

The diagnosis of Paget's disease of bone

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Summary

Paget's disease of bone is a focal disorder of the skeleton whose presentation is variable. Although skeletal deformities and bone pain may be features of the disease, the diagnosis frequently is determined by chance. Unexpected elevations of serum alkaline phosphatase activity and clinically silent lesions found on X-rays or other imaging modalities are a common source of discovery of the problem. X-ray appearance of the lesion is usually sufficient for diagnosis and a bone biopsy is rarely necessary to determine the nature of the pathology.

KEY WORDS: Paget's disease, diagnosis.

Introduction

Paget's disease of bone is a skeletal disorder usually diagnosed in patients over the age of 50 years whose clinical presentation is highly variable. It may be suspected based on physical examination alone but more commonly is brought to attention by unexpected radiological or biochemical findings when an individual is under evaluation for another purpose.

Signs and symptoms

Deformity

A hallmark of Paget's disease is the presence of one or more skeletal deformities (1). The most readily apparent, but sometimes subtle, is enlargement of the skull (Figure 1). This usually produces somewhat asymmetric enlargement of the cranium. In individuals who wear hats a history of a slow increase in hat size may be volunteered or mentioned in answer to a direct question. Hearing loss has been noted in 40-50% of patients with skull involvement and is more common with skull enlargement. The degree of hearing loss is often sufficient to require the use of one or two hearing aids. Tinnitus, vertigo, or both has been reported in about 20% of patients (2).

The lower extremity is another area which may call attention to the presence of Paget's disease. Gradual bowing of either the

femur, the tibia, or occasionally both may proceed so slowly that even the patient may not be aware of the problem. Bowing of a lower extremity bone is usually unilateral and when bilateral can produce a major impairment in ambulation. With increasing severity of the bowing degenerative changes in the articular cartilage of hips, knees, or even ankles may be accelerated. On physical examination this is manifested most obviously in the hip as evidenced by reduced range of motion. Two other features of Paget's disease of the lower extremity are a discernable enlargement of an affected bone and increased skin temperature over the affected bone. This may be associated with enlargement of superficial veins in the region. Edema is occasionally noted, but is more likely related to varicose veins. The increased skin temperature reflects the increased vascularity of the underlying bone and concomitant increased blood flow to the surrounding soft tissue (3). This finding is easily reversed by treatment of Paget's disease with effective drugs. Suppression of disease activity reduces vascularity of pagetic lesions.

Less commonly enlargement and deformity may be noted in a clavicle or upper extremity long bone. Patients with Paget's disease may have kyphosis or scoliosis of the spine but the discernment of enlarged vertebrae by physical examination is difficult.

Bone pain

Bone pain is considered a prominent feature of Paget's disease, although it is present in a minority of patients. The bone pain associated with Paget's disease is generally persistent, moderate in severity, and only slightly increased by weight bearing. Patients with pain are more likely to have degenerative arthritis as the cause. In the absence of physical features of Paget's disease, bone pain is useful in the detection of the disease by directing the appropriate region of the skeleton to undergo radiological evaluation.



Figure 1 - Enlarged skull in a man with deafness who has Paget's disease.

Biochemistry

In 1929 Kay reported that patients with Paget's disease have considerable elevation of serum alkaline phosphatase activity (4), an enzyme found in the plasma membrane of osteoblasts. Subsequently this test has become the most widely used for judging the extent and activity of the disease. Because serum alkaline phosphatase activity has been commonly part of routine chemistry panels since the 1960's, the finding of an elevated level as part of an annual physical examination is a not unusual presentation of Paget's disease. However, the finding of an isolated elevated alkaline phosphatase in the absence of typical physical features of Paget's disease is not sufficient for diagnosis. This requires radiological evaluation, generally begun with a bone scan surveying the entire skeleton.

Other markers of bone formation, such as bone specific alkaline phosphatase, and type I procollagen, carboxyterminal peptide, may be elevated in patients with Paget's disease (5), but these tests are not nearly ordered to the same extent as serum total alkaline phosphatase activity in clinical practice.

As the primary underlying abnormality in Paget's disease is increased osteoclastic activity, parameters of bone resorption are commonly elevated in serum and/or urine of most patients. These include hydroxyproline, N- and C- telopeptides of type I collagen (5) and pyridinolines. As before, none of these tests are ordered as frequently as serum total alkaline phosphatase activity, so that an index of bone resorption would be unusual in calling attention to Paget's disease.

Radiology

In the great majority of patients with Paget's disease the diagnosis is made by X-ray evaluation of the affected region(s) of the skeleton. Although the lesions may be complex, comprised of osteolytic, osteosclerotic and/or mixed abnormalities, experienced evaluators of bone usually have little difficulty in distinguishing the characteristics of Paget's disease from other disorders (6). Occasionally it may be difficult to distinguish Paget's disease from disorders such as osteoblastic metastases or fibrous dysplasia. In these instances other clinical features, such as an elevated serum prostate specific antigen level or an endocrine disorder found in McCune-Albright syndrome, respectively may aid in assuring the appropriate diagnosis. In only a few cases is a bone biopsy necessary to confirm a diagnosis of Paget's disease.

