Imaging of Primary Musculoskeletal Lymphoma: Diagnostic pearls and potential pitfalls

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Learning objectives

To provide a review of imaging findings in Primary Musculoskeletal Lymphoma, emphasizing on imaging clues that may promote a more specific diagnosis.
Background

Introduction

Primary bone lymphoma (PBL) is an uncommon malignant neoplasm, usually manifesting as a solitary bone lesion. PBL mainly involves extranodal non-Hodgkin's lymphoma (NHL), with B-cell subtype being the most common. On the contrary, Hodgkin’s PBL is strikingly rare and patients may have concurrent nodal disease detected at staging. Multifocal subtype of the disease is infrequent. Primary muscular lymphoma (PML) is also uncustomary.

Clinical features

PBL/PML manifest with non-specific symptoms, usually subtle intermittent pain. Other symptoms include soft-tissue edema, palpable mass, and rarely "B-symptoms" (almost exclusively seen in stage IV). Patients may also present with a pathological fracture or hypercalcemic crisis. Neurological disorders (radical symptoms, spinal cord compression) may be the presenting symptoms in case of vertebral involvement.

Etiology

Etiology remains unidentified, although relation to immunological and DNA disorders, virus infections, Paget's disease and traumas, has been reported.

Demographics

The majority of patients are >45 years old, with a peak prevalence in the sixth and seventh decades. The disease rarely presents under the age of 10 years. The male population demonstrates a slightly higher predilection.

Location
While any part of the skeleton may be involved in the disease, PBL usually affects the appendicular skeleton, customarily the femur (involving approximately 50% of the cases) and the pelvis (affected in a percentage of about 20%). Multifocal subtype may incorporate both axial and appendicular lesions, usually in the distal femur, proximal tibia and spine. Conversely, secondary osseous lymphoma shows a preference for the axial skeleton (spine, skull, ribs and facial bones).

PML is more common in the thigh and upper arm, presenting as a focal mass or diffuse muscular infiltration.

It should be mentioned that PBL is one of few entities where lesions may involve adjacent bones by invading joint or vertebral spaces. Infection, chordoma, chondrosarcoma and metastases are also included in the differential diagnosis list.

**Imaging**

On suspicion of PBL/PML, imaging investigation includes X-rays, CT, PET-imaging, scintigraphy and MRI. Plain radiograph remains the initial study for osseous lesions whereas MRI provides excellent depiction of bone-marrow replacement, soft-tissue mass and cortical erosion. PET-CT is currently used for staging and follow-up.

**PBL:**

- The results of **plain radiographs** are usually normal at the time of presentation. Krishnan et al. [14] presented the following classification of radiographic patterns: i) The lytic-destructive (permeative or moth-eaten) pattern, ii) The blastic-sclerotic pattern (rare) with/without areas of mixed sclerotic-lytic appearance, iii) Subtle or "near-normal" findings.

In case of locally aggressive disease, x-rays might demonstrate a localized lytic lesion near the end of a long bone, with a permeative appearance and associated periosteal reaction. These findings are similar to that of Ewing's sarcoma, osteosarcoma and metastatic bone lesions, which should be considered in the diagnostic process.

- **CT** is excellent in delineating cortical erosion, although imaging features are usually non-specific. It is also useful for post-treatment follow-up, demonstrating bone remodeling with an appearance similar to Paget's disease of the bone.
• PBL shows a hypermetabolic behavior on FDG-PET. PET-CT is sensitive for evaluating response to therapy, particularly in determining a complete response.

• MRI depicts PBL marrow involvement as low intensity on T1-WI and high intensity on T2-WI, while low intensity areas within the tumor on T2-WI correspond to fibrosis. Peritumoral edema and reactive marrow changes are also depicted as bright on T2-WI. STIR images further help delineate the normal from abnormal marrow. Contrast-enhanced MRI demonstrates areas with variable patterns of enhancement (homogeneous, heterogeneous, focal, diffuse). MRI allows earlier detection of cortical destruction, compared to CT and it is also useful for the assessment of extra-osseous soft tissue.

• Bone scintigraphy with 99mTc-methylene diphosphonate is a valuable study in PBL staging, detecting multifocal involvement, which may alter the therapeutic plan and disease prognosis.

