

Paget's disease of bone: review with emphasis on radiologic features, part II

Joseph M. Mirra, M.D.¹, Earl W. Brien, M.D.¹, Jamshid Tehrzanadeh, M.D.²

¹ Orthopaedic Oncology Service, Orthopaedic Hospital, Los Angeles, California, USA

² Department of Radiologic Sciences, University of California, Irvine, Orange, California, USA

Abstract. Part I discusses the correlation between the clinical, radiologic and histologic features with the three phases (incipient, mid- and late phase) of Paget's disease. In this section, we will discuss in detail the radiologic features by location as well as aberrant radiographic presentations in addition to secondary tumors such as post radiation sarcomas and giant cell tumors which occur in Paget bone. Because Paget's disease generally affects people in their middle and late ages, the differential diagnosis often includes metastatic disease and the differentiation can often be quite challenging. Moreover, metastatic disease to bones afflicted with Paget's disease can further add diagnostic confusion. These critical aspects will be discussed in this section of Paget's disease of bone.

Key words: Paget's sarcoma – Giant cell tumor – Metastatic disease

The radiographic findings associated with Paget's disease are unique throughout the skeleton. The skull has radiographic findings such as osteoporosis circumscripta, platybasia, cotton-wool exudates and thickening of the vault. The spine may reveal a picture frame pattern, ivory vertebrae or vertical stripping. Protrusion and thickening of the ileopectineal line may be seen in the acetabulum. However, these cardinal radiographic features may not always be present and aberrant radiographic presentations may be seen. In addition, sarcoma and giant cell tumor may be secondary tumors associated with Paget bone. The purpose of this section is to review these findings and to discuss the differential diagnosis, principally metastatic disease and its association with Paget's disease of bone.

Radiologic features by anatomic site

Skull bones

Any portion of the skull can be involved in Paget's disease, in particular the cranial vault and bones of the skull base. About one-third of patients develop weakening and softening of the bone at the base of the skull, with eventual platybasia and basilar invagination or upward protrusion along the base of the foramen magnum) [1].

Platybasia occurs when the basilar angle is more than 140°. The *basilar angle* is measured where a line drawn from the nasion to the tuberculum sellae crosses the line from the anterior margin of the foramen magnum (basion) to the tuberculum sellae. *Basal invagination* can be measured by *Chamberlain's line*, which is a line drawn from the hard palate to the posterior margin of the foramen magnum (opisthion). The odontoid peg should not extend more than 2.5–3.0 mm above this line. The opisthion is often difficult to pinpoint on lateral skull radiograph, so *McGregor's line* (Fig. 1B) has been adopted instead, which is a line drawn from the hard palate to the lowest margin of the occiput. An odontoid process extending more than 5 mm above McGregor's line is indicative of basal invagination.

Early phase. This phase begins with a sharply circumscribed focus of lysis without sclerotic rim: *osteoporosis circumscripta* (See Fig. 9 in part I [2]). The osteolysis usually begins in either the frontal or the occipital region, from where it may spread to involve the entire skull. The outer table is thinned but not breached, and there is no evidence of soft tissue mass (cortical loss with soft tissue extension typifies lytic metastasis and Langerhans cell histiocytosis). The lysis in Paget's disease usually extends across suture lines, involving both sides of the skull. Rarely, two or three foci of osteoporosis circumscripta develop. The inner table is generally well preserved.

Middle phase. “Cotton-wool” exudates (Fig. 1) develop predominantly along the base of inner table within the

Correspondence to: Joseph M. Mirra, M.D., Orthopaedic Hospital, 2400 South Flower Street, Rm 524, Los Angeles, CA 90007, USA

