

Primary Lymphoma of Bone: Imaging Findings to Improve Diagnosis of a Rarely Considered Disease Prior to Biopsy

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Abstract

Objective: Primary lymphoma of bone (PLB) is a rare malignant bone tumor often presenting in the fifth-sixth decades involving appendicular long bones. Published radiological findings indicate that PLB typically presents as a moth-eaten osteolytic lesion with periosteal reaction, while MRI commonly demonstrates marrow infiltration with extraosseous extension. Given rarity and variable appearances, PLB may not be primarily considered prior to biopsy. Our objective was to evaluate preoperative imaging findings in effort to increase awareness and improve a perceived deficiency in preoperative diagnosis. **Materials and Methods:** Following IRB approval, retrospective review identified 60 patients with newly diagnosed bone lesions proven to represent PLB in accordance with WHO definition. Preoperative radiographs (n = 46), MRI (n = 33) and PET (n = 37) were independently reviewed by two radiologists. At radiography, lesions were classified: purely lytic, mixed, purely sclerotic, or occult; lytic lesions were graded utilizing Lodwick's classification. At MRI, lesions were defined as focal or infiltrative and the presence or absence of extraosseous disease was recorded. Extraosseous masses were defined as small (<1 cm) or large (>1 cm) and subjectively correlated with degree of cortical destruction. At PET, lesions were recorded as FDG-avid or not. Primary radiograph reports when available (n = 33) were reviewed and exact wording of differential considerations was recorded. **Results:** Radiographs demonstrated mixed (n = 22), lytic (n = 15), and sclerotic (n = 8) appearances; one radiographically occult lesion was seen by MRI. Lytic lesions were graded: IB (n = 3), IC (n = 5), II (n = 4), and III (n = 3); none were IA. At MRI, 30 lesions were infiltrative and 3 were focal; 11 were not associated with extraosseous extension, while 22 showed bony disease with small (n = 7) or large (n = 15) soft tissue mass. Of large masses, 13 demonstrated minimal cortical destruction. At PET, 36 demonstrated FDG uptake; one study was technically limited. Review of reports found that only 5 included "lymphoma" as a

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diagnostic consideration. Conclusion: Contrary to most published data, we suggest that PLB typically demonstrates some degree of osteosclerosis, often a mixed pattern of sclerosis and lucency; purely lytic lesions may be less common. Similar to existing reports, MRI commonly demonstrates marrow infiltration with extraosseous extension of disease, typically a large soft tissue mass with disproportionate (minimal) cortical destruction. Familiarity with these findings should improve preoperative consideration of PLB in the appropriate clinical scenario when a new osteoblastic lesion is identified.

Keywords

Primary Lymphoma of Bone, Preoperative Diagnosis, Radiological Findings

1. Introduction

Primary lymphoma of bone (PLB) is an uncommon osseous neoplasm comprising less than 5% of primary bone neoplasms, much less common than other primary bone malignancies such as multiple myeloma, osteosarcoma, and chondrosarcoma [1]. Meanwhile, PLB accounts for less than 1% of malignant lymphomas [2]. Further, metastatic disease accounts for a far greater number of malignant bone tumors than primary bone cancers. In this context, PLB is a rare disease which may not be considered preoperatively in the evaluation of a newly identified bony lesion. However, when the differential diagnosis does include PLB, the approach to diagnostic biopsy, treatment planning, and prognosis differ significantly from other primary bone tumors; for example, prophylactic intramedullary rod fixation of an impending fracture may be considered in cases of PLB, but contraindicated in chondrosarcoma. For this reason, diagnostic radiologists, orthopedic oncologists, and medical oncologists would benefit from greater familiarity with the common imaging characteristics of PLB. In our opinion, PLB is less often considered preoperatively than other aggressive bone pathologies, though identification of certain imaging features may improve this area of perceived deficiency.