The earliest lesions of Paget's disease are osteolytic in nature, and are most likely to be detected in the skull and long bones. In the skull the lesions are most frequently seen in the frontal and occipital bones (Figure 2). In the long bones, most frequently in the lower extremities, the lesions generally begin at the ends of the bones, rarely in the diaphysis. In patients who are untreated, the osteolytic process has been measured to progress at a rate of about 1 cm per year.

Osteosclerotic bone appears to be present in areas which previously were osteolytic in nature. This is readily seen in the long bones where osteolytic lesions in the shape of an arrowhead may be seen to evolve from an area of sclerotic bone (Figure 3). Another typical feature of the osteosclerotic bone is an increase in the dimensions of the bone.

In the most advanced stage of the disease an entire bone becomes sclerotic and often considerably increased in size. This is readily seen in radiographs of the skull (Figure 4). It should be noted that, if there is concomitant severe osteoporosis, extensive osteosclerosis may be overlooked.

It is not uncommon to discover Paget's disease when X-rays are done for another purpose. Silent Paget's disease may be noted in vertebrae during an intravenous pyelogram or during a



Figure 2 - Osteolytic lesions (arrows) in the frontal and occipital regions of the skull in a woman with Paget's disease.



Figure 3 - Advancing osteolytic lesions (arrows) which evolved from both ends of the tibia in a man with Paget's disease.

small bowel series. Occasionally, Paget's disease may be found when computerized tomography or magnetic resonance imaging are ordered as part of a medical workup.

Bone scans which utilize a technetium 99m-labeled bisphosphonate are the most sensitive means of detecting Paget's disease (7), although X-rays are required to validate the diagno-

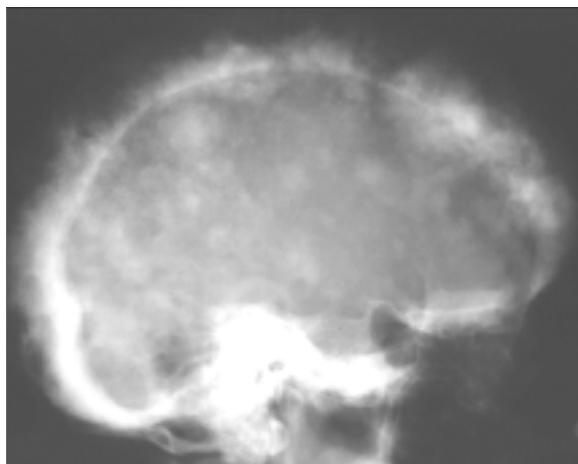


Figure 4 - Osteosclerotic skull of a woman with Paget's disease. Note the thickened cranium and the "cotton-wool" appearance in some areas.

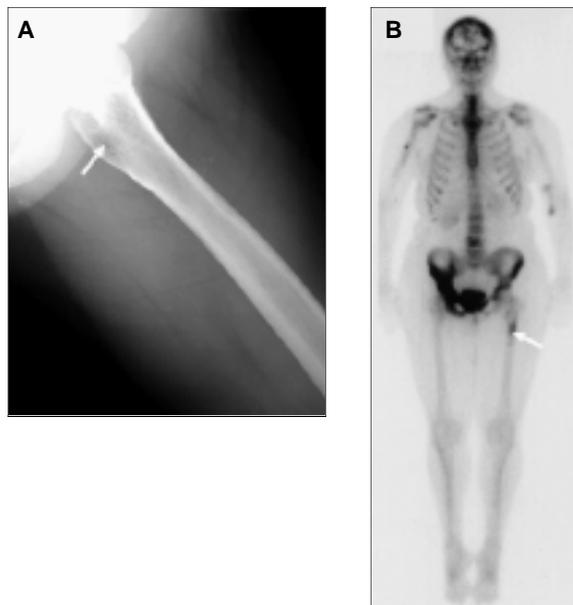


Figure 5 - A. subtle osteolytic lesion of the proximal femur in a 43 year old woman with Paget's disease which was not seen on anterior or posterior view of this area. B. Bone scan in the 43 year old woman with Paget's disease with increased uptake in the skull, one lumbar vertebra, the pelvis and in the proximal femur in the area of the lesion in 5A.

sis. In some patients the osteolytic lesions of Paget's disease are barely discernable on standard X-rays while the bone scan indicates avid uptake of tracer by the lesion (Figure 5 A, B). Rarely, sclerotic lesions on X-ray have no tracer uptake, presumably reflecting "burned out" metabolic activity of the disease.

The role of bone biopsies

Since the X-ray appearance of a skeletal lesion is almost always sufficient to determine a diagnosis of Paget's disease it is seldom necessary to obtain a bone biopsy. This may prove necessary when even an experienced interpreter of skeletal X-rays is uncertain of the diagnosis. This might occur when a solitary osteolytic lesion is detected in the diaphysis of a long bone rather than at either end. Biopsies are certainly indicated when there is evidence of disruption of the cortex, a finding which may indicate a malignant lesion is present.

The pathology of active Paget's disease is characterized by the presence of numerous osteoblasts and large multinucleated osteoclasts, considerable woven bone and a fibrovascular bone marrow (8). The presence of these findings should exclude all other bone disorders.

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