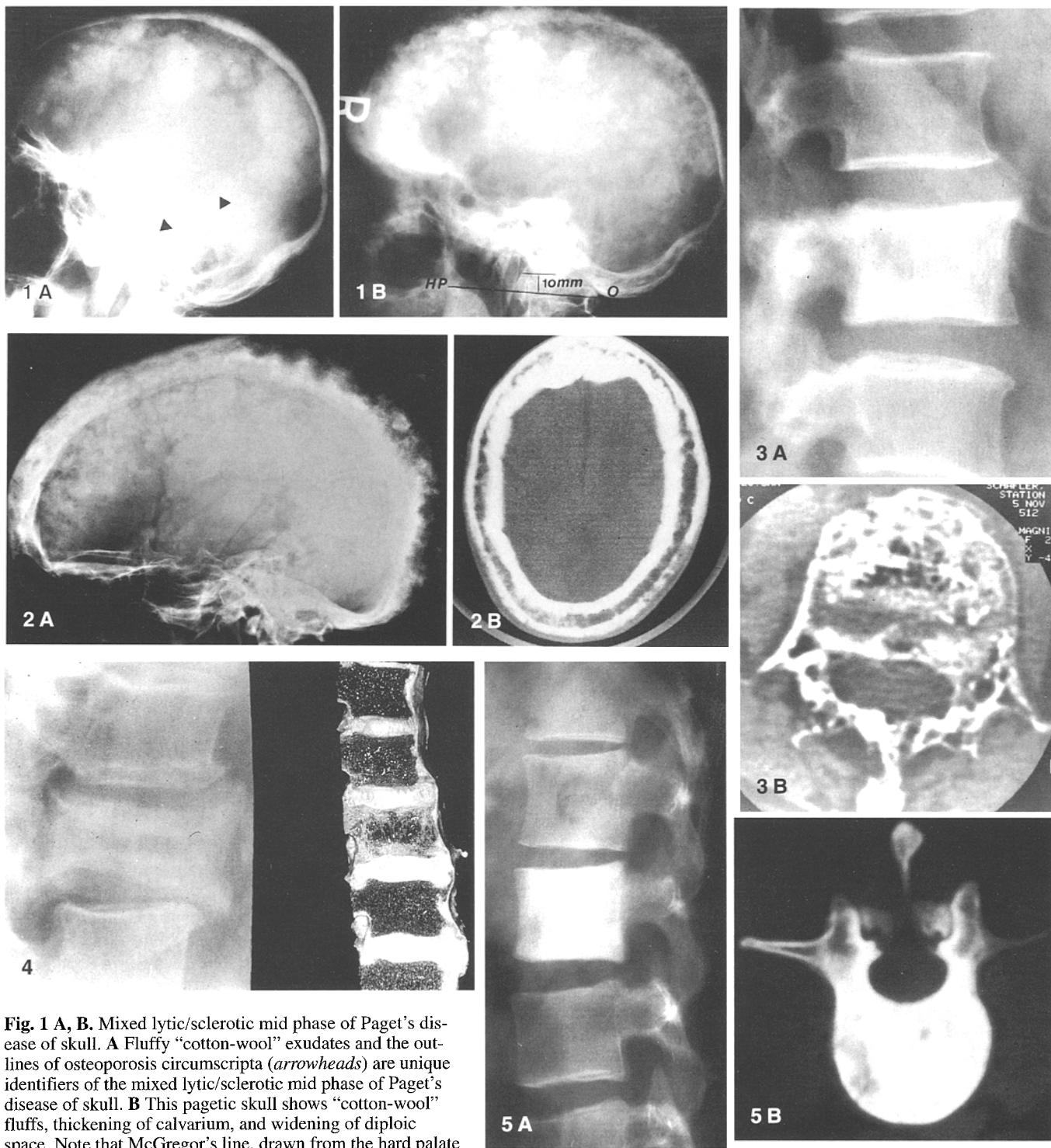


Fig. 1 A, B. Mixed lytic/sclerotic mid phase of Paget's disease of skull. **A** Fluffy "cotton-wool" exudates and the outlines of osteoporosis circumscripta (arrowheads) are unique identifiers of the mixed lytic/sclerotic mid phase of Paget's disease of skull. **B** This pagetic skull shows "cotton-wool" fluffs, thickening of calvarium, and widening of diploë space. Note that McGregor's line, drawn from the hard palate (*HP*) to the basiocciput (*O*), is 10 mm below the tip of the odontoid peg (normal <5 mm), indicating basal invagination

Fig. 2 A, B. Advanced Paget's disease of skull. **A** This skull of an 87-year-old woman demonstrates diffuse proliferation of "cotton-wool" deposits, most intense along the inner table. The outer table has migrated peripherally, leading to marked enlargement of the skull. Platibasia, basilar invagination, and drooping of the occiput are striking – a common radiographic finding in advanced Paget's disease of skull. Pronounced "flattening" is resulting in the so-called tam-o'-shanter skull. The grooves of the middle meningeal artery have enlarged secondary to the hypervascularity of the pathologic process **B** Computed tomographic (CT) scan of a similarly affected skull showing sclerosis of the entire cranium, thick-

est along the inner table and diploë of the occipital region. These knobby thickenings would correspond to the "cotton-wool" fluffs seen on standard roentgenograms

Fig. 3 A, B. Classical Paget's disease of spine. **A** Pathognomonic features of Paget's disease in this vertebral body include: (1) coarsening of the vertical trabeculae, (2) enlargement of the body as compared to its normal neighbors above and below, (3) extension of the sclerotic process into the arch, and (4) a mild degree of flattening of the normally concave anterior curve. **B** CT scan of chronic Paget's disease of spine shows involvement of body and arch associated with marked coarsening of trabecular structure

zone of osteoporosis circumscripita (combined lytic-blastic phase). Eventually, widening of the bone becomes apparent, particularly by sclerosis of the inner table and diploë. The sharp line of lysis between affected and normal bone and the bone widening rule out hyperparathyroidism and metastasis.

Late phase. All remnants of osteoporosis circumscripita disappear, being replaced by condensing foci of sclerosis and obscuration of the inner and outer tables combined with considerable bony sclerosis and widening. Sclerotic bone occurs primarily along the inner table. Marked thickening of the skull vault and peripheral migration of the outer table correlate with the clinical finding of an enlarged head diameter (Fig. 2).

Bone softening of the skull in Paget's disease may lead to basilar invagination, "dropping" of the occiput, and platybasia (Figs. 1B,2). The odontoid process may rise high into the foramen magnum with the potential of lethal brainstem compression or obstructive hydrocephalus. In the lateral view, less than one-third (2.5 mm) of the odontoid peg normally rises above Chamberlain's line. Pressure on the pons and cerebellum may lead to loss of muscle strength, control of respiration, balance, and coordination. An enlarged, mottled cranial vault that appears to overlie unaffected facial bones, coupled with basilar invagination, forms the pathognomonic *tam-o'-shanter skull* of Paget's (Fig. 2A). (A tam-o'-shanter is a Scottish bonnet or cap that is broad and flattened.)

Cranial nerve palsies involving the third, sixth, and seventh nerves may occur and hearing may be impaired from involvement of the labyrinth of the petrous portion of the temporal bone, and/or auditory nerve compression, and/or otosclerosis of the bones of the middle ear. Neurologic dysfunction in Paget's disease is more common in men [3].

Spinal bones

Involvement of one or more bones of the spinal column is frequent, occurring most commonly in the lumbar ver-

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Fig. 4 A, B. "Picture-frame" effect in a vertebral body. **A** The pathognomonic features of Paget's disease in this vertebra are bone enlargement and subchondral, lateral, and medial sclerosis (the "picture-frame" effect). There has also been moderate collapse. **B** The gross specimen shows a single affected vertebra demonstrating the characteristic peripheral vertebral body sclerosis and accentuation of the vertical trabeculae centrally

Fig. 5 A, B. A typical "ivory" vertebra as a feature of Paget's disease in a lumbar vertebra. **A** This 38-year-old male demonstrates a dense "ivory" vertebra. The preoperative radiologic diagnosis favored solitary metastasis or Hodgkin's disease. Biopsy revealed Paget's disease. The clues to the true diagnosis are subtle sclerosis of the arch and mild flattening of the anterior convexity. Due to absence of definite enlargement of the body and lack of accentuation of the vertical trabeculae, biopsy was justified to rule out the usual malignant diseases associated with "ivory" vertebra. The lack of demonstrable enlargement of the body is rare; most cases of "ivory" vertebra caused by Paget's disease show enlargement. **B** The CT scan demonstrates sclerosis of the body that is extending into the arch

tebrae and sacrum [4]. The radiodensity of the bone is variable, ranging from predominantly lytic to extremely sclerotic.

In the spine, radiographic changes may not be pathognomonic in the early phase. Although cutting cones are not observed either, by the middle to late phase other features set Paget's disease of the spine apart from virtually any other entity. These include:

1. An accentuated, coarse trabecular pattern, particularly in a vertical direction (*vertical stripe pattern*; Fig. 3). Hemangioma is associated with a more delicately accentuated vertical stripe pattern and is not associated with other, more unmistakable features of Paget's (see below).
2. *Enlargement* of vertebrae as compared to unaffected vertebrae above and below. Widening of bone was found to be the most common cause of spinal stenosis in 70 patients [5]. Following compression fractures, the bone loses height and thus may only show enlargement in the sagittal and lateral planes.
3. Increased sclerosis along all four margins of the vertebral body, especially the superior and inferior margins, giving rise to a pathognomonic "*picture-frame*" pattern (Fig. 4).
4. A marked increase in density, often extending to posterior elements, which may result in an "*ivory*" vertebra. Rare examples of pagetic "*ivory*" vertebra do not demonstrate bone enlargement or other tell-tale features (Fig. 5). In such instances differentiation from lymphoma and metastasis may be difficult without biopsy [6] unless, of course, other bones are discovered by radionuclide scans with the features that characterize Paget's. In most instances the body is also enlarged, a feature not seen in other diseases (Fig. 6). In addition, the enlargement and sclerosis of the involved pedicles compared to the uninvolved pedicles are diagnostic.
5. *Flattening*, "*squaring*", or "*rounding*" of the normal concavity of the anterior margin of vertebral body with enlargement of the vertebral body on the lateral view (Fig. 6).
6. Sclerosis and widening typically extending to the posterior elements. On rare occasions only the spinal process demonstrates tell-tale pagetic sclerosis and widening (Fig. 7).
7. Vertebrae with lytic or lytic sclerotic components are weakened and generally begin to develop biconcave deformities ("*fish vertebrae*"), which in later stages can culminate in fracture collapse with loss of height and neurologic impairment.

