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Review Article

The role of CT and MRI in imaging of Paget bone disease

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Abstract

Paget disease (PD) is a common bone disease characterized by abnormal bone turnover that follows a disorderly osteoclastic overactivity. In typical PD, imaging assessment is accomplished with conventional radiography and bone scintigraphy. CT and MRI may have complementary roles in the imaging workflow of PD preventing inappropriate investigation and helping the management planning at an early stage. Apart from discovering incidental findings, CT and MRI contribute substantially to the diagnosis of less typical cases, the delineation of PD pathology in complex anatomic areas, the differential diagnosis from sinister causes and the accurate assessment of specific complications.

Keywords: Paget, Bone, Computed tomography, Magnetic resonance imaging

Paget bone disease (PDB) is the 2nd most common bone disease after osteoporosis affecting individuals over 50 years of age[1]. It is classically described as having three phases: an initial lytic phase in which normal bone is resorbed by disorderly osteoclastic overactivity, an intermediate mixed phase consisting of both osteoclastic and osteoblastic activity with an abnormal newly made bone, and a delayed sclerotic phase with predominant osteoblastic activity producing a disorganized boney pattern (woven bone). Eventually, osteoblastic activity also declines resulting in a fourth quiescent and chronic "inactive sclerotic" phase with general reduced bone activity. Interestingly, all these phases can occur in the same patient at different sites of the skeleton or even in the same bone at different sites, simultaneously.

Traditionally, imaging assessment of PDB is accomplished with conventional radiography and bone scintigraphy which, combined with the characteristic laboratory findings, complete the initial evaluation, establish the diagnosis and demonstrate the extent and severity of the disease in the majority of cases. The structural changes noted on **radiography** are usually characteristic to the point of being pathognomonic and until today radiographs are the first-line modality for investigating suspected cases. Functional imaging with **bone scan** remains the most sensitive means of identifying active pagetic sites. It evaluates the extent and distribution of active PBD and establish the dormant nature in the delayed phase depicting no evidence of increased uptake[2]. Bone scan is, however, not specific -any process causing increased osteoblastic activity is identified- and may underestimate the initial lytic phase of PBD when osteoclastic activity predominates.

Most patients with PBD may not have any clinical features. Given the frequency with which cross sectional imaging -computed tomography (CT) and magnetic resonance imaging (MRI)- is performed nowadays for several clinical indications (in the vertebral column and around the knee, MRI may be performed even before a radiograph), PDB is often discovered as an incidental finding during a workup with CT or MRI for some unrelated disease or trauma. Thus, awareness of typical appearances or subtle findings of PBD on CT and MRI may prevent misdiagnosis or/and inappropriate investigation, particularly of metastatic disease, in this age group of patients[3]. Careful examination of the imaged skeleton can be also very helpful. For example, a suspicious focus in the vertebra may be confirmed by the obvious evidence of multifocal PD in the sacrum and/or ilium that may be included in MRI scan of the lumbar spine.

But apart from discovering incidental findings, CT and MRI play an important role in the imaging workflow of PDB.

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Computed tomography (CT) gives superior detail of the cortical and trabecular bone owing to the higher contrast resolution, the feasibility of "bone window" setting and the cross-sectional display. In a recent review, Theodorou et al[4] reported that CT is particularly suited to showing trabecular coarsening, cortical thickening, osseous expansion and osteolysis facilitating the depiction of plain radiographic pagetic bone abnormalities[2]. The fine evaluation of bone texture in the spine allows, for example, the differentiation from other conditions, such as vertebral hemangioma and to some extent, metastatic disease and lymphoma[5]. The exquisite anatomical bony details can be improved by high resolution technique (e.g. in temporal bone). In addition, CT permits a three-dimensional assessment of complex bone structures and gives valuable information about marrow attenuation and soft tissues.

Magnetic resonance imaging (MRI) is less useful for imaging cortical and trabecular bone which are primarily affected by PBD but gives an excellent depiction of bone marrow and soft tissues. In pagetic bone various alterations can occur in the marrow such as increased vascularity, residual hematopoiesis, fibrosis and fatty marrow replacement, resulting in a wide range of possible MRI signal variations[6,7]. A *completely normal MRI signal* may be seen when there is no change in the intervening marrow at the microscopic level. *Increased fat signal* may be depicted (a) in the early lytic phase, due to the osteoclastic resorption of the trabecular bone and the proportionately higher fat content in the marrow, and (b) in delayed phases of PBD when there is repopulation of the marrow with fat. A *heterogeneous signal intensity appearance in both T1- and T2-weighted sequences* with reduced fat signal and increased water signal is seen in the mixed phase of PBD as reactive changes in the marrow make it more vascular and the intervening osteoid is more active and cellular. In this phase the cortex may also show slight increased signal compared with the cortex in the adjacent normal bone. A signal reduction on all MRI sequences is seen in the sclerotic and delayed dormant phase, due to the disproportionately increased signal contribution from the trabecular thickening and coarsening compared with the fatty marrow, to the reduced water content in the tissues and to some marrow fibrosis.

