# Paget's Disease or Densifying Metastasis: How to Sort It Out

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## Abstract

Although the prevalence of Paget's disease has decreased over the past 20 years, incidental discovery on imaging is not unusual. The challenge is to establish the diagnosis, especially in unusual forms that may be mistaken for metastases. This review describes the typical imaging features of Paget's disease and some rare presentations that may be more difficult to recognize.

**Keywords**

- Paget's disease
- osteitis deformans
- bone metastasis
- diagnostic imaging

## Paget's Disease

### Epidemiology

Paget's disease, or osteitis deformans, was first described in 1877 by Sir James Paget.[1] It is a bone pathology characterized by abnormal excessive remodeling of one or more long bones. The exact frequency is hard to determine because the disease is usually asymptomatic.[2] Prevalence has decreased significantly over the past 20 years, whereas it was 3 to 4% of patients > 45 years of age in the 1990s.[3] Etiology remains unknown, although several hypotheses have been proposed: inflammatory, vascular, hormonal, autoimmune, infectious, metabolic, or neoplastic.[4] In 1974, the discovery of intranuclear viral inclusions in affected cells strengthened the viral hypothesis, although no specific virus could be identified.[5] The decrease in prevalence suggests environmental factors.

### Pathophysiology

Progression comprises three phases, each associated with specific clinical, radiologic, and pathologic features.[6]

The *early,* or *lytic phase,* is characterized by intense osteoclastic activity with resorption of normal bone by multinuclear giant cells and formation of Howship's lacunae. It is usually clinically asymptomatic. Radiographs show an advancing wedge of bone resorption. In this phase, the bone marrow is relatively normal.

The *intermediate active phase* is characterized by intense reactional osteoblastic activity stimulated by the osteoclastic resorption of the previous phase. Bone resorption continues, but osteoblasts repopulate the resorption areas and cement themselves to the denuded bone. When osteoblastic repair exceeds bone resorption, the trabeculae thicken and become lined with several layers, resulting in the classic mosaic bone pattern of Paget's disease. Abnormal remodeling follows, repair being poor in collagen fibers, and alters bone architecture. The bone marrow is usually hypervascularized. The disease is most often discovered in this phase.

The *late inactive phase* is characterized by a progressive decline in osteoblastic and osteoclastic activity. Fatty marrow predominates and hematopoietic elements disappear, although dilated vessels persist.[6] Once affected, the bone never recovers its initial or its normal state. In this late phase, affected bones continue to enlarge, thicken, and weaken due to defective bone production.

## Typical Imaging Features

Imaging features follow the histologic findings seen during the three phases, although they are also influenced by the involved bone (►**Table 1**).[6]

Radiographically, in the early phase, osteoclastic activity results in an advancing tip of V-shaped bone resorption,

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**Table 1** Classical aspects of Paget's disease

| | Early phase | Intermediate phase | Late phase |
|---|---|---|---|
| Radiograph/CT | Bone advancing wedge of resorption | Advancing wedge of resorption<br>Trabecular thickening, cortical thickening, bone segment enlargement | Bone segment enlargement and deformation |
| CT | Like radiograph | Like radiograph plus disorganized trabeculae, persistent fatty density areas between trabeculae; very dense star-shaped focal intracancellous areas | Like radiograph |
| MRI | Fatty signal | Fatty signal<br>Possible edematous remodeling | Hypervascularized fibrous bone marrow |
| Technetium99m scintigraphy | Low-intensity fixation | Intense fixation | Fixation sometimes less marked |
| FDG-PET/CT | Low-intensity or no fixation | Low-intensity fixation | Low intensity or no fixation |

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

extending toward the diaphysis.[7] To be detectable on radiographs, resorption in the affected area has to involve sufficiently thick cortical bone, and the progression front tends not to be identifiable in areas mainly comprising cancellous bone, such as the spine, pelvis, or long-bone epiphyses. In the skull, the advancing wedge of resorption is noted as enlarged areas of radiolucency usually in the frontal and occipital bones and designated as "osteoporosis circumscripta" (►**Fig. 1a**). Skull lesions are most prominent in the inner calvarial tables and usually cross the suture lines.