The 2013 World Health Organization (WHO) classification system of bone and soft tissue tumors defines primary lymphoma of bone as a neoplasm composed of malignant lymphoid cells, producing one or more masses within bone, without any supra-regional lymph node involvement or other distant sites of extra-nodal disease such as the lungs or solid abdominal viscera [3] [4]. Primary bony involvement with distant bone marrow involvement as the only other site of extra-nodal disease, which has been reported to have a similar prognosis to that of localized disease, may also be considered as PLB. Conversely, bone lesions with evidence of systemic disease or a primary soft tissue mass secondarily involving an adjacent bone are not considered primary lymphoma of bone [5] [6]. Several subtypes of primary lymphoma of bone exist with diffuse large B-cell lymphoma (DLBCL) being the most common histological subtype followed by follicular lymphoma (FL). Meanwhile, T-cell lymphoma is relatively uncommon and Hodgkin lymphoma of bone is extremely rare. The prognosis for most cases of PLB is excellent when treated with chemotherapy and/or radiation therapy, though T-cell lymphoma and systemic lymphoma with osseous involvement have a worse prognosis [4].

Primary lymphoma of bone may have a variable radiographic appearance from a purely radiolucent lytic lesion to a purely sclerotic osteoblastic lesion. As such, findings may overlap with numerous non-neoplastic etiologies and benign or malignant neoplasms. Most data suggests that PLB typically presents as an aggressive osteolytic lesion with a moth-eaten or permeative appearance and lamellated periosteal reaction [1] [7]-[9]. PLB is most common among patients in the fifth or sixth decades, often affecting the metadiaphysis of long bones of the appendicular skeleton such as the femur, tibia, and humerus; meanwhile, the pelvis and spine are not uncommon sites of disease [9]-[12]. Computed tomography (CT) better demonstrates the degree of cortical destruction including pathologic fracture, while magnetic resonance imaging (MRI) better demonstrates the degree of marrow involvement and an associated extraosseous soft tissue mass when present. PLB is typically avid at ^{18}F -fluorodeoxyglucose-positron emission tomography (PET) [13].

In addition to moth-eaten and permeative osteolysis, other radiographic appearances of PLB have been described including a mixed pattern of lucency and sclerosis [1] [7] [8]. When lesions appear purely lytic, Lodwick's widely accepted classification system of lytic lesions may be applied with PLB presenting as a geo-

graphic, well-defined lesion without marginal sclerosis (IB) or a geographic, ill-defined lytic lesion with a wide zone of transition (IC) [7]. PLB may be radiographically occult presenting with normal radiographs, identified by alternative imaging modalities such as MRI or PET. At MRI, primary lymphoma of bone typically appears as an infiltrative medullary, marrow-replacing lesion with an extraosseous soft tissue mass [1] [7] [14]. Of note, PLB has been reported to often present with a much larger soft tissue mass than may be expected given the degree of cortical bone destruction. In other words, the presence of a large soft tissue mass with minimal to no obvious cortical destruction may be typical of PLB [14]. It has been suggested that this pattern of disease results from tunneling of small round blue tumor cells through cortical bone or permeation of cells along vascular channels into the surrounding soft tissues rather than frank cortical disruption [7] [14].

With these ideas in mind, the objective of our study was to evaluate the frequency of radiographic and MRI findings in primary lymphoma of bone, adding to the limited descriptive data for this rare disease and highlighting more common findings at diagnostic imaging which may allow for improved preoperative diagnosis. We also present our findings from a review of diagnostic radiography reports illustrating a perceived deficiency in consideration of lymphoma when encountering a newly diagnosed bone lesion.

2. Materials and Methods

2.1. Patient Selection

Under the guidelines of the Scientific Research Committee and Institutional Review Board, a retrospective review of electronic medical records was performed to identify cases of primary lymphoma of bone treated at our institution between 1998 and 2013. Initially, a search of the histopathology database was performed using the keywords “lymphoma” and “bone” to identify 206 patients with bone lesions proven to represent osseous lymphoma following percutaneous or surgical biopsy. From this list, the Picture Archiving and Communication System (PACS) at our institution was searched to identify patients with available preoperative imaging examinations including any combination of diagnostic radiographs, MRI, and/or PET. Eighty-one patients did not have preoperative imaging available and were excluded leaving 125 patients. Of these, a review of the electronic medical record and imaging studies was performed to confirm a diagnosis of primary lymphoma of bone as defined by the World Health Organization (WHO) in 2013 [3]. Applying the WHO classification, 33 patients were excluded due to evidence of systemic disease seen as extra-regional lymphadenopathy, pulmonary, solid visceral organ, or CNS involvement. Additionally, 32 patients were excluded due to a previously known history of lymphoma. The remaining 60 patients represent our study population—patients with newly diagnosed bone lesions referred to our center with subsequently proven primary lymphoma of bone according to the 2013 WHO classification of soft tissue and bone tumors. Among the 60 study patients, most underwent more than one preoperative radiological study including 46 diagnostic radiographs, 33 MRIs, and 37 PET scans. Additionally, the primary original diagnostic radiography reports from either an outside facility or our institution were available and reviewed for 33 of 46 preoperative X-ray examinations (13 outside reports were not available with the radiographic images).

