

Pathology of Paget's disease of bone

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Summary

Paget's disease of bone is a common metabolic disorder, which is in most cases diagnosed on the basis of its radiographic findings. Its primary bone alterations and subsequent complications constitute a complex range of pathologic pictures, which may pose diagnostic difficulties upon histologic examination. This article illustrates the spectrum of pathologic features of Paget's disease of bone and its complications, with emphasis on the differential diagnosis from a diagnostic standpoint. The areas in which the histopathologic diagnosis appears to be most relevant are the characterization of neoplasms that may arise in the course of the disease, and more importantly, their separation from benign pseudosarcomatous conditions.

KEY WORDS: Paget's disease of bone, diagnosis, histopathology, Paget's sarcoma.

Introduction

Paget's disease of bone represents a common disorder affecting 3-4% of the population over the age of 40 years. The diagnosis is usually made on the basis of clinical and radiographic findings, and therefore pathologists infrequently deal with bone biopsies performed to confirm or exclude the diagnosis, and may not be familiar with the highly variable morphologic features of this disease. Pathologic examination may be also required for surgical specimens deriving from joint replacement procedures for osteoarthritis, a common complication of Paget's disease of bone, or from treatment of fractures.

Probably, the most important aspect of histopathologic diagnosis in the course of Paget's disease of bone is the evaluation of tissue taken when tumour degeneration can be suspected on clinical and radiological basis. Therefore a number of pathologic manifestations, each with its own differential diagnosis, can be associated with this disease, resulting in an extremely complex picture. This article illustrates the spectrum of pathologic features of Paget's disease of bone and its complications with emphasis on the differential diagnosis from a diagnostic standpoint.

Pathologic features of Paget's disease of bone

The histologic appearance of bone tissue in Paget's disease is variable, and it depends on the stage of the disease. Usually, three phases can be recognized, which parallel the radiologic features of the disease; however the disease process is a *continuum*, and often more than one aspect can co-exist in the same specimen. The histologic alterations are observable in affected bones, but interestingly 12% of patients without involvement of pelvic bones on radiographic studies or bone scan had positive iliac crest biopsy (1). In addition, histologic signs of an increased bone remodeling attributed to a hyperparathyroidism secondary to the high calcium demand of pagetic bones can be found in up to 45% of iliac crest biopsies (2).

The initial phase (incipient-active) is dominated by active resorption: numerous osteoclasts are present at the surface of bone trabeculae, which become slender and sparse, or in cortical bone, where they form large resorption cavities. The bone marrow spaces are occupied by vascular fibrous tissue. At the same time, new bone formation is started by osteoblasts and the matrix produced is predominantly of woven type. The overall picture is that of an extremely increased cellular activity, with several osteoclasts and osteoblasts simultaneously present over the same trabeculae (Figure 1). Such an increase in

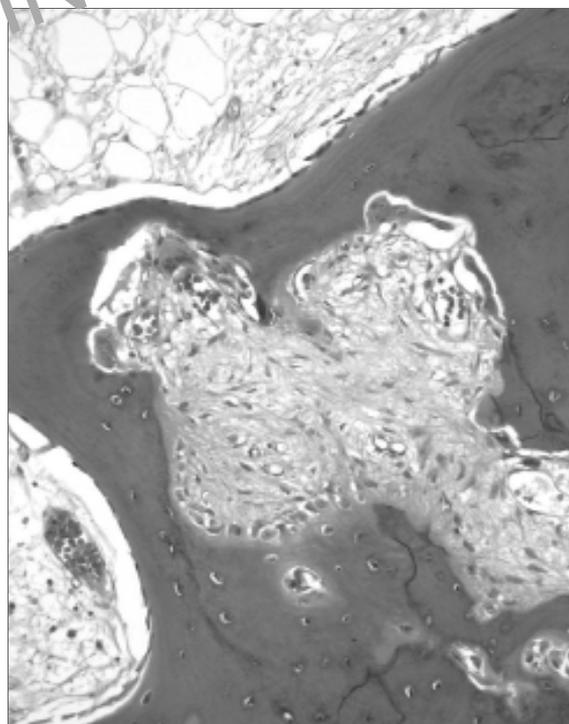


Figure 1 - Photomicrograph showing osteoclastic and osteoblastic activity in early phase of Paget's disease.

bone cell populations has been interpreted as the consequence of an increased birthrate of the basic multicellular units (2). At this stage the histologic differential diagnosis is mainly with hyperparathyroidism, which is characterized by a similar increased cellular activity. However, in Paget's disease the osteoclasts are usually bigger and contain 10-20 nuclei, while osteoclastic resorption taking place in hyperparathyroidism is often of the "tunnelling" or "dissecting" type, in which osteoclasts are displaced within the bone trabeculae, rather than on their surface (Figure 2).