The intermediate phase features the four cardinal signs of Paget's disease:

- Advancing wedge of resorption
- Trabecular thickening
- Cortical thickening
- Bone segment enlargement

These four radiographic features are essential to the diagnosis. Their presence rules out the main differential diagnoses for densifying bone lesions: fibrous dysplasia, osteitis, bone-densifying metastasis, and lymphoma. When identified, they are in themselves pathognomic, and biopsy is unnecessary. In the late phase, bones are enlarged, deformed, and brittle due to abnormal bone production.

Overall abnormal bone formation results in osseous weakening, despite the increased density of bone, with deformity and fracture. Anterior or lateral bowing of the tibiae and femora is typical; in the hip, deformity may manifest as protrusio acetabuli.

On computed tomography (CT), in addition to the four cardinal radiographic features, these features are apparent:

- Fewer but thicker and disorganized trabeculae, giving a honeycomb aspect (►**Fig. 2**)
- Persistent areas of fatty density between trabeculae
- Very dense focal star-shaped intracancellous areas mimicking enostosis

There are no soft tissue abnormalities.

In the spine, often the region in which the question of differential diagnoses arises, screening looks for these characteristics (►**Table 2**):

- Harmonious involvement of the whole vertebral body and posterior arch (►**Fig. 2**)

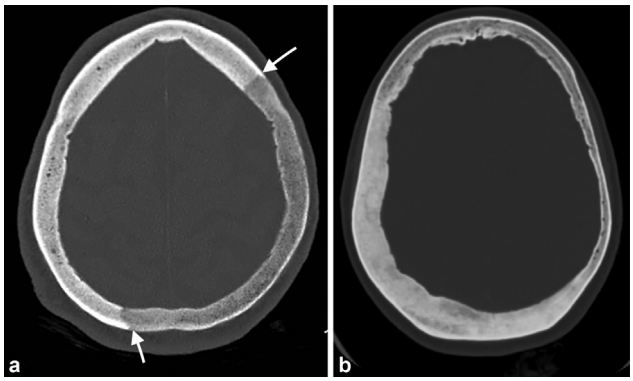


**Fig. 1** Typical imaging features in the skull. (**a**) "Osteoporosis circumscripta" seen as a large area of radiolucency (between arrows). (**b**) Bone resorption associated with areas of osteocondensation with blurred contours, giving the skull a cotton wool appearance.

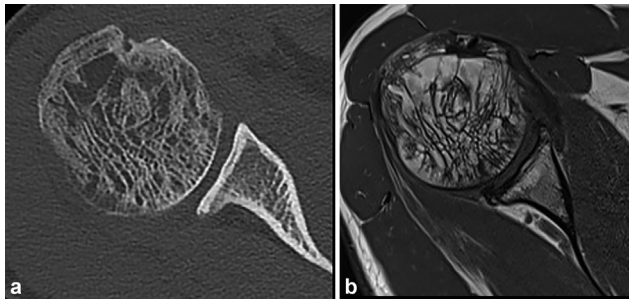


**Fig. 2** Incidental discovery of Paget's disease in a patient with lung cancer (fluorodeoxyglucose positron emission tomography/computed tomography hyperfixation of the right humeral head). (**a**) Axial computed tomography image shows fewer but thicker disorganized trabeculae, resulting in a honeycomb appearance with persisting fatty density areas between trabeculae. (**b**) Axial T1-weighted image shows normal fatty bone marrow between the trabeculae.

 

**Table 2** Aspects suggestive of Paget's disease in the spine

| |
|---|
| Thick, rough vertical trabeculae |
| Transverse and anteroposterior vertebral enlargement compared with unaffected vertebrae |
| Increased sclerosis along the four edges of the vertebral body, particularly the superior and inferior edges, leading to a "frame" aspect |
| Strong increase in bone mineral density, often extending to posterior elements, sometimes leading to "ivory" vertebra |
| Flattening of the normal concavity of the anterior edge of the vertebral body |
| Sclerosis and enlargement of the posterior arch |
| Biconcave deformation by vertebral plate microfracture, leading to "fish" vertebra |

- Transverse and anteroposterior enlargement of the vertebral body or loss of anterior concavity in incipient forms
- Spinous process hypertrophy
- Cortical thickening along the four margins of the vertebral body with cortexes producing the characteristic picture frame appearance[8]

In the skull, bone resorption is associated with areas of osteocondensation with blurred contours, predominantly at the level of the internal table and giving the skull a cotton wool appearance (►**Fig. 1b**). Skull lesions are most prominent in the inner calvarial tables and usually cross the suture lines.