2.2. Evaluation of Radiological Images and Reports

Imaging examinations were reviewed independently by two board-certified diagnostic radiologists (JTC, 9 years of experience; TR, 5 years) with interest and expertise in imaging of musculoskeletal and soft tissue neoplasms. Preoperative imaging examinations were interpreted individually and predetermined descriptive terminology was applied and recorded for each lesion with consensus reached in all cases. When available, radiographs, cross-sectional imaging, and nuclear medicine studies were reviewed in conjunction to confirm all findings.

At diagnostic radiography, bone lesions were described as being: 1) purely lytic, 2) mixed sclerotic and lytic, 3) purely sclerotic, or 4) radiographically occult. Among purely lytic lesions, findings were further classified according to Lodwick’s classification system of lytic bone lesions. This system defines five appearances of lytic bone lesions: geographic and well defined with peripheral sclerosis (Lodwick IA lesion); geographic and well defined without peripheral sclerosis (IB); geographic but ill-defined (IC); moth-eaten (II); or permeative (III). When present, associated cortical thickening and periosteal reaction was noted.

At magnetic resonance imaging, sites of medullary involvement were described as “focal” or “infiltrative” and the presence or absence of extraosseous or epidural extension of disease was recorded. When present, the

extraosseous mass was recorded as small (<1 cm) or large (>1 cm), and the degree of cortical destruction was subjectively graded as “mild” or “severe”.

At ^{18}F -FDG positron emission tomography, sites of disease were noted to be positive when increased radio-tracer localization above background was seen.

The primary imaging reports of preoperative radiographs were also reviewed. The exact wording in the radiology reports pertaining to the most likely diagnosis or differential diagnostic considerations was recorded exactly as it appeared in the report.

3. Results

Of 60 patients in our study with newly diagnosed primary lymphoma of bone, patient age ranged from 17 - 89 years (mean = 56.5 years) including 28 females and 32 males. Subtypes of lymphoma included primary diffuse large B-cell lymphoma (n = 51), follicular lymphoma (4), primary anaplastic large cell lymphoma (3), and low grade B-cell lymphoma, not otherwise classified (2). Sites of disease included the femur (n = 16), spine (15), pelvis (11), humerus (10), tibia (7), and skull (1).

Preoperative radiographs of 46 patients with primary lymphoma of bone demonstrated a mixed sclerotic and lytic appearance (n = 22), a purely lytic appearance (15), and a purely sclerotic appearance (8), while one lesion was radiographically occult (**Table 1**). Purely lytic lesions were graded as Lodwick IB (n = 3), IC (5), II (4), and III (3); none were graded as Lodwick IA.

At MRI, sites of disease were described as focal (n = 3) or infiltrative (30). Three focal medullary lesions were not associated with an extraosseous soft tissue mass. Of infiltrative bone lesions, 8 involved the medullary canal only without extraosseous or epidural tumor, while 22 demonstrated extraosseous disease including 7 with small soft tissue masses such as epidural tumor infiltration measuring less than 1 cm in thickness and 15 with a large soft tissue mass ranging from 1 to 15 cm. Of these 15 with a large extraosseous mass, 13 demonstrated minimal cortical destruction despite the presence of a large soft tissue mass.

At PET, 36 of 37 cases demonstrated FDG uptake over background levels. One outside PET did not show increased uptake, though there were technical limitations of the study described in the imaging report.