This phase is followed by the mixed (active) phase, in which the osteoblastic activity progressively predominates over osteoclastic resorption process. Osteoblasts produce thick, irregular plates of bone, with increased number of basophilic cement lines, which imparts the "mosaic" or "jigsaw" pattern to the bone (Figure 3). The disorganized pattern of the pathologic bone is sometimes better appreciated using polarized light. The increased number of cement lines together with the alteration in trabecular microarchitecture result in weaker bone.

In the third and final phase (late inactive), osteoblastic activity gradually decreases, resulting in bone tissue characterized by irregularly thickened trabeculae with mosaic pattern, with few osteoblasts and osteoclasts, and a relatively normal or slightly fibrotic bone marrow (Figure 4). Thus, in the final phase, the main histologic feature which should guide the pathologist in the diagnosis of Paget's disease is the presence of the mosaic pattern in bone trabeculae. However, it should be remembered that this pattern is not specific for Paget's disease, and the final diagnosis should be done only after careful review of the radiologic imaging of the lesion. Indeed, Riminucci et al. (3) have described a "pagetoid" variant of fibrous dysplasia involving the craniofacial bones, characterized by dense sclerotic bone formation with prominent cement lines closely resembling that seen in Paget's disease of bone. Pagetoid bone formation has also been reported in parosteal osteosarcomas (4) and in central low grade osteosarcomas (5) and it is probably the result of a very slow growth of the tumour, with heavy bone matrix production and remodeling. The differential diagnosis between Paget's disease and osteosarcoma with pagetoid bone formation is of extreme importance, because if a low grade osteosarcoma is misdiagnosed as Paget's disease and the patient is not treated with tumour resection, than dedifferentiation of the tumour may occur, with development of distant

metastases which may ultimately lead the patient to death (5). Since the histologic picture of low grade osteosarcoma with pagetoid bone formation may resemble quite closely that of late stage of Paget's disease, especially in biopsy material where invasion of host bone may be difficult to demonstrate, it becomes essential to evaluate carefully the radiologic aspect

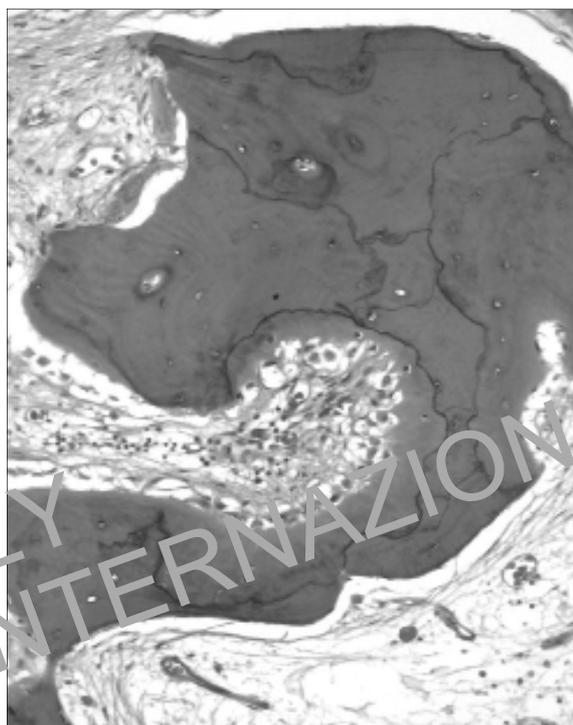


Figure 3 - Active phase of Paget's disease. Osteoblasts produce thick, irregular plates of bone, with increased number of basophilic cement lines, which imparts the "mosaic" or "jigsaw" pattern to the bone. The marrow spaces show fibrosis and angiogenesis.