On magnetic resonance imaging (MRI), Paget's disease can be overlooked because the affected bone may present normal or relatively preserved signal intensity of the fatty bone marrow on T1-weighted images. Cortical thickening and trabecular coarsening can be difficult to identify on MRI, but a contrast between obvious radiographic or CT abnormalities and a seemingly normal fatty marrow signal on MRI is highly suggestive of Paget's disease (►**Fig. 3**). In advanced stages, decreased corticocancellous differentiation can be responsible for fatty signal intensity of the cortical bone. In the late phase, the bone marrow becomes hypervascularized and fibrous.

There may be regions of fibrosis or sclerosis showing low T1 and T2 signal, or hypervascularized marrow with low T1 and high T2 signal, enhancing after gadolinium administration. In these difficult cases, once again, screening should search for islands of residual fatty marrow to rule out medullary replacement of tumoral origin (►**Fig. 4**). In very active forms, an adjacent edematous soft tissue reaction may be noted. However, there is no soft tissue mass. Presence of the latter suggests either sarcomatous degeneration or metastatic colonization.

On conventional technetium 99m-hydroxydiphosphonate bone scintigraphy, fixation is intense in the intermediate phase and highly suggestive; this is a marker of osteoblastic activity, with increased resorption in the active phase (►**Fig. 5**). In the late phase, fixation decreases. Scintigraphy is more sensitive than radiographs, revealing up to 30% more lesions, especially in the ribs, sternum, and scapulae, which are difficult to analyze on radiographs.[9] In noncomplicated cases, F-18 fluorodeoxyglucose uptake on positron emission tomography is slight, a marker of glycolysis rather than of osteoblastic activity.[10] This examination can provide a key element in the differential diagnosis versus metastasis.[11]

## Atypical Presentation of Paget's Disease

Presentation of Paget's disease may be unusual clinically (e.g., age at onset $< 40$ years), in topography (limbs, extremities), or

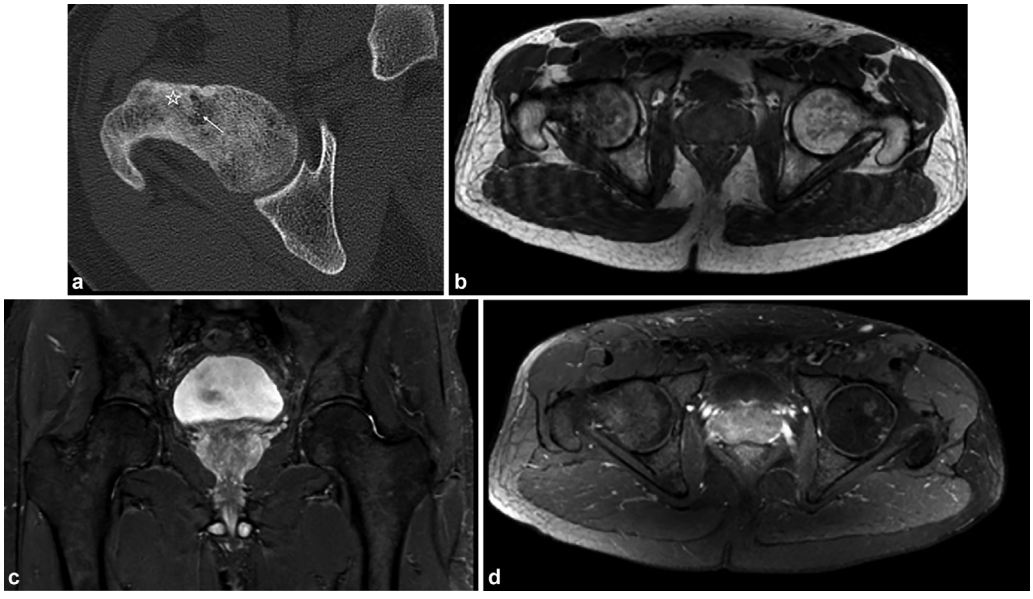


**Fig. 3** Incidental discovery of Paget's disease in a patient with colon cancer. (**a**) Axial computed tomography image shows loss of corticomedullary differentiation, with sclerotic focal areas (star) and a fatty area (arrow). The bone marrow signal intensity of the right femoral head is mildly decreased on T1 (**b**), normal on T2 short tau inversion recovery (**c**), and shows a mild enhancement after gadolinium administration (**d**). Biopsy confirmed Paget's disease.