The presence of a solitary bone lesion with a permeative/moth-eaten appearance and associated layered periosteal reaction on x-rays, and an extra-osseous soft-tissue mass on MRI, particularly in a patient older than 30 years, is highly indicative of PBL lesion.

PML:

• Ultrasonography shows non-specific findings, usually a heterogeneously hypoechoic solid mass with irregular or ill-defined borders.

• CT reveals a lesion isodense or slightly hypodense comparing to normal muscle and varying contrast enhancement.

• FDG-PET is used for assessment of post-treatment response, due to its ability to distinguish between viable tumour and necrosis/fibrosis in residual masses.

• On MRI, the tumour appears as a discrete mass or abnormal signal intensity within the muscle. It is depicted as isointense or slightly hyperintense to normal muscle on T1-WI, while on T2-WI it demonstrates intermediate signal intensity between muscle and fat. On contrast MRI the lesions show diffuse homogeneous, predominately peripheral (ring-like), enhancement or marginal septal enhancement, with/without irregular enhancement of deep and/or superficial muscular fascia. Imaging characteristics highly suggestive of lymphoma, when present, include: orientation of the tumour along muscle fascicles, involvement of more than one muscle compartment with traversing vessels within involved muscles, extension along the neurovascular bundle and adjacent subcutaneous stranding with/without skin thickening. Decrease
in size, T2 signal intensity and contrast enhancement are indicative findings of response on post-treatment MRI.

**Staging**

According to the Ann Arbor system [5], PBL is divided into the following four stages, determined by histology:

- **Stage I:** Single bone lesion with or without soft tissue infiltration.
- **Stage II:** More than two lesions beside one side of the diaphragm, or a single bone lesion with soft-tissue infiltration.
- **Stage III:** Lesions beside two sides of the diaphragm.
- **Stage IV:** Infiltration of the central or peripheral nervous system, or bone marrow.

**Differential diagnosis**

- **Lytic-destructive pattern:** Differential diagnosis is varied, including infection, eosinophilic granuloma, metastasis and Ewing’s sarcoma. In case of well-defined lytic lesions, the appearance may mimic multiple myeloma. Presence of bone sequestrum should incorporate osteomyelitis, bony tuberculosis, radiation necrosis and eosinophilic granuloma in the differential diagnosis list.
- **Blastic-sclerotic pattern:** Purely sclerotic lesions are mostly described with Hodgkin disease, although it may also demonstrate a lytic radiological appearance. Differential diagnosis includes post-therapeutic sclerosis of lytic lesions, osteoblastic metastases, Paget’s disease of the bone, osteosarcoma and osseous lymphoma.

Osteosarcoma, Ewing’s sarcoma and osteomyelitis should be considered in the differential diagnosis list of the younger population, whereas the main differential diagnosis in older patients is bone metastasis of solid-organ tumors.

**Treatment - Prognosis**
Therapy is multifaceted, incorporating surgery, radiotherapy, chemotherapy and rituximab. Nowadays, the role of surgery is usually limited to the diagnostic biopsies and the management of pathological fractures.

PBL/PML have an improved prognosis compared with other bone malignancies, such as osteosarcoma or secondary involvement of the bone with lymphoma. A younger age has been identified as an independent survival predictor. Disease stage has a significant effect on five-year survival. Multifocal PBL has a poorer prognosis than localized PBL tumor. Periosteal reaction, presenting either diffuse or as lamellated onion peel, is an indicator of poor prognosis.
Imaging findings OR Procedure Details

Imaging studies of 14 patients with suspected musculoskeletal lymphoma were retrospectively reviewed. Two patients presented with palpable mass (PML cases, Fig. 11, 13-14), whereas pain was the major symptom in the rest (PBL patients).

PBL was located in the extremities in 5 patients (Fig. 1-2,3-4,7), the pelvis in 2 patients (Fig. 9-10,12) and the spine in 3 patients (Fig. 5,6,8). Two patients presented with multifocal PBL (Fig. 6,8). Associated soft-tissue mass was depicted in four PBL cases (Fig. 8).

X-rays showed a permeative pattern in long bone lesions with variable degrees of bone erosion (ranging from "near normal" to extensive) and periosteal reaction (Fig. 1,3-4).

CT better demonstrated soft-tissue extension and cortical involvement, a finding often elusive on X-ray (Fig. 1,3,9).