Pelvis and hip

The extent of involvement of pelvis and hip can vary from extensive disease on one side with complete sparing of the other to variable disease affecting the entire pelvis. The major manifestations of involvement of the pelvic bone are as follows:

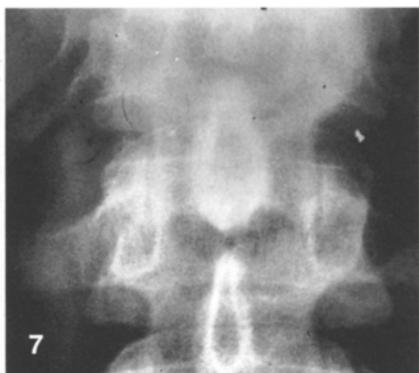


Fig. 6. Classical "ivory" vertebra in Paget's disease. This "ivory" vertebra is easily diagnosed as due to Paget's disease since it shows definite bone enlargement and rounding instead of convexity of the anterior face of the vertebral body, as well as the mixed lytic/sclerotic phase and accentuated vertical stripe pattern of the affected bodies above and below

Fig. 7. Paget's disease of spinous process. This rare finding of sclerosis and enlargement of the spinous process is nevertheless a pathognomonic radiographic finding

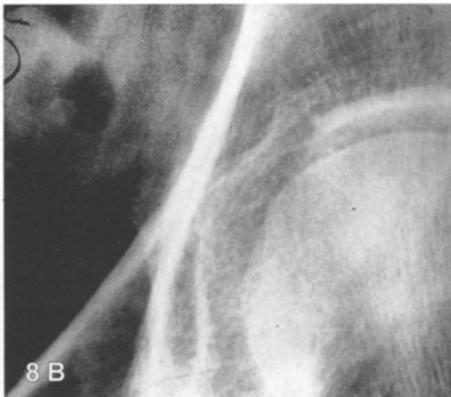
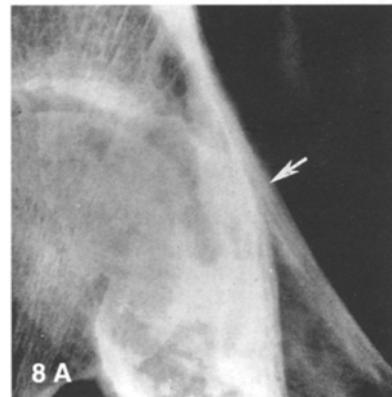


Fig. 8 A, B. Paget's disease of pelvis; thickening of the iliopecten line **A** Paget-involved side. Note thickening of the iliopecten line (white arrow) as compared to the uninvolved side (**B**). Comparison to the other, normal side discloses other signs of Paget's disease, including sclerosis of the medial acetabular roof and subtle accentuation of trabeculae in the femoral head and superior acetabular roof

Fig. 9. Advanced Paget's disease of pelvis, on side. Marked sclerosis, accentuated trabeculae, a cross-hatched pattern, narrowing of joint space (pagetic arthritis), and protrusio acetabuli are typical features of advanced Paget's disease

Fig. 10. Mid-phase Paget's disease of tibia. The tibia shows two cutting cones, one proximal diaphyseal and the other distal metaphyseal (arrows). Although the radiologic diagnosis of this case is

certainly not complicated, the radiographic features that are unusual for Paget's disease of long bones are (1) the lack of involvement of either proximal or distal subarticular portion and (2) the central site of the lesion within the distal diaphysis and the lack of subarticular extension of the distal cutting-cone. The latter two features imply that the pagetic focus began within the distal diaphysis itself, an unusual or even rare site for a primary focus

Fig. 11 A-C. Anterior bowing of tibia and saber shin in Paget's disease. **A** In this example of advanced disease, the tibia shows sclerosis, widening, and considerable anterior bowing. **B** Saber shin deformity of Paget's disease. **C** Section of pagetic tibia with advanced saber shin deformity. The distal quarter is normal, with disease advancing along a V-shaped cutting cone. (**B, C** Reproduced from [8a], with permission)



Fig. 14 A–C. Pseudotumorous lysis in Paget's disease. **A** This distal ulna of a 57-year-old woman with acute pain shows a long area of tumor-like lysis, thinning of the cortices, mild expansion, and a subtle fracture (arrow). The expected diagnosis on the basis of this radiographic appearance would be fibrous dysplasia. The only clue to Paget's disease, diagnosed after biopsy, is perhaps the sharp declination of the most distal zone of lysis, which in light of the unequivocal biopsy finding must represent a cutting cone. It could be argued that this case represents the rarely observed pure, incipient phase of Paget's disease of long bone, prior to accentuation of trabeculae, osseous sclerosis, and extension to one subar-

ticular portion – in essence, the long bone equivalent of pure osteoporosis circumscripta of skull. **B** Close-up radiograph of tibia shows, in addition to significant osteosclerosis, a long segment of cortical resorption which simulates malignant change (arrows). **C** Coronal T1-weighted image of the tibia in **B** shows cortical thickening and tibial bowing. Note that the marrow is preserved and there is no evidence of a soft tissue mass. These findings speak against the diagnosis of malignant degeneration. Small, discrete areas of low signal intensity against a background of fatty marrow are believed to represent granulation tissue or areas of reactive, sclerotic bone. (Reproduced from [11], with permission)

1. Mixed blastic-lytic activity typifies most cases at presentation.
2. *Thickening of the ileopectineal line ("pelvic brim sign")* is one of the earliest and virtually pathognomonic signs of pelvic involvement (Fig. 8). Thickening may also occur along the iliopubic and ilioischial lines.
3. An accented trabecular pattern is often evident. The pattern can be "stringy," "striated," "honeycombed," "cross-hatched," or even "cystic" (Fig. 9).
4. Paracetabular involvement can result in *protrusio acetabuli* (Fig. 9).

Other less frequent, less diagnostic patterns include: intense iliosacral sclerosis (*osteitis condensans ilii*) [7] and blurring of the sacroiliac syndesmosis. A "cystic" pat-

tern can be mistaken for tumor, but areas of accented trabeculae, thickening of the ileopectineal line, and absence of soft tissue mass on CT scan should resolve the issue.