 

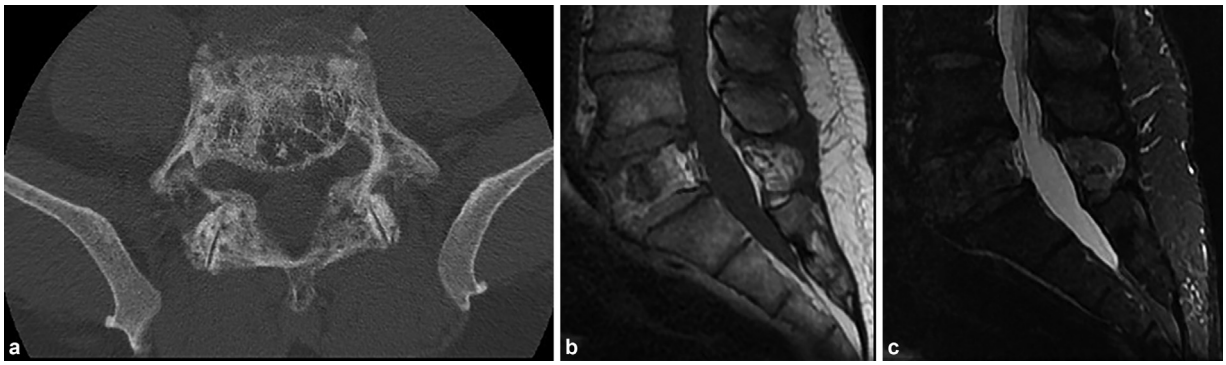


**Fig. 4** Incidental discovery of Paget's disease in a patient with endometrial cancer (L5 vertebra scintigraphic hyperfixation). (**a**) Axial computed tomography image shows disorganized vertebral trabecular architecture, affecting both body and posterior arch. (**b**) Sagittal T1 and (**c**) short tau inversion recovery (STIR)-weighted images show involvement of the whole vertebra with a partial fatty bone marrow signal on T1 and an edematous signal on STIR.