Complex anatomic areas with overlapping structures and/or complex bony anatomy

PDB can affect any bone in the body, with the most common sites of involvement to be the pelvis (30-75%), the spine (29-57%)[5,8], the sacrum (30-60%) and the skull (25-65%)[9]. In the peripheral skeleton, radiographs have a very high sensitivity and specificity in the depiction of PBD, being the mainstay of imaging. However, in anatomic areas with overlapping structures, obtaining good images -especially in obese patients- is difficult and bony details may not be readily appreciated on radiographs alone[10]. Similarly, in bones with complex anatomy such as the skull (i.e. facial bones, skull base, neural foramina, middle ear), the spine (i.e. arc or laminae lesions) and the pelvis, the bony details may not be sufficiently depicted. In fact, in sites where findings in radiography can be obscured by overlapping structures or complex bony anatomy, the disparity reported in diagnostic sensitivity for PBD between bone scintigraphy and radiography is especially noticeable[4]. Thus, CT and MRI are often necessary to demonstrate the classic features of PBD in axial skeleton and distinguish it from other diseases[11].

For example, a very important consideration when assessing for spine PBD is the vertebral body expansion. PBD causes an increase in the anteroposterior and the lateral dimensions of the vertebral body but cannot cause an increase in the vertebral height. Cross sectional imaging may help delineate these subtle differences[5]. Another highly suggestive finding of PBD, even when non-specific vertebral body changes are found, is the visualization of concomitant spinous process involvement. For example, an "ivory vertebra" is a diffusely sclerotic vertebra due to trabecular and cortical bone apposition that needs to be differentiated from metastases, osteosarcoma, lymphoma and carcinoid. The depiction of the spinous process by cross sectional imaging is very helpful because isolated involvement of the neural arch or the vertebral body is very rare in PBD[5,11].

Early lytic phase

The early lytic phase is considered to be the rarest clinical manifestation of PBD. Dell'Atti et al[8] explained that this pagetic form is most often seen radiographically in bones with a low trabecular-to-cortex ratio (i.e. skull vault, femur, humerus) by a clear leading edge at the interface with normal bone, but cannot usually be detected in bones with a high trabecular-to-cortex ratio (i.e. vertebra, sacrum, pelvis). Scintigraphy may also underestimate the early purely lytic phase because osteoclastic activity predominates and no increased uptake is seen (in scintigraphy the radioisotope used, being a diphosponate, is a marker of osteoblastic activity only)[12]. On contrary to radiography and bone scan, CT may depict subtle loss of normal trabeculae and subtle cortical resorption[2].

Atypical cases or monostotic form

Many diagnostic difficulties are encountered in atypical cases or monostotic form of PBD, especially when the levels of serum total alkaline phosphatase are also within the reference range. This problem is quite often given that PDB can be monostotic in up to 50% of cases[13].

a. Focal osteolysis

Focal significant osteolysis can occasionally occur in an area affected by PBD, in the lytic phase as a monostotic form, or in advanced PBD due to metastases, malignant disease, or immobilization. An advancing zone of rarefaction,

often incidentally found, is difficult to be evaluated only by radiographs and bone scan, especially when PBD is monostotic[14]. The aggressive appearance of the entity, the often increased uptake in scintigraphy[2] and afflicted individuals usually being in the fifth decade of life or beyond, engender differential diagnostic problems. An unnecessary biopsy should be avoided if possible, because the risk of pathological fracture through lytic PD is high[15] and in these cases CT/MRI may have a certain role.