Long bones and patella

Early-stage involvement of these bones is generally asymptomatic. When first discovered within a long bone, especially if discovered because of symptoms, more than one-third of the bone is involved. Paget's disease in long bones typically begins as an advancing wedge of resorption occupying the meta-epiphyseal region, typically with extension to one subarticular (subchondral) portion (Fig. 8 in part I [2]). Uncommonly, only the metaphysis and/or diaphysis is involved (Fig. 10).

Fig. 12 A, B. Pagetic involvement of patella. **A** Normal patella. **B** The other patella of the same patient shows features typical of late-phase Paget's disease, including enlargement, sclerosis, and prominent trabecular coarsening along stress lines

Fig. 13. Paget's disease of hand. Although Paget's disease involving hand and foot bones is rare, the enlargement and the accentuated trabeculae along stress lines of the fourth metacarpal and third proximal phalanx are diagnostic

Rarely are lesions observed that are confined exclusively to the diaphysis.

Moderate to severe involvement of long bones is characterized by:

1. The four classic features (*resorption wedge, accented trabecular pattern, cortical thickening, bone widening*), as described and illustrated in part I of this review; see (Fig. 10 in part I [2]). In the mid to chronic (late) phase, accented trabeculae impart a "reticulated" to "honeycomb" appearance. In the proximal femur accentuation of the lines of stress can be subtle to dramatic (Fig. 11 in part I [2]). In the late phase, extensive widening with complete blurring of the corticomедullary interface is possible.
2. Typically, involvement of both metaphysis and epiphysis.
3. *Weakening, stress fissures, and ultimately gross fatigue fractures* (see Fig. 14 in part I [2]). The fissures begin on the side of the cortex that is under maximal tensile forces. Microscopically, they are composed of highly irregular masses of ischemic-appearing, deep blue, poor quality woven bone and fibrous tissue. As the disease becomes more chronic, the fissures may proliferate in number or propagate into a grossly displaced fatigue fracture [8]. Because of the poor quality of the fissure "callus", the fissures may remain for many years or even indefinitely without healing. Due to the gross deficiency of the woven-lamellar bone produced in Paget's disease, fractures occur straight across the shaft, as if an ax had been taken to the bone ("banana" fractures; see Fig. 14 in part I [2]). Lamellar bone of the usual adult skeleton fractures in a spiral or comminuted fashion.
4. *Bowing*. Femurs bow laterally, tibias anteriorly and outwardly, leading clinically to the *saber shin* deformity similar to that described in syphilis (Fig. 11).
5. Patellar involvement is uncommon, but shows the usual features of this disease (Fig. 12). It is frequently associated with knee pain.

Bones of the hands and feet

Although involvement of short tubular bones of the hands and feet is quite unusual, radiologic features are typically diagnostic: *accentuated trabecular pattern* and *bone enlargement* (Fig. 13). Often there is associated degenerative joint disease with small osteophytes and mild joint narrowing. Involvement of carpal and tarsal bones is rare, with the possible exception of the calcaneus. Accentuation of the calcaneal stress lines is often pronounced. Involvement of distal phalanges is exceedingly rare.

Aberrant radiographic presentations

In relation to Paget's disease, we will define an aberrant radiographic presentation as one in which at least three

of the four cardinal features are absent. Some examples follow:

1. *Skull with small hole(s)*, one or two, each less than 3 cm in diameter. This is a very rare presentation and would typically cause confusion with metastases, myeloma, or histiocytosis. A biopsy result revealing Paget's disease would be unexpected. This presentation probably represents an extremely early phase of osteoporosis circumscripta before the zone of lysis has reached a sufficient size to become easily recognizable.
2. *Extensive "moth-eaten" osteolytic pattern* (accelerated disuse osteoporosis). This is a possible complication of pathologic fracture, occurring particularly after immobilization, in the process obscuring the tell-tale signs of Paget's. It is often mistaken for infection or primary or secondary malignancy [9]. Following mobilization, remineralization occurs and the ease of radiographic diagnosis returns.
3. *Pseudotumorous lysis*. Non-neoplastic zones of lysis bereft of some or all of the cardinal features of Paget's disease are easily mistaken for neoplasm. Osteolytic, pseudotumorous Paget's [10] appears to be composed of three variants: (1) early to midphase lesions with a wide, subtly slanted cutting-cone (Fig. 14A); (2) lesions associated with chronic (late) disease, developing diffuse, idiopathic bony osteolysis which may be due to marked loss of calcium following stress fracture with immobilization; and (3) lesions associated with chronic disease showing focal tumor like zones of lysis (Fig. 14B,C). Kumar et al. [12] published a case of diffuse tumor-like osteolysis of the left pubis with focal cortical destruction, without CT demonstration of a mass. It responded well and healed with sclerosis following 4 months' treatment on aminohydroxypropylidene diphosphonate (ADP). They surmised that the lysis was consequent to a nonvisualizable stress fracture.
4. *Eccentric subperiosteal mass* showing only pagetic osseous tissue. This is an extremely rare event, having been described in one case by Bowerman et al. [13]. In the great majority of patients with Paget's disease, evidence of an eccentric soft tissue mass would indicate either sarcoma, metastasis, or the associated benign giant cell tumor. Due to its extreme rarity, there are no published radiologic features to distinguish a pagetic exostotic mass from neoplastic conditions; therefore, biopsy is forced in all patients showing soft tissue mass. One could speculate that the benign, eccentric intraperiosteal mass described by Bowerman et al. is a pagetically ossified old subperiosteal hematoma.

Paget sarcoma

Background and incidence

Sarcomatous transformation is the dreaded complication of Paget's disease [14]. It follows in the wake of chronically damaged osseous tissue. Most patients have evidence of moderate to severe polyostotic disease prior to

Table 1. Distribution of anatomic sites of sarcomatous transformation of Paget's disease (247 cases)

Pelvis	25%	Sacrum, spine	3% each
Femur	24%	Rib	1%
Humerus	19%	Other flat bones, hand, foot	<1% each
Tibia	10%	Ulna	<1%
Skull	9%	Radius, fibula	0%

Data from [14, 15, 24, 25]

malignant change. In severely afflicted patients there is an approximately 10% incidence of malignant transformation [14]. However, if one counts all patients, including those with minimal and asymptomatic Paget's disease, the incidence falls to around 1%. Wick et al. [14], in a study of 3964 pagetic patients with all degrees of severity of disease, found 38 patients who developed sarcoma of bone (1%), while Hadjipavlov and Lander [5] uncovered, from amongst 1078 patients with a hospital diagnosis of Paget's disease, 8 cases of sarcoma (0.7%).

The typical setting for malignant transformation is a patient of about 65 years of age who has had symptoms of moderate to severe polyostotic disease for 15–25 years. Age at presentation ranges from 38 to 87 years (mean age 64 years) [15, 16]. After age 50, Paget's disease is the most common precursor to bone sarcoma, accounting for about 25% of cases. In this age group the risk of developing bone sarcoma is some 30 times higher with Paget's disease than in the control population. Approximately 75% of patients with this complication are male, compared to 55% with uncomplicated Paget's disease [17].