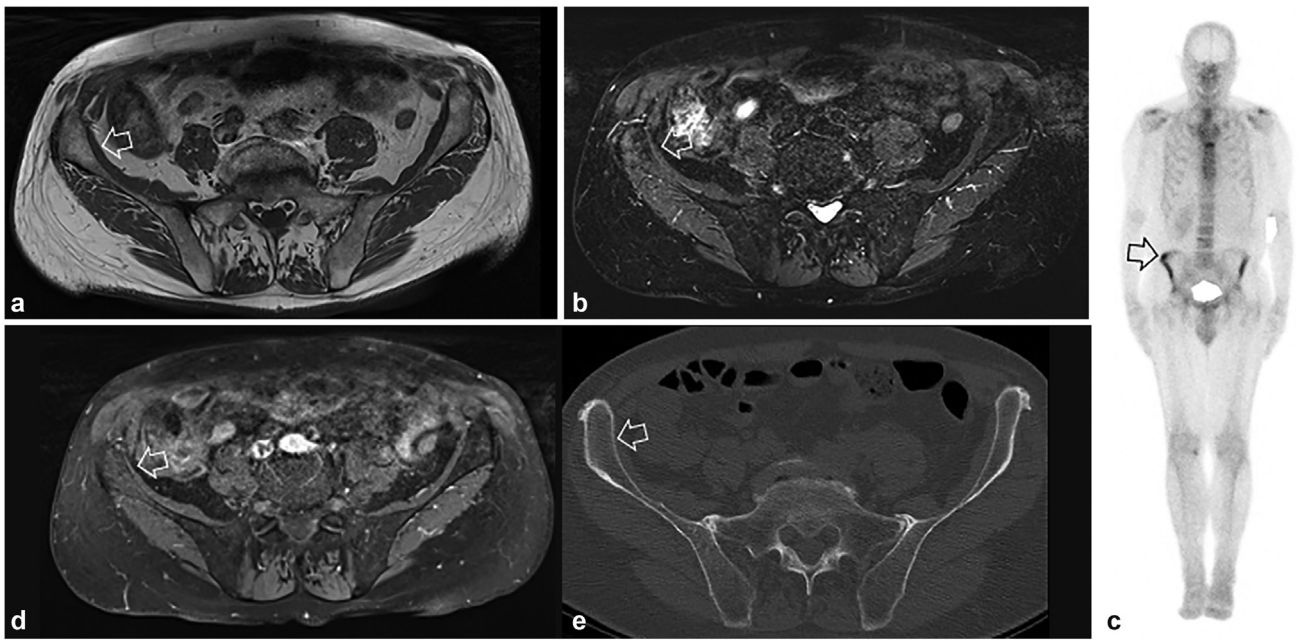


**Fig. 5** Incidental discovery, on prostate cancer extension assessment, of abnormal right iliac wing signal (arrow), heterogeneous with persistent large fatty areas on T1 (**a**) and edematous remodeling on STIR sequences (**b**), with enhancement under gadolinium (**c**). (**d**) Scintigraphy shows intense fixation. (**e**) On computed tomography, remodeling is subtle with slight sclerosis and global enlargement of the iliac wing compared with the contralateral side. Biopsy confirmed Paget's disease.

in imaging, raising the question of a differential diagnosis with other bone diseases, notably tumoral. Even so, in most cases, evidence from patient interview, clinical examination, and imaging leads to a diagnosis without the need for biopsy.

## Lesion Topography

Paget's disease begins in the long-bone epiphysis, progressively extending to the diaphysis. The entire bone may thus be involved. In the spine, concomitant involvement of the spinous apophysis on imaging strongly suggests Paget's disease[12] (►**Fig. 6**). The pathology rarely originates in both extremities of a given bone. It does not cross the joints, except in the case of bone ankylosis. In multifocal lesions, remodeling may differ from bone to bone, suggesting differences in time of onset.[13] Thus phase, extension, and radiologic and pathologic characteristics vary considerably from bone to bone or even from region to region within a given bone.

## Progression

Progression is slow, estimated at a little less than 1 cm per year.[14] In atypical Paget's disease, comparative analysis of previous examinations is essential to rule out differential diagnoses.

After a fracture or prolonged immobilization, the pagetic bone may present significant bone rarefaction with loss of cortical sharpness that may mimic a metastasis. This pseudotumoral bone rarefaction is classic in the pelvis and femora.

## Biology

Densifying metastasis, like Paget's disease, can lead to alkaline phosphatase elevation. Levels may be normal in the early

 

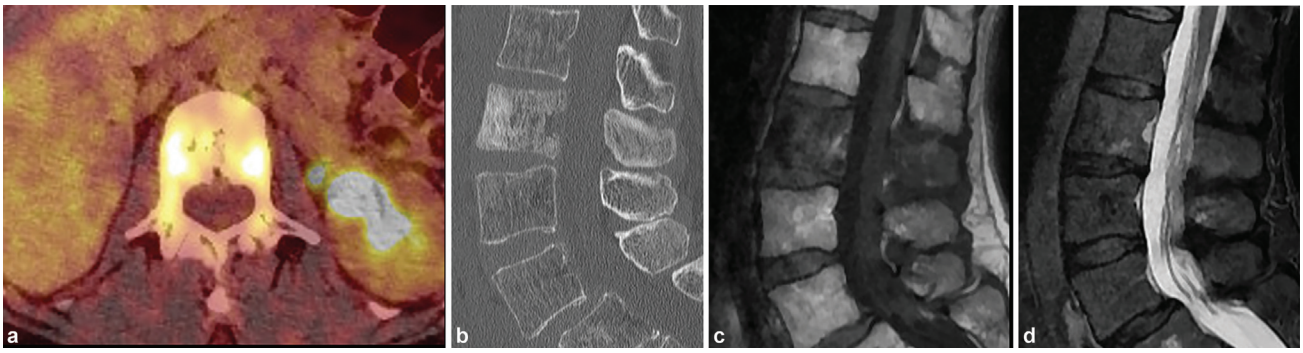


**Fig. 6** (**a**) Incidental discovery, on breast cancer extension assessment, of moderate intensity L3 vertebral body fluorodeoxyglucose-positron emission tomography fixation. (**b**) Axial computed tomography image shows heterogeneous sclerosis of the vertebral body, with concomitant involvement of the spinous process, suggesting Paget's disease. (**c**) Sagittal T1-weighted images show a persistent fatty area at the posterior aspect of the vertebral body, despite the diffuse sclerosis. (**d**) Sagittal short tau inversion recovery–weighted images show a mild enlargement and increased signal of the vertebra.

phase or in very late phases, between which the assay does not discriminate. But high levels of acid phosphatase or prostate-specific antigen suggest metastatic disease of prostate origin.

