Paget's Disease in a Patient with Breast Cancer

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CASE PRESENTATION

A 55-yr-old, postmenopausal white female was found to have a right breast mass during an admission for depression. She complained only of symptoms of depression and weight gain. The patient had a medical history of trigeminal neuralgia and a family history of breast and gastric carcinoma. A mammogram showed a lesion highly suspicious for breast carcinoma. Laboratory studies, chest radiograph and computed tomography (CT) of the head were within normal limits. A needle aspiration confirmed the diagnosis of breast adenocarcinoma.

A staging work-up included a total body bone scan that demonstrated diffusely increased radiotracer uptake in the right hemipelvis and the second lumbar vertebra, including the spinous process (Fig. 1). This finding was thought to be consistent with Paget's disease, although bony metastases could not be definitively excluded. Radiographs subsequently obtained showed "sclerosis and enlargement of the second lumbar vertebra and sclerosis with prominence of the trabeculae in the right iliac bone" (Fig. 2). This finding supported the diagnosis of Paget's disease. The patient was temporarily discharged after treatment of her depression and was later admitted for management of her breast carcinoma.

The patient underwent a partial right mastectomy and right axillary node dissection with pathology revealing infiltrating ductal carcinoma with involvement of three of ten lymph nodes. She was started on radiation therapy and adjuvant chemotherapy. The patient's course was essentially unremarkable for the next 2 yr, except for an episode of syncope which resulted in fractures of her right 8th and 9th ribs diagnosed on radiographs. Serial total body bone scans demonstrated persistent, increased uptake in the second lumbar vertebra without interval changes or new lesions. A lumbar spine film repeated approximately 1 yr after the initial diagnosis was without significant interval change and again was consistent with the diagnosis of Paget's disease.

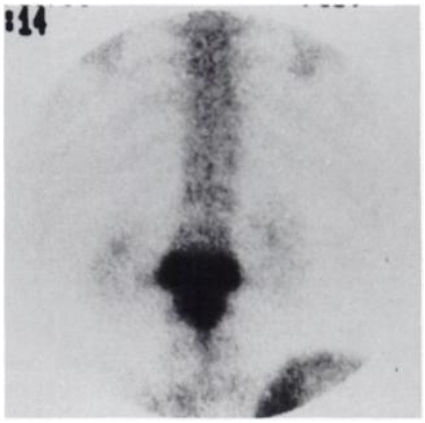

FIGURE 1. Bone scan shows the "Mickey Mouse" sign in the second lumbar vertebra: the pattern of uptake forms an inverted triangular pattern of three dots. Increased uptake in the superior portion of the right iliac bone is seen as well.

DISCUSSION

Paget's disease or osteitis deformans was first described in 1877 by Sir James Paget as a form of chronic bone inflammation. It is characterized by rapid bone destruction and simultaneous excessive bone repair, resulting in a distortion of bone architecture. The distorted architecture

FIGURE 2. Plain film shows sclerosis with prominence of the trabeculae in the second lumbar vertebra and the right iliac bone.

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causes weakened and deformed bones which are also enlarged and prone to fractures. The cause of Paget's disease remains unknown, and many etiologies have been proposed, including viral, neoplastic and familial causes.

The disease most commonly affects middle-aged persons. Three to four percent of all individuals over 40 yr of age are affected with the disease (*1,2*) in prevalent areas, and the incidence increases with age (*3,4*). Men are affected by Paget's disease more frequently than women. Geographic and racial variations in its prevalence have also been reported. It occurs more frequently in the northern United States, England, western Europe, Australia, New Zealand and in areas where western Europeans have migrated (*1,3,5*).

Approximately 10%–20% of patients are asymptomatic and are diagnosed incidentally through unrelated radiographs or laboratory studies (*4–6*). It is usually polyostotic and asymmetrical in distribution, or it can be monostotic in approximately 20% of patients (*7*). Serum calcium and phosphate levels remain normal, whereas serum and urinary hydroxyproline and serum alkaline phosphatase levels are generally elevated. Patients with symptomatic Paget's disease may present with arthritis, pain, pathologic fractures, skeletal deformities, neurologic deficits, such as deafness, and occasionally cardiovascular complications. The extent and type of symptoms depend on the distribution and severity of Pagetic involvement. Axial skeletal involvement occurs in approximately 80% of patients (*2*). Frequent sites of distribution are: pelvis (30%–76%), spine, especially lumbar and sacrum (31%), femur (25%–35%) and skull (25%–65%) (*4,8*).