Review of 33 primary preoperative radiography reports found that only 5 included “lymphoma” as a primary diagnostic consideration. Eleven reports suggested that findings were “most consistent with metastatic disease”, while 4 others listed metastatic disease, infection, and multiple myeloma as differential considerations. Seven cases reported that findings were most consistent with “malignancy”, “neoplastic process”, “neoplastic infiltration”, or an “aggressive lesion”. Other diagnostic considerations included “sarcoidosis” for a sclerotic lesion, “giant cell tumor or chondroblastoma” for an epiphyseal lesion, “Paget’s disease” for calvarial thickening and sclerosis, “trauma” for a sclerotic lesion with periosteal reaction, and “postoperative inflammatory changes”. In one case, no differential diagnosis was provided.

4. Discussion

As has been previously described and supported by our findings, primary lymphoma of bone may present with

Table 1. Summary of imaging findings of primary lymphoma of bone.

	Radiographic Findings (n = 46)	MRI Findings (n = 33)	PET Findings (n = 37)
Purely Lytic	15		
Purely Sclerotic	8		
Mixed Lytic/Sclerotic	22		
Radiographically Occult	1		
Focal Lesion		3	
Infiltrative Lesion		30	
Extra-Osseous Extension		22	
FDG Avid			36

variable radiographic findings posing a challenge to accurate preoperative diagnosis. Recognizing more common imaging characteristics of PLB should increase suspicion prior to intervention which is important as the approach to biopsy, treatment planning, and patient counseling will be significantly different for PLB than other primary bone malignancies such as osteosarcoma and chondrosarcoma. For example, flow cytometry would be included with fine needle aspirate and biopsy in cases of suspected lymphoma. As another example, intramedullary rod fixation may be considered for impending fracture in the setting of lymphoma, but contraindicated in sarcoma to avoid distant tumor seeding which could complicate complete surgical resection. Certainly, more common entities such as metastatic disease and osteomyelitis may initially be considered when an aggressive pattern of bone destruction is identified at diagnostic radiography. However, we suggest certain findings should increase the suspicion for PLB, which presently may be under considered preoperatively. Identification of these features should, in turn, direct an appropriate approach to diagnostic biopsy and patient management.

4.1. Radiographic Findings

Most reports of PLB describe an ill-defined moth-eaten or permeative osteolytic pattern of bone destruction. However, the majority of cases of PLB in our cohort demonstrated variable degrees of osteosclerosis (Figure 1 and Figure 2). As such, the presence of an osteoblastic or mixed bone lesion should raise question of primary lymphoma of bone in the appropriate clinical scenario. PLB most commonly occurs in the fifth or sixth decades