### Absence of the Four Cardinal Radiographic Signs

In Paget's disease, imaging features may be unusual, such as the absence of one or several cardinal features. Sclerotic changes may represent the main imaging feature, especially in the spine.[15] Different patterns of diffuse or focal texture abnormalities, best visualized on CT, have been described.[16] In diffuse abnormalities, the microcystic pattern is the most common: thin sclerotic or normal remaining trabeculae delineate "cystic" spaces that range in size from small (1–5 mm) to large ($>$ 5 mm). The mesh pattern is characterized by scarce and thick intersecting bone trabeculae (►**Fig. 2**). The diffuse sclerotic pattern (ivory vertebra) shows diffuse homogeneous increase in bone density of the vertebral body, whose size and contours remain normal. This presentation is very difficult to distinguish from metastatic disease or lymphoma (►**Fig. 3**). In the spine, depiction of concomitant involvement of the spinous apophysis or of mild enlargement of the bone is highly suggestive of Paget's disease (►**Fig. 6**).

Three types of focal bone texture abnormalities can be encountered[16]:

- Sclerotic foci seen as foci of compact bone with thorny edges (►**Fig. 3**), usually associated with typical diffuse involvement, facilitating diagnosis of Paget's disease
- Bone-within-bone appearance produced by bone apposition at the periosteal surface of the vertebral body, resulting in a "double contour" sign
- Focal thickening of horizontal trabeculae converging toward the pedicles

In early forms, texture abnormalities may be absent. In such unusual forms, there is never periosteal apposition or destruction of the cortical bone (►**Fig. 7**).

In these difficult cases lacking the cardinal radiographic signs, complementary MRI is indispensable. A fatty signal intensity of bone marrow favors Paget's disease in doubtful cases. Scintigraphy showing hyperfixation, with normal bone marrow signal on MRI, reinforces the diagnosis of Paget's disease.

### Misleading Bone Marrow Appearance

Several misleading bone marrow appearances can be encountered[16]:

- At the earliest stages, the bone marrow is preserved or only minimally involved. Paget's disease may therefore be overlooked on MRI (►**Fig. 5**).
- At the intermediate stage, nonspecific bone marrow edema can be seen. It occurs in 30% of patients with vertebral Paget's disease. Features suggesting edema rather than bone marrow replacement include mild and homogeneous signal intensity changes on both T1- and T2-weighted images, mild homogeneous enhancement after gadolinium administration, preservation of bone texture, and absence of an adjacent soft tissue mass on all MRI sequences (►**Fig. 4**).[17]
- A sclerotic pattern with low signal intensity on both T1- and T2-weighted images. The presence of vertebral shape abnormalities, involvement of the entire vertebra, and depiction of residual fatty foci are particularly helpful for the diagnosis.

In diffuse densifying Paget's disease, MRI shows the bone marrow as hypointense in both T1 and T2 due to increased trabecular thickening, bone marrow sclerosis, and fibrosis (►**Fig. 6**). In these particular cases, abnormal vertebral morphology and involvement of the whole vertebra favor the diagnosis of Paget's disease.

The clues for the diagnosis of Paget's disease on MRI in the presence of unusual presentations include comparison with radiographs, CT, or bone scintigraphy, depiction of residual fatty foci, depiction of minor shape abnormalities, involvement of the whole vertebra in the spine, and the absence of an adjacent soft tissue mass (►**Table 3**).

### Particular Case of Metastasis in Paget-affected Bone

Given the advanced age of most Paget patients, association with other malignancies such as metastases, myeloma, and

 