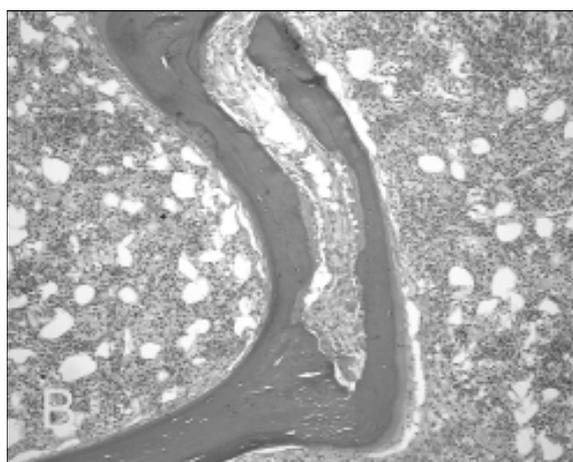
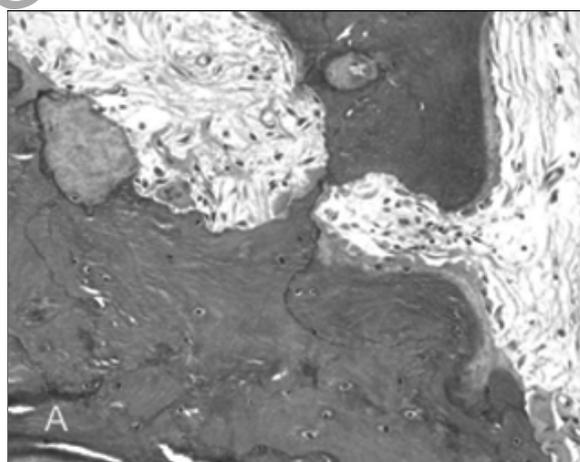


Figure 2 - A. In hyperparathyroidism, the bone trabeculae may be irregularly thickened, as in this example, with prominent basophilic cement lines. Numerous osteoblasts and osteoclasts are present at the trabecular surface. This aspect may resemble that of Paget's disease of bone. However, hyperparathyroidism usually shows areas of bone with "tunnelling" or "dissecting" resorption (B).

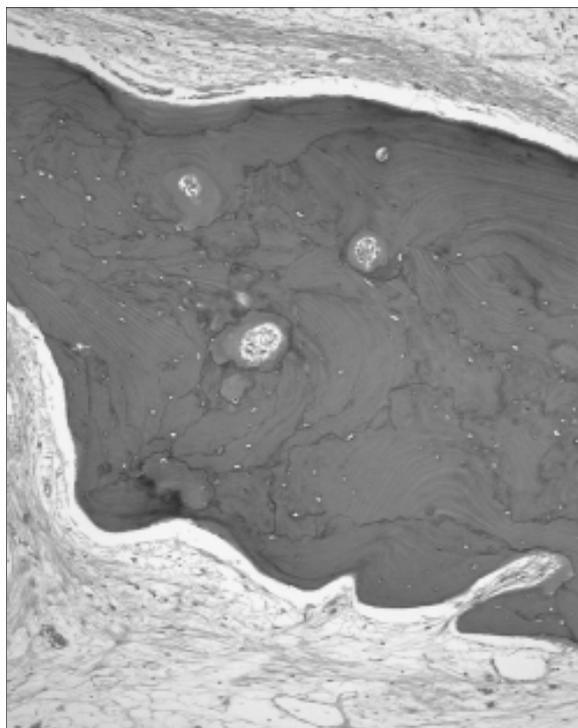


Figure 4 - Late inactive phase of Paget's disease. Bone tissue is characterized by irregularly thickened trabeculae with mosaic pattern.

of the affected bone. Low grade osteosarcoma with pagetoid bone formation appears as a metaphyseal densely sclerotic poorly defined irregular lesion with cortical invasion and extrasosseous extension, features indicative of malignancy that are not part of the radiologic spectrum of Paget's disease of bone (9). In addition, bones affected by low grade osteosarcoma with pagetoid bone formation do not show radiologic signs of Paget's disease, and this feature exclude the possibility of a

malignant tumour arising in Paget's disease (see below for discussion).

Complications of Paget's disease of bone

Paget's disease has several complications, including non-neoplastic conditions, like fractures resulting from bone weakening, deformities, osteoarthritis, and neurologic abnormalities. Histologic examination may be required for specimens deriving from total joint replacement for osteoarthritis in Paget's disease. In these cases, the diagnosis is usually straightforward, as the histologic picture is characterized by the coexistence of cartilage alterations due to osteoarthritis and bone alterations due to Paget's disease (Figure 5). In addition, Paget's disease is a skeletal disorder which predisposes to the development of bone tumours. This aspect will be discussed in greater detail, because the diagnosis of neoplastic complications of Paget's disease mainly rely on histopathologic examination of a biopsy specimen.