Clinical features

The most common presenting symptoms of Paget sarcoma are: unrelenting pain with or without swelling (mass; 85%), pathologic fracture (22%) [15], and neurological symptoms (18%) including cranial palsies, lower limb weakness, and incontinence [18]. About 75% of patients have documented Paget's disease years before the onset of sarcoma, and 90% of these have polyostotic involvement [18]. The ultimate prognosis is grave, with over 90% of patients dying within 3 years of diagnosis [14–19].

Histologic variants

As reviewed by Hadjipavlov and Lander [5], the reported range of histological types varies considerably: osteosarcoma (22–90%), malignant fibrous histiosarcoma (MFH; 26%), fibrosarcoma (3–25%), chondrosarcoma (1–15%), giant cell sarcoma (3–10%), lymphoma and so-called reticulum cell sarcoma (3%), and angiosarcoma (<1%). Many Paget sarcomas are very high grade, poorly differentiated malignancies. The marked variation in histologic classification is heavily dependent upon individual author bias in the utilization of terminology. For

example, some authors categorize both poorly differentiated sarcomas with a prominent storiform pattern and minimal osteoid production and multinucleated giant cell sarcomas under MFH. In contrast, others, including the authors of this review, classify any sarcoma with even minimal, but definite osteoid production as an osteosarcoma, even if 99% of the remainder of the tumor has the pattern of so-called MFH. In addition, there are some authors who believe that Paget's patients can also develop giant cell sarcomas of probably osteoclastic origin (malignant osteoclastomas) [20, 21], and they separate these from the category of MFH as well. We have no clear-cut explanation for the remarkable range of reported chondrosarcoma, other than that perhaps what some might classify as chondroblastic osteosarcoma with minimal osteoid production is being coded by others as chondrosarcoma.

In our own series of 16 cases of Paget sarcoma the breakdown is as follows: osteosarcoma 44% (two presenting with multiple osteosarcomatosis), fibrosarcoma/MFH (poorly differentiated sarcoma) 38%, and malignant osteoclastoma 18%.

Anatomic sites

In general, the sites of sarcomatous transformation are in direct proportion to the frequency distribution of uncomplicated Paget disease, with the exception of the humerus (much higher incidence than expected) and the skull and spine (lower incidence than expected) [14, 22, 23]. In our literature review of 247 cases of Paget sarcoma reported in four large series [14, 15, 24, 25], the skeletal distribution is shown in Table 1. Although the radius was not implicated in these 247 cases, of interest is the fact that the first patient with malignant transformation reported by James Paget died of a sarcoma emanating from the radius [26]. A case of solitary sarcoma arising from involvement of the fibula has recently been published [18].

Cardinal clinical and radiologic signs of malignant transformation

Especially ominous features for which sarcoma must be very seriously considered include:

1. Development of an *unrelenting pain* that may wake the patient at night. The pain generally has been present a few months before the patient seeks medical attention.
2. New, *rapidly developing focus of poorly demarcated lysis* or mixed lytic-blastic activity in a symptomatic area of any size (Fig. 15). Unfortunately, periosteal reactions, an important radiographic indicator of bone sarcoma in younger individuals, are typically meager or entirely absent in most cases of Paget sarcoma. As individuals age, the periosteum attaches more and more firmly to the cortex, and perhaps because of aging, the elderly are much less able to produce radiologically visible, reactive bone in response to assault by tumor or infection.

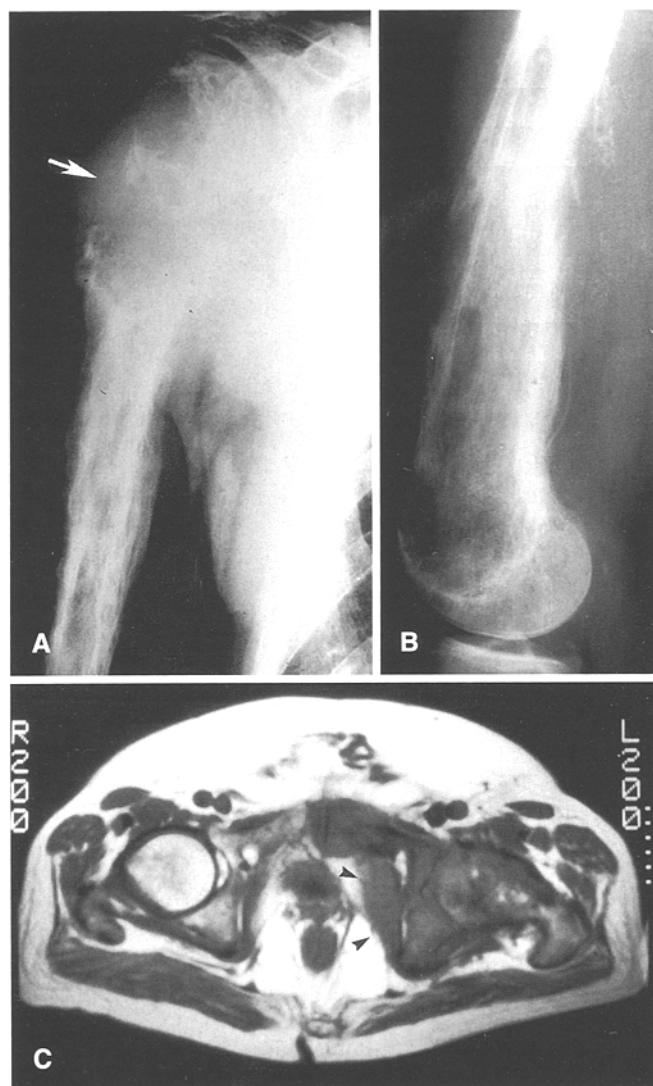


Fig. 15 A–C. Paget sarcoma: standard radiography and magnetic resonance findings. **A** The proximal humerus shows characteristic features of Paget's disease, including bone widening and thickened trabeculae along stress lines in the upper half of the photograph. The signs of malignant transformation are the tumor-like area of destructive lysis in the distal epi-metaphysis and, of even greater significance, a large soft tissue mass (arrow). **B** This distal femur shows characteristic signs of malignant change, including hazy destruction of the posterior cortex with a definite posterior soft tissue mass and spotty, irregular periosteal reaction. In addition, there is destruction of the anterior cortex by a tumor-like zone of lysis. **C** Fibrosarcoma of the left proximal femur, acetabulum, and pubis arising in pagetic bone. The axial T1-weighted image shows diffuse loss of marrow fat signal in affected bones with a mass involving the obturator internus muscle (**C** Reproduced from [11], with permission)

3. Focal cortical destruction [27].

4. A soft tissue mass of any kind (either lytic or containing densities), especially in the region of the skull. Association with periosteal reactions or Codman's triangle is unusual [28].

