopeptide/creatinine ratio and the fasting 8 a.m. serum C-telopeptide level provide information about bone resorption activity that responds rapidly to treatment.

- In the evaluation of a patient with a high total serum alkaline phosphatase level, it is useful to test for hepatobiliary involvement, using the gamma-glutamyl transpeptidase (gamma GT) level, and test for bone activity with P1NP. Once it is established that the source is bone, scintigraphy is the next step, followed by radiography.

Important complications include degenerative joint disease, deformity, fracture, deafness due to cochlear involvement, and spinal cord symptoms due to “steal” of circulation.

- Degenerative joint disease commonly occurs in joints involving bones with Paget’s disease, especially those that are weight-bearing. Hip and knee replacement procedures are relatively common in Paget’s patients, but it is important to have the disease under good control prior to such surgery.
- Chronic structural weakness may result in progressive deformity, particularly in weight-bearing bones, such as the femur or tibia, or vertebral bodies.
- Bowed bones are especially susceptible to subacute cracking, called “fissure fractures” along the outer cortex of the bow. These are under chronic distractive forces and may not heal. They can result in complete fractures. If the bow is extreme, prophylactic rod placement may be challenging. The same consideration can be problematic with respect to the stem in arthroplasties.
- In the past, it was thought that hearing loss in Paget’s disease could be due to compression of the 8th cranial nerve, or involvement of the ossicles. It is now clear that the cause in most cases is involvement of the cochlea. The degree of involvement will usually require CT scanning of the skull base with specific attention to the cochleas.
- When one or more vertebral bodies are affected, the function of the spinal cord may be compromised, resulting in paraplegia or quadriplegia, depending on the level. This is thought to be due to a vascular “steal” syndrome. The intravenous infusion of an aminobisphosphonate can rapidly correct this and usually results in reversal of the paralysis. In most instances, surgical intervention will not be necessary.

Treatment:

- In most instances, intravenous zoledronic acid is the preferred treatment, with some exceptions, due to renal impairment or other concerns about adverse effects of that medication. It is very important to correct systemic problems such as vitamin D deficiency prior to treatment, and for the patient to take adequate calcium and vitamin D, in order to minimize the risk of hypocalcemia. Oral bisphosphonates may pose less risk of nephrotoxicity but are generally less efficacious.
- Surgical intervention is often necessary for fractures and other orthopedic complications. It is very important to have the Paget's disease adequately treated prior to surgery in order to minimize the risk of hemorrhage, and to ensure optimal bone strength.
- It is important for the surgeon to have experience with Pagetic bone, as its structural properties can vary widely. For example screws may not hold well.
- Similarly, experience on the part of neurological and neuro-otological consultants can be of great value, especially when there is a question as to whether Paget's disease is an adequate explanation for clinical symptoms or findings.

CONCLUSIONS:

- Paget's Disease of Bone is a focal or multifocal disorder characterized by accelerated, disorderly bone resorption and formation.
- Paget's Disease causes elevation of alkaline phosphatase and other bone turnover markers.
- Pain, deformity and fracture are common features, and the disease can also cause such specific complications as hearing loss and paraplegia, depending on the site of involvement.
- Bisphosphonates are effective in treatment, especially zoledronic acid, unless contraindicated.