MRI showed extensive bone-marrow involvement in all cases, with/without soft-tissue mass or cortical disruption. Differential diagnosis included osteosarcoma, Ewing's sarcoma, osteomyelitis and non-specific bone-marrow edema (younger population, Fig. 2,3,13), and solid-tumor metastases (older patients, Fig. 11,12).

MRI/DCE-MRI and PET-CT were used in the follow-up evaluation. Scintigraphy was available in two cases (Fig. 1,3).

Biopsy revealed primary bone NHL in all but one patients, who was diagnosed with primary Hodgkin's lymphoma of the bone (Fig. 9,10).

Follow-up imaging with CT and MRI mediated the evaluation of response to treatment and in some cases designated alterations of therapy (Fig. 7,8,9-10,14).

Emphasis was put in the differential diagnosis of lymphomatous musculoskeletal lesions, from both benign entities, such as seronegative spondyloarthritis (Fig 5) and Paget disease of the bone (Fig. 12), as well as from other osseous malignancies or metastatic disease.
Fig. 1: 21-year-old female presented with chronic intermittent pain in the right humerus, lasting over a year. Initial x-ray (a) showed no specific findings. As the pain increased, plain radiograph after two months (b) demonstrated a subtle lytic lesion in the proximal diaphysis of the humerus, with associated cortical erosion and lamellated periosteal reaction (outline), as well as pathological fracture of the humeral neck (arrow). Findings were confirmed with corresponding scintigraphy (c) and CT imaging (d,e). Note that CT better delineates the cortical and periosteal abnormalities (arrows, e). Differential diagnosis included eosinophilic granuloma, bone lymphoma, osteosarcoma and Ewing's sarcoma (see also Fig. 2).
Fig. 2: Same patient as in Fig. 1: In the differential diagnostic process, further investigation with MRI depicted, besides the fracture, bone-marrow heterogeneity, with the humeral lesion appearing hypointense on T1-WI (a), with associated periosteal reaction (outline), while STIR image (b) demonstrated abnormal increased bone-marrow signal with prominent high-intensity peritumoral edema (asterisk). Results of CT-guided biopsy (c) revealed primary non-Hodgkin B-cell lymphoblastic lymphoma of the bone. Treatment included combined chemoradiotherapy and surgery with intramedullary nailing of the fracture (d).
Fig. 3: 39-year-old patient suffering from increasing pain in the left knee, with no history of trauma: Initial x-ray (a) demonstrated a radiopaque lesion at the distal metadiaphyseal region of the left femur (asterisk), with associated periosteal reaction (arrow). Corresponding bone scintigraphy (b) showed two adjacent lesions with increased uptake in the area (arrow), while CT (c) better depicted two lytic lesions (asterisks), one within the medial epicondyle and another at the distal diaphysis with eminent cortical disruption, extraosseous expansion and multilayered periosteal reaction (arrow). MRI depicts the lesions as homogeneously hypointense on T1-WI (asterisks, d) and homogeneously hyperintense on STIR (asterisks, e), showing intense enhancement on contrast-enhanced T1-WI (asterisks, f). Differential diagnosis included metastatic carcinoma, bone lymphoma, osteosarcoma and osteomyelitis. Histopathology revealed
primary NHL of the bone. Combined chemoradiotherapy was the initial therapeutic plan (see also Fig. 4).

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Fig. 4: Same patient as in Fig. 3: Follow-up radiographs 6 months after therapy (a,b) reveal decrease in size of both the intraosseous and extraosseous part of the tumour (asterisks), while the periosteal reaction remains (arrows). MRI confirms the size reduction of the lesion, which is depicted inhomogeneous with sparse areas of low signal intensity on T1-WI (asterisk, c), yet still significant heterogeneous bone-marrow contrast enhancement is present, in both the medial and distal diaphysis, as depicted on contrast-enhanced T1-WI (outlines, d). Periosteal reaction is also pointed with arrows on c and d.

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**Fig. 5:** PBL, sagittal STIR images at different levels (a,b,c): High signal foci in the vertebral bone-marrow (red arrows/outlines). High signal of bone-marrow in the anterior and posterior corner of a vertebra (red outlines) mimics seronegative spondyloarthritis. In this case, biopsy revealed primary NHL of the bone.