The incidence of benign and malignant tumors in patients with widespread Paget's disease of bone as been estimated as high as 10% (6), but malignant degeneration is far less frequent. A chart review of 1078 symptomatic and asymptomatic patients with Paget's disease revealed an incidence of malignant transformation of 0.7% (7), but the true incidence is probably even lower, because many cases of Paget's disease are undiagnosed. Patients with polyostotic disease have a higher risk of malignant transformation, although rarely a tumour may arise in monostotic Paget's disease. Men are more frequently affected than women, and the median age is between 60 and 70 years (6-8). The skeletal sites most commonly affected are the pelvic bones, the femur and the humerus (6-8). Cases with synchronous multifocal sarcomatous degeneration in polyostotic Paget's disease have been reported (9). The most common presenting symptoms are the acute onset of pain or an increase in the intensity of chronic pain, as well as swelling or associated soft tissue masses (6-8). Radiologically, most lesions present as lytic-destructive, while the others show a sclerotic, mixed or permeative character. When sarcomatous degeneration is suspected, a biopsy is necessary to establish a definitive diagnosis. In about one half of the cases, the histologic appearance is that of a high grade osteoblastic osteosar-

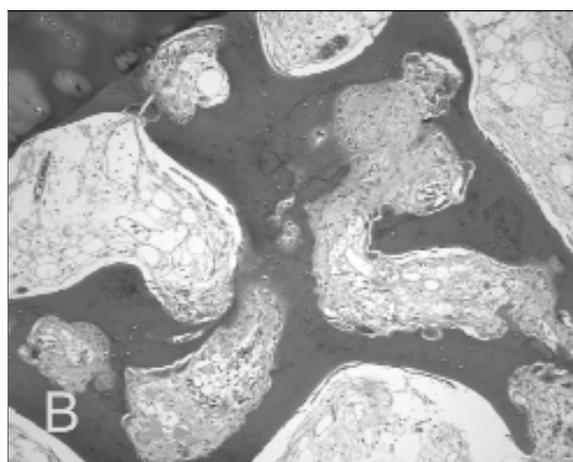
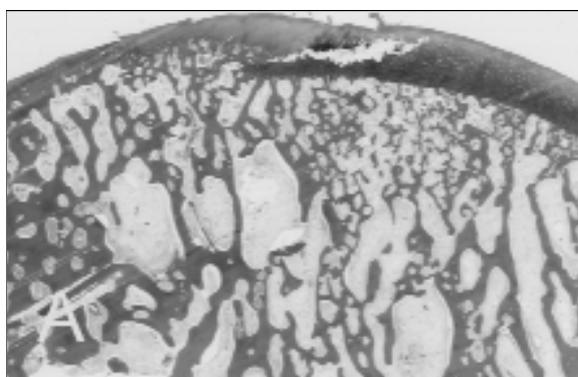


Figure 5 - A. Histologic section from a femoral head treated for osteoarthritis in a patient with Paget's disease of bone. Erosion of the articular cartilage is evident at the top left. Sub-chondral bone shows a disorganized trabecular pattern, with irregularly thickened trabeculae. B. At higher magnification, the cancellous bone shows the typical features of Paget's disease.

coma or of fibroblastic osteosarcoma (6-8) (Figure 6). Other sarcomas that have been reported in patients with Paget's disease are chondrosarcomas (10) and angiosarcomas (11). Overall, the prognosis of patients affected by sarcoma is poor, despite aggressive therapeutic regimens including amputation, chemotherapy, and radiotherapy. The majority of patients die of disease within few months from diagnosis, and 5 year survival rates have ranged between 0% (12) and 15% (13), which is a significantly less favourable behaviour than osteosarcoma arising "de novo" in the same age group.

Other malignancies which have been reported to arise in bones affected by Paget's disease are non-Hodgkin lymphomas (14, 15). They present as lytic lesions within pagetic bone, with soft tissue mass. Morphologically, they appear as large cell lymphomas with B cell phenotype. The diagnosis requires the distinction between secondary bone involvement by systemic lymphoma, and primary lymphoma of bone. Treatment with chemotherapy and radiotherapy may result in a better outcome than patients affected by sarcoma (14, 15). Another rare malignant neoplastic complication of Paget's disease is the occurrence of a solitary metastasis from carcinoma, in which physical, radiographic, and scintigraphic findings may be indistinguishable from those of sarcomatous degeneration, and again the diagnosis is based on biopsy findings (16).

A benign neoplasm which may be associated with Paget's disease is giant cell tumour. In this setting, giant cell tumour presents several peculiar aspects. It typically occurs in patients with polyostotic involvement (17-24), and the most commonly affected bones are the skull and facial bones and, less frequently, the spine, pelvis, clavicle, or tubular bones. Some patients are affected by extraskelatal masses involving the soft tissues. Familial and geographic clustering in patients from Avellino (Italy), whose ancestors are native of this town, have been well documented (19). Whether these lesions in Paget's disease of bone are true giant cell tumours or an atypical proliferative process with a similar or identical histological picture to giant cell reparative granuloma has been controversial. Histologically, these lesions have either the appearance of conventional giant cell tumour, or sometimes they show a lower number of smaller giant cells, predominantly localized around areas of haemorrhage, a picture that is more similar to that of giant cell reparative granuloma. Ultrastructural studies have demonstrated the presence of intranuclear aggregates of microfilaments suggestive of viral inclusions (25, 26). Being aware of

this entity is important because the appearance of lytic lesions with soft-tissue extension in patients with Paget's disease does not necessarily imply a malignant neoplasm with a dismal prognosis. Notably, giant cell tumours associated with Paget's disease of bone are responsive to dexamethasone treatment (19, 21-23).