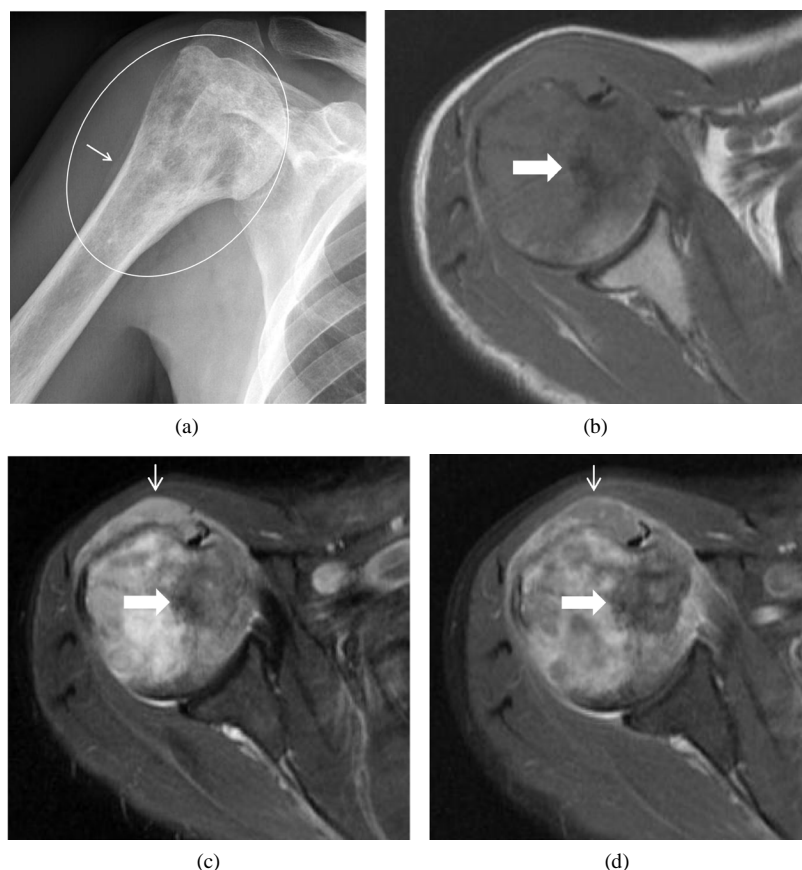


Figure 1. A 37-year-old male with diffuse large B-cell lymphoma of the proximal right humerus. (a) AP radiograph demonstrate an ill-defined mixed sclerotic and lytic lesion of the humeral head and neck (oval) with periosteal reaction (thin arrow); (b)-(d) Axial T1-weighted (b); short tau inversion recovery (c); and contrast-enhanced fat-suppressed T1-weighted (d) MR imaging demonstrates an infiltrative marrow replacing lesion of the proximal humerus with anterior extraosseous extension of disease (thin arrow); note patchy areas of low signal intensity on all pulse sequences correlating with sclerosis on radiograph (thick arrows).

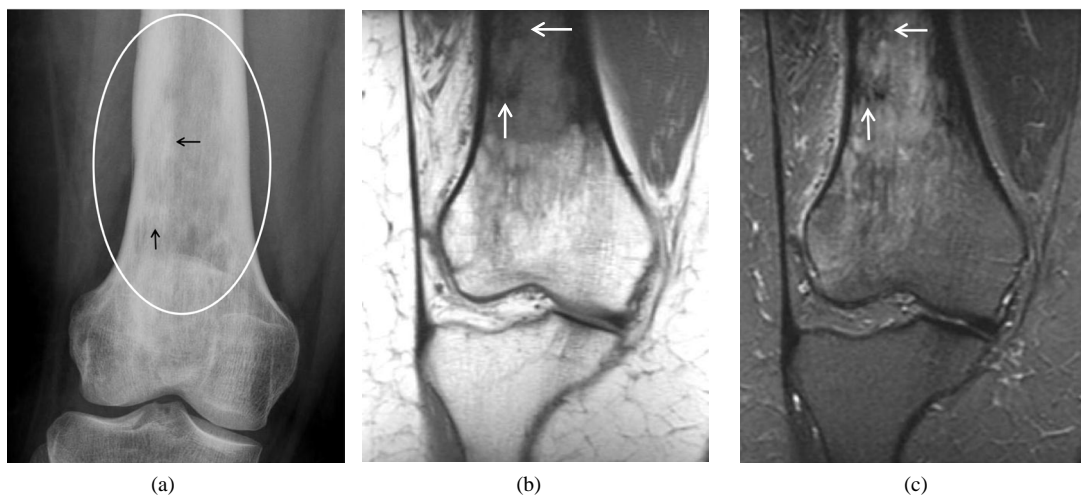


Figure 2. A 25-year-old female with diffuse large B-cell lymphoma of the distal femur. (a) AP radiograph demonstrates a mixed sclerotic and lytic lesion of the distal femur with cortical thickening and periosteal elevation (oval); (b) (c) Coronal T1-weighted (b) and short tau inversion recovery (c) MR imaging from outside knee MRI obtained for pain demonstrates a partially visualized infiltrative medullary lesion with patchy areas of low signal intensity correlating with sclerosis on radiograph (arrows point to corresponding areas of sclerosis on radiograph and MRI).

nearly equally effecting males and females. In accordance with WHO definitions, PLB may be considered in patients without a previously known history of lymphoma or evidence of systemic disease. The majority of lesions in our study (30/46; 65%) demonstrated variable degrees of sclerosis at diagnostic radiography—of these, 73% (22/30) demonstrated a mixed sclerotic and lytic appearance, while 27% (8/30) were purely sclerotic. Associated cortical thickening and irregular periosteal reaction were commonly associated findings. A purely lytic lesion without any appreciable sclerosis on radiographs was less frequently seen in our population. Differential diagnostic considerations for a sclerotic bone lesion may include osteoblastic metastasis, chronic osteomyelitis, and osteosarcoma. Primary malignancies with a propensity for osteoblastic metastases include prostate, breast, urothelial, and neuroendocrine cancers. In these cases, past medical history or imaging to detect unknown neoplasm may reveal primary malignancy. Patients with chronic osteomyelitis typically present with systemic signs of infection such as elevated erythrocyte sedimentation rate. While more common in children and young adults, osteosarcoma does have a bimodal distribution usually occurring in elderly patients with predisposing risk factors such as prior radiation therapy or Paget's disease. In the absence of primary malignancy or signs of systemic infection, PLB should be strongly considered in middle to advanced aged patients presenting with a new sclerotic bone lesion.