Four stages of the disease have been described. Stage 1, the destructive or active resorption phase, occurs early in the disease process and may result in a flame-shaped or "blade of grass" osteolytic lesion along the bone. It is characterized by giant "killer" hypernucleated osteoclasts with intranuclear inclusion bodies (*3,4*). Stage 2, the combined or active formation phase, is the most commonly detected, and its radiographic appearance is pathognomonic for Paget's disease. The newly formed bone is abnormal, immature, disorganized or "woven" and has increased vascularity (*3*). Stage 3, the sclerotic or inactive phase, is due to a decline in the rate of resorption and formation, and is seen infrequently. Stage 4, the sarcomatous conversion or malignant transformation, may occur late in life after several decades of disease, with approximately a 1%–5% incidence, depending perhaps on the extent of Pagetic involvement (*4*). The first three stages may be encountered simultaneously in the same patient and even in the same bone. The radiographic appearance is usually diagnostic, typically demonstrating sites of bone resorption and formation, trabeculation and cortical thickening. The bones typically appear enlarged, thickened and deformed.

In many situations, roentgenograms may not be diagnostic and radionuclide bone scintigraphy is helpful in establishing the diagnosis, especially in the early stages of the disease when radiographs may appear normal. Bone scans frequently reveal areas of intense radiotracer uptake during the active phases of the disease due to increased vascularity and active bone remodeling and less uptake as the disease "burns out" (*7,9*). A more ominous finding is the development of a cold area, which can mean sarcomatous or malignant degeneration (*4*). Bone scans also allow total body imaging and may demonstrate all areas of involvement not evident on limited studies with plain films. Serial total body bone scans may be useful in assessing the efficacy of therapeutic regimens (*9,10*).

Unusual radiographic or scintigraphic patterns in Paget's disease have been described and are usually found in patients who are undergoing treatment for Paget's disease or have coexisting diseases such as malignancies (*11–13*). It is the latter situation that often poses a diagnostic dilemma to the clinician since the diagnosis of Paget's disease in patients with cancer and no definite evidence of metastasis may save them from further unnecessary examinations and aggressive therapy.

Paget's disease frequently involves the spine and sacrum. Patients may present with loss of vertebral body height, compression fracture and/or cord compression. In Paget's disease of the spine, the most common finding is monostotic vertebral involvement in the combined lytic and sclerotic phase (*2*). The vertebral body has the classic "picture-frame" appearance of cortical thickening and a relatively radiolucent center in the enlarged, flattened body on radiographs (*3,4*). In the sclerotic phase, the vertebra may appear enlarged and homogeneously dense, with a "squaring" of the anterior margin known as the "ivory" vertebra (*1,4*). The posterior elements may be involved in conjunction with or separately from the vertebral body (*4*). The neural arch may be thickened and the spinous process may be involved. These characteristics help differentiate Paget's disease from malignancies such as metastatic lesions, but not always with certainty.

We have noticed an unusual pattern of uptake on bone scans not previously described that appears to be relatively specific for Paget's disease. This pattern is increased tracer uptake in the vertebral body, posterior elements and spinous process which forms an inverted triangular pattern of three dots that resembles the Mickey Mouse silhouette, the "Mickey Mouse" sign (Fig. 1). Higher intensity in the lateral portions when compared with the middle of the vertebral body is probably due to an overlap of bilateral posterior elements and vertebral body.

Three hundred eighty-one studies were randomly selected from all bone scans performed in a 1-yr period and were reviewed by two physicians. Twelve cases of the "Mickey Mouse" sign were identified. The 12 patients were referred for various reasons: for the evaluation of possible metastasis in 6, for back pain in 3 and for Paget's disease with and without therapy in 3. Eleven of the 12 patients had correlative radiographic studies (plain films, CT and/or MR scans) of the corresponding lesions.

After reviewing the correlative radiographic studies, the

causes of the abnormality at the site of the "Mickey Mouse" sign were: metastasis in two patients and Paget's disease in nine patients. Overall, the positive predictive value of the "Mickey Mouse" sign for Paget's disease was about 82% (9 of 11).

Of the six patients with malignancies who were referred for the evaluation of possible metastasis, two were found to have metastases in the vertebrae with the "Mickey Mouse" sign, and the remaining four patients had Paget's disease.

Of the six patients referred for the evaluation of back pain or Paget's disease, no one was found to have a metastasis at the site of the "Mickey Mouse" lesion.

In summary, the "Mickey Mouse" sign appears to have a fairly high positive predictive value for Paget's disease. It is more suggestive of Paget's disease than metastasis, even in patients with cancer. These patients should not be assumed to have spinal metastases without first having a correlative radiographic study. They could be saved from further aggressive therapy for a presumed metastasis.

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