5. Pathologic fracture.

Differential radiologic diagnosis

To be included in the differential diagnosis are: *metastasis*, *fracture callus*, and *giant cell tumor of Paget's disease*. Giant cell tumor is a rare, benign secondary complication of Paget's disease that radiologically displays an area of lysis which corresponds histologically with the numerous osteoclasts and stromal cells often indistinguishable from solitary, neoplastic giant cell tumor of epiphysis [29–32]. This tumor is easily mistaken radiographically for an osteolytic osteosarcoma of Paget's disease, but histology will establish the diagnosis. *Pseudomalignant, aggressive-appearing lytic lesions* (see Fig. 14B,C), which are an exaggerated form of pagetic lysis without histologic evidence of neoplasm, have been reported [13, 24].

MRI in relation to sarcoma detection

In relation to many Paget sarcomas, malignant patterns of bone destruction with or without soft tissue extension may be difficult to visualize by conventional radiography. Magnetic resonance imaging (MRI) is especially effective in revealing soft tissue extension (Fig. 15C). It may even reveal small soft tissue masses that can be completely transparent on standard radiography. Can MRI play a role in the detection of sarcoma prior to the development of a soft tissue mass?

Kaufman et al. [11] performed a limited MRI study of four patients with Paget's disease (three with osteolysis, two with Paget's disease only, one with sarcoma, one with a fracture only). Cases of pure Paget's disease without acute fracture, they surmised, should reveal normal to relatively normal fat signal on T1- and T2-weighted images (see Fig. 14C). They believe that in a symptomatic patient, extensive low signal area on short repetition and echo time (TR/TE) images without visible sclerosis or fracture deserves either biopsy or close follow-up to exclude sarcoma. They are of the opinion that MRI can be a useful procedure in the overall evaluation of symptomatic patients with chronic Paget's disease in which sarcoma needs to be ruled out [11, 33].

Roberts et al. [34], in a larger MRI study of 13 patients with Paget's disease (only one of whom had a sarcoma), indicate that about half may show focal regions in the marrow that are not consistent with normal marrow fat. They used three combinations of short and long TR and TE. Their results showed considerable variability in MRI marrow signal intensities. They believe these results are due to a large range of histological processes that Paget's disease is capable of demonstrating, including: (a) normal marrow fat and hematopoiesis; (b) excessive fat with diminution in hematopoiesis; (c) fibrosis; (d) large- and small-vessel hypervascularity; (e) hemorrhage with hemosiderin; (f) degenerative foci; and (g) thickened bone spicules and cortices. In some tumor-free patients the sequences were similar to that expected of tumor, i.e., hypointense regions on short TR/TE with increased signal intensity on long TR/TE images. Granulation tissue, they believe, can have a similar signal pat-

tern. Other patients had signal patterns similar to those seen in infection, sclerotic metastases, sclerosing lymphoma, and other conditions, yet 11/13 of these patients had no clinical or biopsy evidence (when performed) to support a diagnosis other than Paget's disease. Due to this marked variability in MRI imaging patterns, they suggest that the usefulness of MRI in the early detection of sarcoma, insufficiency fracture, infection and metastatic disease is limited.

Taking into consideration the results of the above two MRI studies, and given the aggressive nature of Paget sarcoma, the following statements would appear justified regarding the use and planning of MRI and CT scans in sarcoma detection and biopsy considerations in cases of clinical suspicions and/or ominous standard radiographs:

1. If MRI shows normal or nearly normal marrow fat signal without an at least 2–3 cm focus of significantly altered signal, sarcoma is extremely unlikely.
2. MRI detection of an extensive, solitary tumor-like focus (greater than 4 cm) of marrow signal alteration is an ominous finding warranting biopsy, or at least (provided there are sufficient reasons to consider nonsarcomatous entities such as tumor-free fracture more likely) repeat radiographic studies and re-assessment in 1–2 months.
3. MRI evidence of a soft tissue mass combined with an intramedullary area of altered signal is an especially ominous sign favoring a diagnosis of sarcoma. However, since MRI is also quite sensitive to the detection of non-neoplastic inflammatory and edema-related soft tissue swelling, adding CT to the radiographic evaluation would in such a case be justifiable before performing biopsy. CT is an excellent tool to demonstrate both focal cortical destruction and neoplastic soft tissue mass, since it is much less sensitive than MRI in visualizing reactive and edematous swellings. If MRI and CT studies demonstrate a soft tissue mass, cortical destruction, and marrow alteration, biopsy is indicated. If CT does not show focal complete cortical destruction and the mass seen well on MRI is not detectable on CT, or is very poorly visualized, repeat radiographic studies in 1–2 months are an alternative to immediate biopsy. Following repeat studies, biopsy is indicated if the suspect region and/or clinical symptoms are progressing. If they are not, further repeat studies in 3–4 months should be considered, since the possibility of a slow-growing giant cell tumor of Paget's disease or a pagetic sarcoma growing much slower than usual remain diagnostic possibilities.

Giant cell tumor of Paget's disease

Giant cell tumor (GCT) of Paget's disease is a very rare tumor. Paget sarcoma is from 10 to 30 times more frequent and conventional GCT of epiphysis is about 50 to 100 times more common than GCT of Paget's disease. GCT of Paget's disease can affect almost any bone, but about half involve the skull and jawbones [35, 36], most of the remainder originating from the pelvis, spine, and long bones. This distribution is quite deviant from that

of conventional GCT of epiphyses, in which long bone involvement predominates. Multicentric forms of GCT in association with Paget's disease are even more rare than solitary forms, and the patients with this presentation typically exhibit familial and geographic clustering to Avellino, Italy [31, 37, 38].

Radiologically, solitary GCT of Paget's disease manifests as a lytic lesion without periosteal reactions, which usually do not have a soft tissue component (apart from the larger multicentric type). In about 25% of cases where curettage is performed, the tumor recurs. Although the tumor is benign, it can vary greatly in size, and behavior can show similar remarkable variation, from easily treatable to locally aggressive tumors with a high recurrence rate where multiple resections and radiotherapy may not fully contain the local lesion. Thus, the range of behavior is between that of a so-called benign "giant cell reparative granuloma" [31] and conventional GCT of epiphyses. The tumor rarely leads to death, however, and does not have metastatic potential. Some tumors, including multicentric ones, have been reported by Potter et al. [38] to respond dramatically to high-dose systemic steroids, although recurrence is possible following cessation of therapy.

Paget's disease versus, and in association with, metastatic disease

Paget's disease must be differentiated from metastatic disease. In most instances this is possible, since metastases do not possess the four cardinal signs described and illustrated in part I [2].