An entirely lytic radiographic appearance was less commonly seen in our patient population than has been reported in the existing literature. Contrary to most reports describing typical moth-eaten or permeative osteolysis, a minority of cases in our study presented as a purely lytic lesion (33%; 15/46). When a purely osteolytic lesion was identified, PLB did largely present with an aggressive pattern of bone destruction (Figure 3). In our study, 80% of purely lytic lesions (12/15) presented with ill-defined margins and a wide zone of transition graded as Lodwick IC, II or III. While the differential diagnosis for lytic lesions is much broader than for sclerotic lesions, several considerations warrant specific mentioning. Metastatic disease may be considered given patient age and significantly increased incidence compared with PLB. In pediatric patients, a moth-eaten pattern of disease is commonly seen in Ewing sarcoma, another small round blue cell tumor, though age should help differentiate. Conventional medullary chondrosarcoma typically presents as an ill-defined lytic lesion with cortical thickening occurring in a similar population to PLB, but chondroid matrix mineralization and lobulated endosteal scalloping should be apparent in cases of chondrosarcoma. While bony sequestra may be seen, tumor mineralization is not typical of PLB.

A very small percentage of cases in our study (7%; 3/46) presented as a geographic, well-defined lytic lesion without marginal sclerosis (Lodwick IB); none presented with peripheral sclerosis or were graded as IA. Depending on location and patient age, IB lesions have a broad differential diagnosis including metastatic disease,

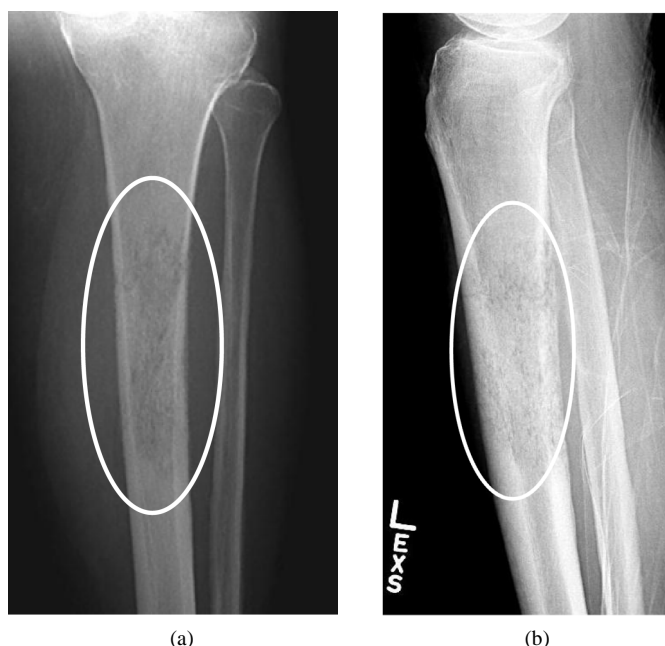


Figure 3. A 51-year-old female with diffuse large B-cell lymphoma of the tibial diaphysis. (a) AP and (b) lateral radiographs of the left tibia demonstrate a permeative osteolytic lesion of the proximal diaphysis (oval) with nondisplaced pathological cortical fracture; note lack of sclerosis in this example.

multiple myeloma, giant cell tumor, and Langerhans cell histiocytosis. In clinical practice, more common entities would be favored over PLB for a geographic, well-demarcated lytic lesion with a narrow zone of transition.

Finally, our study did include one radiographically occult lesion identified by MRI. Radiographically occult bone lesions identified at MRI, bone scan, or PET are considered highly suspicious lesions as tumor growth exceeds host bone osteoclastic activity in response to the underlying lesion resulting in normal appearing radiographs.