In the exceptionally rare cases of lytic PBD in vertebrae presenting on radiographs, the marked osteopenia gives a "ghost vertebra" appearance - the osteolytic process involves the vertebral body almost completely- making it indistinguishable from a malignant process with conventional imaging[16,17]. CT can depict the cortical thickening, the trabecular bone hypertrophy and the vertebral expansion, that along with the absence of cortical destruction and soft tissue extension may confirm the lytic phase of PBD[11]. Similarly, a "cystic" pattern in pelvis 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. This is also one of the very few situations where an osteolytic "lesion" on radiographs does not show the usually encountered low signal on T1-weighted sequences[15]. In uncomplicated by either fracture or sarcoma osteolytic PBD the bone destruction is caused by resorption and not infiltration and so fatty marrow and its corresponding MRI signal may be preserved on T1-weighted sequences. According to Saifuddin and Hassan[18] CT and MRI allow accurate differentiation between lytic PBD and sarcomatous degeneration in the majority of cases, by revealing normal soft tissues, lack of cortical interruption and normal areas of fatty marrow.

MRI is also valuable in the differentiation of disuse osteoporosis, a possible complication of pathologic fracture in PBD occurring particularly after immobilization. The resultant marked reduction of bone density can be focal creating an extensive "motheaten" osteolytic pattern that obscurs the tell-tale signs of PBD and mimics bone destruction by primary/secondary tumor. MRI depiction of normal fat signal in the area of osteolysis helps to exclude malignancy in the area[2]. In fact, there are only two pathologies that can demonstrate focal osteolysis on radiographs and preservation of fat signal on MRI, PBD and an intraosseous lipoma[19].

b. Aberrant radiographic presentation in the mixed phase

In the mixed phase of PBD there are characteristics of both the incipient and the chronic (late) phase. An aberrant radiographic presentation was defined by Mirra et al[14] as one in which at least three of the four cardinal radiographic features are absent (1. enlargement of bone contours, 2. accentuation and coarsening of trabecular pattern along stress lines, 3. cortical thickening and 4. advancing wedge of resorption). Saifuddin and Hassan[18] and Vande Berg et al[20] argued that correlation between MR and radiographic or CT findings facilitates the recognition of uncomplicated atypical PBD, as the mineralized and non-mineralized elements of bone can both be assessed respectively.

Complications

Regarding follow-up, repeated imaging is usually unnecessary, unless new symptoms develop or current symptoms become significantly worse. Radiography is often sufficient for the evaluation of the type and extent of several characteristic complications and no compelling data exist to suggest that CT and MRI should be used as a substitute for radiography or as a routine screening tool (e.g. for sarcoma)[21]. On the other hand, CT and MRI are by far the best imaging methods for evaluating diagnostic dilemmas or certain complications, including neurologic symptoms, neoplastic degeneration, osteoarthritis and fractures in axial skeleton[2,11,22].

Spine complications

Spine is the second most commonly affected site in PBD and apart from fractures, osteoarthritis and neoplastic degeneration, specific complications include spinal stenosis and spondylolisthesis. In the majority of cases the evaluation of complicated PBD in vertebral column is difficult on radiographs alone.

Pagetic spinal stenosis is reported in up to 33% of patients with PBD and has been defined as compression of the spinal cord, cauda equina or spinal nerves by expanded pagetic bony tissues[8,23]. CT better assesses the overall bone expansion (i.e. posterior expansion of vertebral body, anterior expansion of neural arch, facet joint arthropathy, or combination) and the severity of spinal stenosis whereas MRI evaluates the degree of spinal cord and nerve root encroachment[24]. Note that when only MRI is used, the neural arch expansion can be confused with epidural fat ossification and the fatty marrow within an expanded posterior neural arch can be confused with epidural lipomatosis[25,26]. Thus, CT and MRI should be used in a complementary way.

In the pagetic spine, CT and MRI can also evaluate other compressive causes of neural element dysfunction including disk degeneration, ligament ossification, spondylolistesis, fracture retropulsion or atlantoaxial subluxation, pagetic intraspinal soft tissue, epidural fat ossification similar to ankylosing spondylitis, epidural hematoma from spontaneous bleeding and rarely pagetic sarcomatous degeneration. Occasionally neural dysfunction may result in the absence of significant stenosis by way of "arterial steal"[27]. The deprivation of blood supply to the spinal cord is thought to be due to arterial compression by the expanding pagetic bone or due to preferential blood flow to adjacent pagetic bone. This non-compressive neurologic dysfunction is important to be diagnosed because it can respond well to medical treatment with calcitonin[28].

PBD spondylolisthesis owing to either spondylolysis

(spondylolytic spondylolisthesis) or to facet OA (degenerative spondylolisthesis) can be also difficult to assess on radiographs. An expanded anterior border of pagetic vertebra may give a false positive impression of spondylolisthesis and on contrary a false negative diagnosis may be done when an enlarged pagetic vertebra has slipped anteriorly but the posterior vertebral contours seem to align normally. In these cases, CT may show the displacement of the neural arches confirming the diagnosis.