Given the advanced age of most patients with Paget's disease, association with other malignancies, especially carcinoma, is common. Despite this, however, proven metastatic disease to pagetic bones is apparently rare. When the association is found, it has been stated that metastatic deposits more often involve the nonpagetic bones, and extremely rarely the pagetic, despite the high vascularity of the latter [39]. Of 987 patients with Paget's disease reviewed by Schajowicz et al. [40], 62 had Paget sarcoma (6.3%), two had giant cell tumors of Paget's disease (0.2%), and six had metastatic carcinoma (0.6%). Of these six cases, only two (lung and prostate carcinoma) were histologically proven to have disseminated to pagetic bone. In both of the cases of metastasis to Pagetic bone, the lesions were both clinically and radiologically confused with Paget sarcoma until after biopsy. Quite recently, one of the authors (J.M.M.) had occasion to review all radiographs and pathology materials of his 59-year-old Québécois brother-in-law who developed pathologic fracture of a pagetically involved proximal femur (Fig. 16). The femoral biopsy showed, in addition to Paget's disease, evidence of squamous cell carcinoma. Shortly thereafter, biopsy of a large unresectable lung tumor demonstrated the origin of the squamous primary. He was a 60-pack-year smoker. He also had classical radiographic changes of Paget's disease of the pelvis and opposite femur. He died 3 months after diagnosis.



Fig. 16 A-C. Lung cancer metastasis to pagetic femur. **A** Femoral radiograph of a 59-year-old male smoker showing characteristic features Paget's disease, including an accentuated trabecular pattern and foci of sclerosis. **B** Lateral view demonstrating ill-defined focus of lysis. Biopsy demonstrated Paget's disease and squamous carcinoma. **C** CT scan of lung demonstrating origin of the metastatic carcinoma

Fig. 17 A-D. Juvenile Paget's disease: 14-year-old male patient with radiological and biopsy diagnosis of juvenile Paget's disease of bone. **A** Radiograph of proximal femur shows an accentuated trabecular pattern and a patch of sclerosis. **B** The distal femur demonstrates abnormality in tubulation and an accentuated trabecular pattern. **C** Bone scan shows increased uptake in the lumbar spine, femur, and proximal diaphysis of humerus. **D** Biopsy specimen. Electron microscopy shows intranuclear inclusion body (arrow)

Circumstances which militate against accurate diagnosis of metastases in association with Paget's disease include: (1) absence of a known primary; (2) the rarity of the association in contrast to the much higher fre-

row) within the osteoclasts of the diseased femur. *Insert:* At high magnification, inclusion bodies show paramyxovirus-like hexagonal structures in cross-section and filamentous arrays in longitudinal section. (Case courtesy of Dr. Joyce Pais, Radiology Department, University California at Irvine)

quency of Paget sarcoma; (3) the general probability, which influences diagnostic expectations, that a solitary pagetic bone with a soft tissue mass represents a primary pagetic sarcoma; and (4) the fact that oligo-ostotic,

small- to moderate-sized metastatic deposits to pagetic bones are difficult, if not impossible, to distinguish from Paget's disease alone or after sarcomatous transformation. On the other hand, circumstances which would favor the diagnosis of combined metastatic and Paget's disease include: (1) a history or clinical evidence of a primary, non-osseous cancer; (2) numerous, obvious blastic or lytic lesions in nonpagetically involved bones, i.e., those which do not reveal any of the cardinal signs of Paget's disease; and (3) the presence of two or more bones with soft tissue mass.

Blastic metastases versus Paget's disease

One of the most important diagnostic considerations is differentiating Paget's disease from metastatic lesions, particularly cancers that stimulate blastic activity, such as prostate and breast carcinoma. Although blastic cancer metastases superficially resemble Paget's disease, careful assessment of clinical, laboratory, and radiographic features should permit distinction between the two in the majority of cases. If metastatic disease is favored, core biopsy is suggested; however, if the features assessed are pathognomonic of uncomplicated Paget's disease, biopsy is not required. Clinical assessment, follow-up supportive measures, and osteoclast inhibitors are sufficient for most Paget's patients.

In the majority of patients with multiple blastic metastases, a history of a primary cancer treated in the past is elicited. Metastatic prostate cancer is also associated with elevated acid phosphatase, prostate-specific antigen (PSA), and alkaline phosphatase levels. Of these three tests, Paget's disease is only associated with elevated alkaline phosphatase (in the mid to late phases of disease). Alkaline phosphatase may be normal in the incipient phase, with minimal (1–2 bone) involvement, or in a very late, "burned out" phase. Radiologically, blastic metastases show fluffy exudates without the cardinal features that define Paget's disease.

Lytic metastases in Paget's disease

Multiple lytic metastases are radiologically dissimilar from Paget's disease even in its lytic phase, since the zone of lysis in Paget's spreads in a distinctive fashion (cutting cone vs. osteoporosis circumscripta). However, in patients with Paget's disease of bone, lytic metastatic cancer, most often from the lung, may mimic primary, lytic sarcomatous transformation. Lytic lesions of myeloma in association with Paget's disease have also been documented [41, 42].

Juvenile and infantile Paget's disease

Despite popular belief that Paget's disease affects adults only, it can also affect infants and children. Because of the large number of bones involved (although rarely, if ever, all), striking deformities, and markedly elevated al-

kaline phosphatase, the disease has been mistaken for an inborn error of metabolism, going by the name of hyperphosphatasia, among others [43]. There are abundant recent data and publications to the contrary, indicating that this rare disease is actually a severe form of Paget's disease manifesting in the young [44–46]. An interesting feature is that many such patients are of Puerto Rican ancestry. We present one such a case, which in addition demonstrated the characteristic intranuclear viral-like inclusion filaments (Fig. 17).