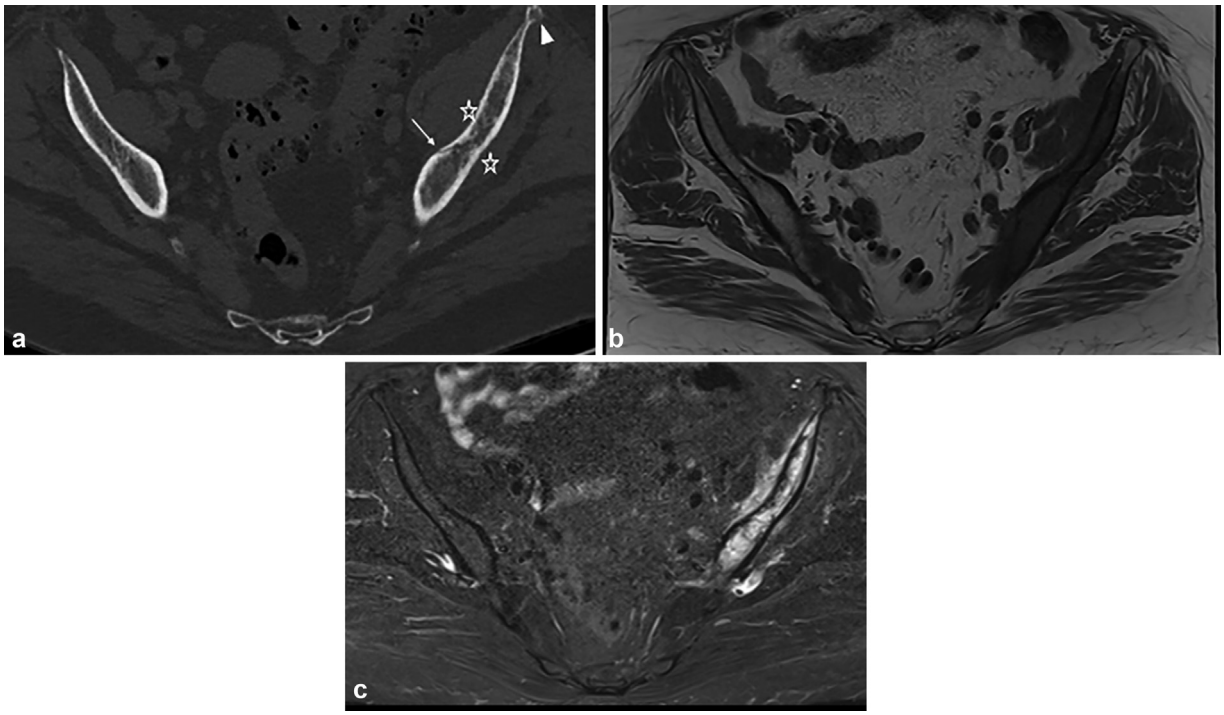


**Fig. 7** (**a**) Computed tomography image of a 69-year-old woman consulting for hip pain. The hypothesis of a fracture (arrow) on Paget's disease due to cortical thickening and disorganized aspect of the cortical trabeculation was proposed. Note that the small areas of cortical osteolysis (arrowhead) and soft tissue thickening (stars) argue against this hypothesis. (**b**, **c**) Moreover, magnetic resonance imaging shows medullary replacement on T1 and soft tissue involvement on short tau inversion recovery. Biopsy confirmed the diagnosis of bone lymphoma.

**Table 3** Checklist for differential diagnosis between Paget's disease and metastasis

| |
|---|
| Bone structure remodeling on radiographs without bone marrow signal abnormality: Paget's disease |
| Radiographic abnormalities without bone marrow abnormality, with intense fixation on scintigraphy: Paget's disease |
| Scintigraphy shows the best sensitivity in detecting polyostotic disease. Involvement may be asynchronous, with aspects varying between affected bone segments |
| In case of signal abnormality or bone marrow enhancement on magnetic resonance imaging, screen for persistent fatty islands to rule out medullary replacement |
| Progression of Paget's disease is very slow; comparison with previous imaging examinations, if available, assessing progressiveness, is a key factor in diagnosing Paget's disease |
| In case of vertebral involvement, posterior arch involvement is characteristic of Paget's disease |
| Soft tissue infiltration is exceptional |

primary lymphoma can be expected.[18] Because metastatic disease is usually multifocal, lesions within pagetic bone are unlikely to pose much of a diagnostic problem.[18] Onset of osteolysis with cortical destruction and an associated soft tissue mass are highly suggestive. Interestingly, metastases tend to occur in an eccentric location when present in long bones, in contrast to the central origin of osteosarcomas.[18] Primary lymphoma superimposed on Paget's disease can also present as a focal permeative lesion with or without a soft tissue mass (►**Fig. 7**).[18] However, metastases, myeloma, and lymphoma may be indistinguishable from Paget's sarcoma when arising within bone affected by Paget's disease. Although not malignant, giant cell tumor can also occasionally involve pagetic bone.