4.2. Magnetic Resonance Imaging Findings

In many cases, cross-sectional imaging is performed for further evaluation of a bone lesion. While CT better demonstrates cortical involvement, pathologic fracture, and matrix mineralization, MRI better demonstrate bone marrow involvement and soft tissue masses. At MRI, PLB often presents as an infiltrative marrow-replacing medullary lesion with hypointense T1-weighted signal, moderately hyperintense T2-w signal, and homogeneous intravenous gadolinium-chelate enhancement. An extraosseous soft tissue mass is often present. Lymphomatous masses tend to be more homogeneous without significant necrosis or internal hemorrhage than seen in other malignant neoplasms. Lymphoma often demonstrates intermediate T2-w signal intensity and low to moderate contrast enhancement compared with other malignancies which typically show markedly increased T2-w signal and avid IV contrast enhancement with internal necrosis [15].

In our study, 91% (30/33) demonstrated ill-defined bone marrow infiltration at MRI, while 3 small lesions were described as focal. Of infiltrative lesions, 73% (22/30) demonstrated an associated extraosseous mass, while 27% (8/30) did not. Of these with extraosseous extension of disease, 7 were recorded as “small” with <1 cm of extraosseous or epidural tumor infiltration and 15 were classified as “large” with soft tissue masses >1 cm. Among these 15 tumors with a large associated extraosseous soft tissue mass, 13 demonstrated only minimal to no obvious cortical destruction (**Figure 4**). Two others presented with pathological fractures.

Our findings at MRI are concordant with previously published descriptions of PLB [7] [9] [14]. In PLB, the size of an extraosseous soft tissue mass is typically disproportionate with the degree of cortical destruction. In other words, PLB often presents with a large extraosseous soft tissue mass, but only minimal cortical destruction. This is thought to result from tunneling or permeation of tumor cells from the medullary canal through the cor-