References

1. Poppel MH, Jacobson HG, Duff BK, Gottlieb C. Basial impression and platybasia in Paget's disease of bone. *Radiology* 1953; 61: 639.
2. Mirra JM, Brien EW, Tehranyadeh J. Paget's disease of bone: review with emphasis on radiologic features, part I. *Skeletal Radiol* 1995; 24: 163–171.
3. Sadar ES, Walton RJ, Gossman HH. Neurologic dysfunction in Paget disease of the vertebral column *J Neurosurg* 1972; 37: 661–665.
4. Steinbach HL. Some roentgen features of Paget's disease. *Am J Roentgenol* 1961; 86: 950.
5. Hadjipavlov A, Lander P. Paget disease of the spine. *J Bone Joint Surg [Am]* 1991; 73: 1376–1381.
6. Harris DJ, Hons CB, Fornasier V. An ivory vertebra. Monostotic Paget's disease of bone. *Clin Orthop Rel Res* 1978; 136: 173.
7. Burgener FA, Perry PE. Pitfalls in the radiographic diagnosis of Paget's disease of the pelvis. *Skeletal Radiol* 1978; 2: 231.
8. Milgram JW. Radiologic and histologic pathology of nontumorous diseases of bones and joints, Vol 2. Northbrook, 1990: chap 45.
- 8a. Remagen W. Paget's disease of bone: clinical and pathological aspects. Monograph. Basel: Sandoz, 1990: figs 1, 16.
9. Mitchell ML, Ackerman LV, Tsutsumi A. Case report 438: osteolytic phase of Paget disease. *Skeletal Radiol* 1987; 16: 498–503.
10. Eisman JA, Martin T. Osteolytic Paget's disease. *J Bone Joint Surg [Br]* 1986; 68: 112.
11. Kaufmann GA, Sundaram M, McDonald DJ. Magnetic resonance imaging in symptomatic Paget's disease. *Skeletal Radiol* 1991; 20: 413–418.
12. Kumar A, Poon PY, Aggarwal S. Value of CT in diagnosing nonneoplastic osteolysis in Paget's disease. *J Comput Assist Tomogr* 1993; 17: 144–146.
13. Bowerman JW, Altman J, Hughes JL. Pseudomalignant lesion in Paget's disease of bone. *Am J Roentgenol Radiol Ther Nucl Med* 1974; 57.
14. Wick MR, Siegal GP, Unni KK, et al. Sarcomas of bone complicating osteitis deformans (Paget's disease). *Am J Surg Pathol* 1981; 5: 47.
15. Huvo AG, Butler A, Bretsky SS. Osteogenic sarcoma associated with Paget's disease of bone. A clinicopathologic study of 65 patients. *Cancer* 1983; 52: 1489–1495.
16. Price CHG, Leeds G. Paget's sarcoma of bone. A study of 80 cases. *J Bone Joint Surg [Br]* 1969; 51: 205–224.
17. Breckenridge CJ. A statistical study of sarcoma complicating Paget's disease of bone in three countries. *Br J Cancer* 1979; 40: 194–200.
18. Moore TE, King AR, Kathol MH, El-Khoury GY, Palmer R, Downey PR. Sarcoma in Paget disease of bone: clinical, radiologic and pathologic features in 22 cases. *AJR* 1990; 156: 1199–1203.
19. Haibach H, Farrell C, Dittrich FJ. Neoplasms arising in Paget's disease of bone: a study of 82 cases. *Am J Clin Pathol* 1984; 83: 594–600.

20. Russell DS. Malignant osteoclastoma and association of malignant osteoclastoma with Paget's disease. *J Bone Joint Surg [Br]* 1949; 31: 281.
21. Mirra JM, Picci P, Gold R, et al. Bone tumors: clinical, radiologic, and pathologic correlations. Philadelphia: Lea & Febiger, 1989: 995–1009.
22. Thompson JB, Patterson RH Jr, Parsons H. Sarcoma of the calvaria: surgical experience with 14 patients. *J Neurosurg* 1970; 32: 534.
23. Miller C, Rao VM. Sarcomatous degeneration of Paget disease in the skull. *Skeletal Radiol* 1983; 10: 102–106.
24. Hailback H, Farrell C, Dittrich FJ. Neoplasms arising in Paget's disease of bone: a study of 82 cases. *Am J Clin Pathol* 1985; 83: 594.
25. Schajowicz F, Santini E, Berenstein M. Sarcoma complicating Paget's disease of bone. A clinicopathologic study of 62 cases. *J Bone Joint Surg [Br]* 1983; 65: 299–307.
26. Paget J. On a form of chronic inflammation of bones (osteitis deformans). *Trans Med Chir Soc Lond* 1877; 60: 37.
27. Sherman RS, Soong KY. A roentgen study of osteogenic sarcoma developing in Paget's disease. *Radiology* 1954; 63: 48.
28. Wilner D, Sherman RS. Bone sarcoma associated with Paget's disease. *CA* 16: 238.
29. Schajowicz F, Slullitel I. Giant cell tumor associated with Paget's disease of bone. *J Bone Joint Surg [Am]* 1966; 48: 1341.
30. Mirra JM, Bauer FC, Grant TC. Giant cell tumor with viral-like inclusions in patient with Paget's disease. *Clin Orthop* 1981; 158: 243.
31. Mirra J, Schiller, Suit HD. Paget's disease and giant cell tumor of bone: CPC case #1. *N Engl J Med* 1986; 314: 105.
32. Donati U, Martucci E. Giant cell tumor in a vertebra affected by Paget's disease of bone. *Ital J Orthop Traumatol* 1979; 5: 253.
33. Griffiths HJ. Radiology of Paget's disease. *Curr Opin Radiol* 1992; 4: VI: 124–128.
34. Roberts MC, Kressel HY, Fallon MD, Zlatkin MB, Dalinka MK. Paget's disease: MR imaging findings. *Radiology* 1989; 173: 341–345.
35. Hutter RVP, Foote FW Jr, Frazell EL, Francis KC. Giant cell tumors complicating Paget's disease of bone. *Cancer* 1963; 16: 1044.
36. Goldstein BH, Laskin D. Giant cell tumor of the maxilla complicating Paget's disease of bone. *J Oral Maxillofac Surg* 1974; 32: 209.
37. Jacobs T, Michelsen J, Polay J, et al. Giant cell tumor in Paget's disease of bone. Familial and geographic clustering. *Cancer* 1979; 44: 742.
38. Potter HG, Schneider R, Ghelman B, Healy JH. Multiple giant cell tumors and paget disease of bone: radiographic and clinical correlations. *Radiology* 1991; 180: 261–264.
39. Wilner D, Scherman RS. Roentgen diagnosis of Paget's disease (osteitis deformans). *Med Radiogr Photogr* 1966; 42: 35.
40. Schajowicz F, Velan O, Arujo EA, Plantalech L, Fongi E, Ottolenghi E, Fromm G. Metastases of carcinoma in the pagetic bone. *Clin Orthop* 1988; 228: 290–296.
41. Gross RJ, Yelin G. Multiple myeloma complicating Paget's disease. *Am J Roentgenol* 1951; 65: 585.
42. Rosenkrantz JA, Gluckman EC. Coexistence of Paget's disease of bone and multiple myeloma. Case report of two patients. *Am J Roentgenol* 1957; 78: 30.
43. Eyring E, Eisenberg E. Congenital hyperphosphatasia. A clinical, pathological, and biochemical study. *J Bone Joint Surg [Am]* 1968; 50: 1099.
44. Choremis C, Yannakos D, Papadatos C, Baroutsou E. Osteitis deformans (Paget's disease) in an 11 year old boy. *Helv Paediatr Acta* 1958; 4: 267.
45. Woodhouse N, Fisher M, Sigurdson G. Paget's disease in a 5-year-old child: acute response to calcitonin. *Br Med J* 1972; 4: 267.
46. Mirra JM, Picci P, Gold R, et al. Bone tumors: clinical, radiologic, and pathologic correlations. Philadelphia: Lea & Febiger, 1989: 932–936.