Skull complications

For patients with a skull lesion, evaluation with CT/MRI is preferred. Skull involvement usually starts at the skull base and extends onto the vault. Basilar invagination and platybasia, reported in up to 30% of patients with skull PBD, can result in lethal brainstem compression, syringomyelia or obstructive hydrocephalus[14]. MR is best suited for this evaluation[3]. Deformities and bone expansion in skull base may lead to cranial nerves' entrapment, involvement of osseous labyrinth in petrous temporal bone, and/or otosclerosis of middle ear bones. CT is the optimal imaging method for assessing skull base and high resolution technique increases the sensitivity for bone evaluation[29].

Osteoarthritis

Secondary osteoarthritis (OA) is caused by altered bone structures and mechanical loading changes across the joints. Common affected sites are the hip, the knee and the spine including disk degeneration, facet joint OA and degenerative spondylolisthesis. Radiography is usually the first-line imaging modality but similarly to any other case of osteoarthritic changes, CT and especially MRI provide best evaluation of joint pathology. Particularly, MRI is indicated in cases where more detailed assessment of cartilage and internal joint structures is needed[22].

Fractures

Pagetic bone is an abnormally remodelled bone, biomechanically weaker, with reduced ability to withstand stress and thus more prone to fracture than normal bone. Bowing of long bones, insufficiency fractures, compression fractures of the vertebral bodies and fractures of pars interarticularis in spine (spondylolysis) resulting in olisthesis are recognized PDB complications.

CT is reserved for further clarification when radiographs, the first-line method for assessing a suspected fracture, are not sufficient or show equivocal findings[22]. In spine, CT may depict pagetic features in the affected vertebra and simultaneously evaluate for spondylolysis, the latter being difficult to appreciate on radiographs or MRI due to hypertrophy and sclerosis in adjacent bony structures. MRI is the appropriate imaging method to early identify the marrow edema caused by fractures[2] and can confirm the benign nature of a fracture excluding malignancy.

Tumor development

Pagetic bone may undergo malignant transformation and many cases of chondrosarcoma, osteosarcoma and giant cell tumor have been described[4,30-34]. However it is not clear if the reported cases of lymphoma and metastatic disease in pagetic bone are coincidental or related to PDB[35,36]. The risk of developing sarcoma in PBD ranges from <1% to >10% and increases with advancing age, longer duration and more extensive involvement of PBD[37].

When malignant transformation is a diagnostic concern, CT/MRI are required for further evaluation so as to prevent diagnostic errors. Radiographic signs of malignant degeneration are similar to non pagetic bone and include osteolysis, cortical destruction, periosteal reaction, soft tissue mass and pathological fracture. Sarcomas can be difficult to diagnose on radiographs due to bone changes from underlying PBD. The appearances on bone scan may also be variable limiting the method's utility. On contrary, malignant transformation is typically quite apparent on both CT and MRI. CT is an excellent tool to demonstrate both focal cortical destruction and neoplastic soft tissue mass, while MRI can easily identify the replacement of normal fatty marrow by tumor and visualize not only a soft tissue mass but also reactive and edematous swellings[17,19].

If a biopsy is indicated, percutaneous biopsy with CT/MRI guidance has been demonstrated to be safe, efficacious, cost-effective, with less morbidity than open biopsy. CT and particularly MRI help to direct the biopsy needle within the area of interest -away from necrotic or hemorrhagic regions- ensuring a reliable diagnosis[38].

In case of clinical suspicion and/or ominous standard radiographs, Mirra et al[14] based on the results of two MRI studies proposed a diagnostic "algorithm" regarding the use and planning of MRI/CT and biopsy in sarcoma detection.

As for any bone sarcoma, CT and MRI also enable accurate staging providing local and regional assessment (tumor size and extend, "skip" metastases, local node disease, neurovascular involvement). Whole-body scintigraphy and chest CT should be also performed for assessment of distant metastases[2].

According to Mirra et al[14] findings which would favor the diagnosis of combined metastatic and PBD include: (1) numerous, obvious blastic or lytic lesions in nonpagetically involved bones, i.e., those which do not reveal any of the cardinal signs of PD; and (2) the presence of two or more bones with soft tissue mass. However, oligo-ostotic, small- to moderate-sized metastatic deposits to pagetic bones are difficult, if not impossible, to distinguish from PBD alone.