The differential diagnosis of neoplasms arising in bones affected by Paget's disease includes other pathologic processes that may cause the appearance of a soft tissue mass. Benign conditions that may determine soft tissue involvement in Paget's disease of bone have been reported, and include fracture, which may also result in loss of normal marrow signal on MRI examination, requiring biopsy in order to exclude sarcoma (27). Another cause of soft tissue mass which may mimic the appearance of a neoplasm in the setting of Paget's disease is benign periosteal bone proliferation. This is a pseudosarcomatous condition of which a number of cases have been reported (28-38), which is characterized by a history of pain and swelling, with evidence of a periosteal based soft tissue mass on imaging. Although the relative incidence of this condition is difficult to assess with certainty, it is clearly much rarer than the occurrence of bone sarcoma in Paget's disease. With the exception of one case, which showed bilateral symmetrical involvement (28), all the reported cases were solitary lesions occurring more frequently in long bones of the lower limbs, particularly the femur and tibia. Imaging shows chronic Paget's disease with a periosteal-based soft tissue mass. In these cases, a biopsy is usually taken to exclude malignancy, and histological tissue shows bone trabeculae with prominent osteoclastic and osteoblastic activity as seen in mixed phase of Paget's disease of bone, and an intertrabecular fibrovascular stroma devoid of cellular atypia. Awareness of these pseudosarcomatous lesions is important also to avoid unnecessary repeated biopsy procedures to patients, due to the mistaken belief that the initial biopsy was not representative (38).

Conclusions

Paget's disease of bone is a common metabolic disorder, which is in most cases diagnosed on the basis of its radiographic findings. Its primary bone alterations and subsequent complications constitute a wide range of pathologic pictures, which may pose diagnostic difficulties upon histologic examina-

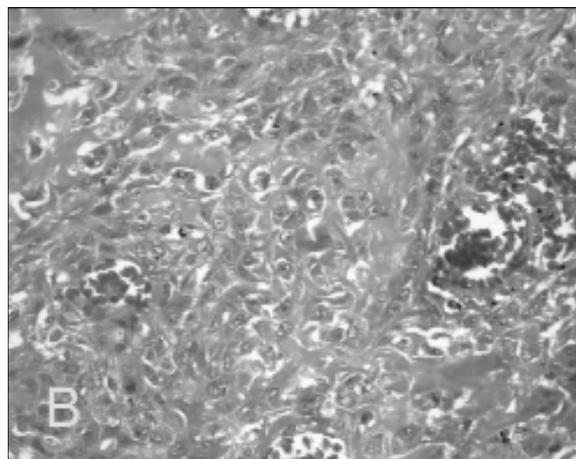
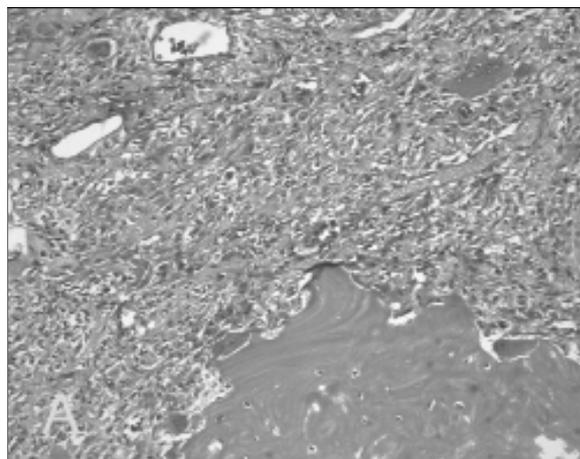


Figure 6 - Paget's sarcoma. A. A high grade sarcoma infiltrates the marrow spaces; residual bone trabeculae have pagetoid appearance. B. This tumour has the histologic features of high grade osteoblastic osteosarcoma, with highly atypical neoplastic cells producing osteoid material.

tion. The areas in which the histopathologic diagnosis is most relevant is in the characterization of neoplasms that may arise in the course of the disease, which may have different biologic behaviour, and more importantly, in the identification of benign pseudosarcomatous conditions.

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