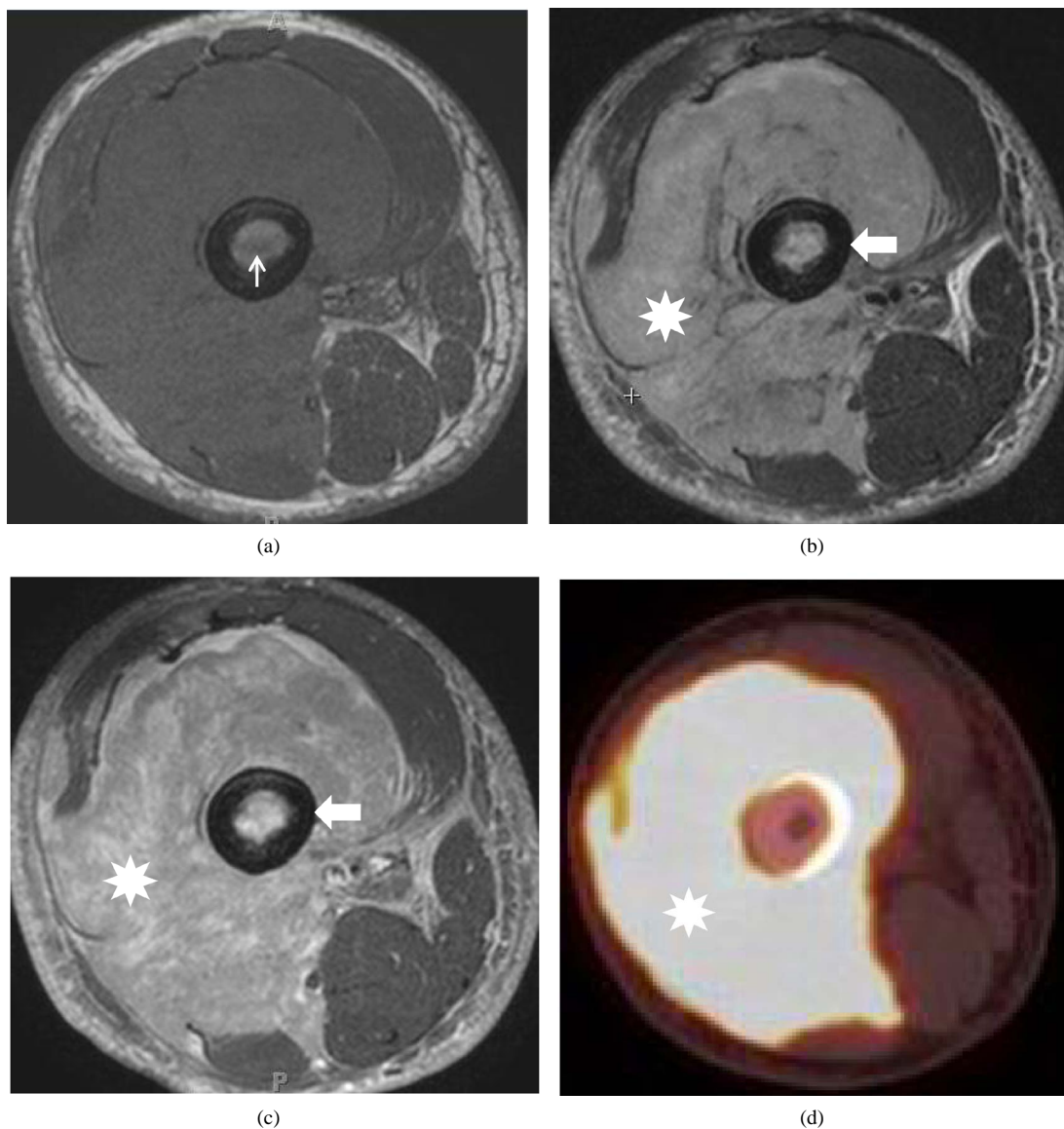


Figure 4. A 20-year-old male with diffuse large B-cell lymphoma of the right femur. (a)-(d) Axial T1-weighted (a), fat-suppressed T2-weighted (b); contrast-enhanced fat-suppressed T1-weighted (c) MR imaging, and fused PET/ CT (d) image demonstrate infiltrative marrow replacing lesion (thin arrow) with a large FDG-avid extraosseous soft tissue mass (star) and cortical thickening, but minimal cortical signal abnormality or cortical destruction (thick arrow).

tex or along penetrating vessels rather than frank cortical destruction more common in other tumors such as chondrosarcoma and metastatic disease. The finding of minimal cortical destruction in the presence of a large soft tissue mass was seen in 87% (13/15) of our patients with this pattern of disease.

4.3. Imaging Reports

Our review of 33 available original preoperative radiograph reports supports our hypothesis that PLB is not a primary diagnostic consideration in most cases of a newly diagnosed bone lesion. Only 15% (5/33) of reviewed X-ray reports included the specific words “lymphoma” or “myeloproliferative disorder” in the report itself. While more than half (55%) did suggest malignancy or metastatic disease, the provided differential diagnoses in this small sample of cases was broad including both non-neoplastic etiologies and benign neoplasms. As mentioned above, the approach to patient counseling, diagnostic biopsy, and treatment planning differ greatly among

these entities—even when concern for malignancy is raised. With improved awareness of common imaging characteristics of PLB, more specific and accurate preoperative differential considerations would hopefully be possible.

5. Conclusion

Our study supports previously published data that primary lymphoma of bone may have a variable appearance on plain radiographs with a more predictable appearance on MRI and PET. However, findings lack specificity and PLB may often be misdiagnosed preoperatively as a nonspecific malignancy or metastatic disease. While most bone metastases and multiple myeloma are lytic in appearance, the presence of osteosclerosis on radiographs should increase suspicion of PLB, particularly in older patients with appendicular lesions. MRI may provide the most specific imaging findings including an infiltrative medullary lesion with a large associated extra-osseous soft tissue mass and minimal cortical destruction. Currently, we believe primary lymphoma of bone is under considered prior to biopsy in part due to rarity of the disease and greater prevalence of other aggressive bone lesions. To this point, we submit that radiologists and clinicians should consider lymphoma when encountering an ill-defined sclerotic or mixed sclerotic/lytic aggressive-appearing bone lesion, even if only to dismiss it in light of other clinical information. Primary lymphoma of bone remains a rare entity, but failure to raise the possibility may impact preoperative approach to diagnosis.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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