Soft tissue complications

CT/MRI are also useful for the assessment of a soft tissue mass adjacent to pagetic bone. Extraskeletal hematopoiesis in the paraspinal region has the same MRI signal/density as the adjacent "intraosseous" marrow and there is usually a communication with the marrow space which confirms the

diagnosis[39]. Unmineralized pagetic periosteal new bone formation causing a "pseudosarcomatous lesion" is another rare entity. In all the cases reported, the mass was exophytic from the bone with normal fatty marrow signal in the medullary cavity[40-42]. This appearance, however, can be seen in periosteal osteosarcomas and biopsy is often warranted for histological confirmation[2,33,43].

Peripheral nerve entrapment such as this of the sciatic nerve between the deformed ischium and the lesser trochanter is another PBD soft tissue complication, best appreciated with MRI[22].

Limitations

Despite their advantages, CT/MRI have their own limitations in PBD imaging. They are more expensive and time consuming methods, with high radiation exposure regarding CT and limited availability speaking for MRI. Radiologists and involved physicians should be aware of the specific technical weaknesses, as well.

CT gives excellent detail of the cortical and trabecular bone. However, subtle reduction in cortical bone density and subtle loss of trabecular bone may not be readily appreciated in the lytic phase unless a high window level and relatively narrow window width are selected.

PBD can be also overlooked on MRI. PBD is a disease that primarily affects cortical and trabecular bone whereas MRI signal is mainly derived from the marrow. Cortis et al[10] emphasize that MRI alone may present a confusing picture, reflecting the natural course of the disease process in different phases, unless radiographs are available for comparison. When the signal on MRI in the affected bone is completely normal -no change in the intervening marrow at the microscopic level- the disease can be easily overlooked. Thus it is particularly important to be vigilant to the other subtle alterations in the involved bone including bone expansion and minor cortical thickening. Scan parameters may also influence the appearance of MR signal. In the sclerotic and delayed dormant phase the lack of signal from bone may make the hallmark features of PBD inconspicuous. Lalam et al[11] described that with a large voxel size and a large field of view, the affected sclerotic bone may appear rather homogeneously low in signal. However, with a smaller voxel size and a small field of view, it may be easier to identify the individual thickened trabecular structures and the intervening normal marrow as separate entities.

Apart from the modalities' weaknesses in the assessment of PBD, there are atypical cases very difficult to be diagnosed. For example, Spretcher et al[44] presented an unusual case of lytic PBD of the cervical spine. In active lytic phase the histologic characteristics account for the nonspecific highly variable MRI appearance that may resemble the findings in tumor or infection e.g. increased signal within the cortex or diffusely in the marrow space on fat-suppressed MR sequences[2]. In such a case the authors[45] suggested that a trial of bisphosphonate therapy might be indicated before resorting to an invasive diagnostic procedure.

In rare instances of PBD, there may be absence of bony expansion if there is little or no periosteal bone remodeling but there may be still trabecular bone changes including patchy sclerosis[45]. These focal areas of reduced signal intensity in the marrow on short and long TR/TE images correlate with areas of increased bone formation, just observed on plain radiograph or CT scan. A diagnostic challenge emerges in patients with known prostatic or breast carcinoma and the differential diagnosis from sclerotic metastases is especially difficult when the abnormality occurs in sites favored by metastases such as in vertebra and in pelvis. The signal features of MRI may not be helpful in this situation because the MR signal returned by sclerotic bone lesions would be low in all MRI sequences irrespectively of the cause of sclerosis. In these cases a biopsy may be necessary to establish the diagnosis.

Conclusion

Different imaging modalities have specific strengths and weaknesses in the assessment of PBD and its multifaceted manifestations. Familiarity with the typical PBD appearances in CT and MRI is important given the frequency with which pagetic disease is depicted by chance in these methods[4,5,11,22]. In typical cases, radiographs and bone scintigraphy remain the most inexpensive imaging modalities for characterization and evaluation of the extent and severity of PBD. CT and MRI are not routinely indicated but have a significant contribution to the diagnosis of less typical cases, to the differential diagnosis from sinister causes, to the delineation of PBD pathology in complex anatomic areas and to the accurate evaluation of the type and extent of certain complications. CT and MRI have complementary roles in the imaging workflow of PBD and despite their own limitations they can contribute substantially to the prevention of inappropriate investigation and to the management planning at an early stage.

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