### Particular Case of Sarcomatous Transformation

Paget's sarcoma is rare, and its incidence is decreasing due to the fall in prevalence and in clinical severity of Paget's disease. Osteosarcoma is the predominant histologic subtype. Onset of pain either due to the tumor itself or secondary to a pathologic fracture is a cause for alarm. Imaging shows a rapidly enlarging osteolysis with cortical destruction and a soft tissue mass.[19] MRI shows medullary replacement of normal T1-weighted hyperintense fatty bone marrow signal intensity.[20]

## Conclusion

Increasing use of imaging leads to more incidental discoveries of asymptomatic bone lesions. Paget's disease is one possible diagnosis. In most cases, semiology is typical and straightforward, with four cardinal signs. When more difficult, imaging associating CT, MRI, and scintigraphy allows diagnosis and rules out differential diagnoses of densifying tumoral bone lesions, without resorting to biopsy.

### Conflict of Interest

None declared.

 

## References


1 Paget J. On a form of chronic inflammation of bones (osteitis deformans). . Medico-Chir Trans 1877;60:37–64.9
2 Ralston SH. Clinical practice. Paget's disease of bone. N Engl J Med 2013;368(07):644–650
3 Poór G, Donáth J, Fornet B, Cooper C. Epidemiology of Paget's disease in Europe: the prevalence is decreasing. J Bone Miner Res 2006;21(10):1545–1549
4 Roodman GD, Windle JJ. Paget disease of bone. J Clin Invest 2005; 115(02):200–208
5 Friedrichs WE, Reddy SV, Bruder JM, et al. Sequence analysis of measles virus nucleocapsid transcripts in patients with Paget's disease. J Bone Miner Res 2002;17(01):145–151
6 Mirra JM, Brien EW, Tehranzadeh J. Paget's disease of bone: review with emphasis on radiologic features, Part I. Skeletal Radiol 1995;24(03):163–171
7 Smith SE, Murphey MD, Motamedi K, Mulligan ME, Resnik CS, Gannon FH. From the archives of the AFIP. Radiologic spectrum of Paget disease of bone and its complications with pathologic correlation. Radiographics 2002;22(05):1191–1216
8 Zlatkin MB, Lander PH, Hadjipavlou AG, Levine JS. Paget disease of the spine: CT with clinical correlation. Radiology 1986;160(01): 155–159
9 Vellenga CJ, Bijvoet OL, Pauwels EK. Bone scintigraphy and radiology in Paget's disease of bone: a review. Am J Physiol Imaging 1988;3(03):154–168
10 Winn N, Lalam R, Cassar-Pullicino V. Imaging of Paget's disease of bone. Wien Med Wochenschr 2017;167(1-2):9–17
11 Shimoyama Y, Kusano M, Shimoda Y, et al. Paget's disease of bone resembling bone metastasis from gastric cancer. Clin J Gastroenterol 2011;4(04):207–211
12 Mirra JM, Brien EW, Tehranzadeh J. Paget's disease of bone: review with emphasis on radiologic features, Part II. Skeletal Radiol 1995;24(03):173–184
13 Renier JC, Audran M. Maladie de Paget: étude de la progression en longueur et en épaisseur des atteintes osseuses, et estimation de l'âge de début de la maladie. Rev Rhum Mal Osteoartic 1997;64:37–46
14 Maldague B, Malghem J. Dynamic radiologic patterns of Paget's disease of bone. Clin Orthop Relat Res 1987; (217):126–151
15 Vande Berg BC, Malghem J, Lecouvet FE, Maldague BM. Magnetic resonance appearance of uncomplicated Paget's disease of bone. Semin Musculoskelet Radiol 2001;5(01):69–77
16 Dohan A, Parlier-Cuau C, Kaci R, Touraine S, Bousson V, Larédo JD. Vertebral involvement in Paget's disease: morphological classification of CT and MR appearances. Joint Bone Spine 2015;82(01):18–24
17 Boutin RD, Spitz DJ, Newman JS, Lenchik L, Steinbach LS. Complications in Paget disease at MR imaging. Radiology 1998;209 (03):641–651
18 Tilden W, Saifuddin A. An update on imaging of Paget's sarcoma. Skeletal Radiol 2021;50(07):1275–1290
19 Theodorou DJ, Theodorou SJ, Kakitsubata Y. Imaging of Paget disease of bone and its musculoskeletal complications: review. AJR Am J Roentgenol 2011;196(06):S64–S75
20 Sundaram M, Khanna G, El-Khoury GY. T1-weighted MR imaging for distinguishing large osteolysis of Paget's disease from sarcomatous degeneration. Skeletal Radiol 2001;30(07):378–383