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Fig. 6: Multifocal PBL: Multiple lesions of high signal intensity on STIR (a,b) and T2-W (c,d) images, in the femur (a), iliac bone (b), sacrum (c) and thoracic spine (d).

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Fig. 7: 61-year-old female with primary B lymphoblastic lymphoma of the left femur, treated with chemotherapy regimen: Follow-up MRI after 4 cycles of therapy (a,b,c) reveals a large area of bone-marrow signal abnormality. The abnormal area is mostly surrounded by geographic fatty margins implying fatty conversion. The most proximal part of the lesion appears hypointense on T1-WI (a) and hyperintense on STIR image (b), without any contrast uptake on contrast-enhanced T1-WI (c), implying necrosis. All findings above were suggestive of tumor response to treatment. Patient received combined chemoradiotherapy and underwent MRI study 10 months later (d,e,f): There is significant increase of abnormal signal in the medullary cavity of the left femur extending in a large area, depicted as inhomogeneously hypointense on T1-WI (d) and hyperintense on STIR (e), demonstrating increased enhancement on contrast-enhanced T1-WI. Signs of fatty conversion or central necrosis are not evident on the current MR study. Notice
the presence of periosteal reaction, with no cortical breech or soft tissue mass (outlines, e/f). Findings were indicative of local relapse.

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**Fig. 8:** 51-year-old female with intermittent lower back pain: Initial MRI (a,b,c) revealed signal abnormality of the L5 vertebral body, demonstrated low signal on T1-WI (outline, a), heterogeneously mottled decreased signal on T2-WI (outline, b) and inhomogeneous increased signal on STIR image (outline, c). There is deformation of the vertebral body with effacement of the anterior surface and the adjacent L5-S1 intervertebral space, and associated soft-tissue mass posteriorly, exerting pressure on the ventral surface of the thecal sac. Biopsy revealed PBL, of NHL type. Follow-up MRI 3 months later (d,e,f), while on chemoradiotherapy, depicts increase in the size of the extraosseous soft-tissue mass imparting greater pressure on the thecal sac (annotation, d). This is an indication of no response. Note the diffusely increased signal intensity of the neighboring L4 and S1 vertebral bodies on STIR image (f), most likely attributed to radiation-induced marrow changes. Coronal T1-WI (g) depicts focal low-signal lesions within the sacrum and the right ilium (arrows), which were found to be foci of lymphomatous infiltration as well. This was a case of multifocal PBL.

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**Fig. 9:** 33-year-old female with subtle intermittent pain at the left side of the pelvis. Initial CT (a) depicted an inhomogeneous lytic lesion of the left iliac crest, with associated moderate endosteal scalloping and cortical thinning (oval outline). Bone malignancy was suspected and patient underwent CT-guided transcutaneous biopsy (rectangular outline, b), which revealed primary Hodgkin's lymphoma of the bone. Patient was subjected to chemoradiotherapy. Follow-up CT imaging three months after diagnosis (c) shows mixed lytic/sclerotic appearance of the tumour, with increase in its size, as well as cortical disruption at the lateral aspect of the crest (oval outline). This was a case of no response, so therapeutic plan was altered. CT imaging 4 months later (d), demonstrated a less sclerotic appearance of the lesion with restoration of the cortical breach (oval outline), implying response to treatment (see also Fig. 10).

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Fig. 10: Same patient as in Fig. 9 (PBL, Hodgkin subtype): Follow-up MRI 6 months after therapy alteration depicts decrease in tumour size as seen in T1-WI (a) and STIR images (b), with no extension to adjacent muscles (outlines). A small linear area of increased signal on STIR image (b) is probably due to red marrow reconversion. Note the diffuse low bone-marrow signal intensity in the pelvis on T1-WI (a), owing to therapy-induced stimulation of red bone-marrow. There is no significant enhancement on dynamic sequences (outlines, c/d). The imaging findings above are signs of good response to treatment.

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Fig. 11: 84-year-old female presented with fever and subtle abdominal pain. CT imaging revealed a well-defined lobulated soft-tissue mass within the right iliac fossa, extending caudally through the inguinal canal to level of the acetabulum (oval outlines, a), with encasement of the femoral vessels, inducing thrombosis of the common femoral vein (arrow). Differential diagnosis included metastatic disease and primary/secondary lymphomatous mass. Follow-up axial CT image at a lower level (b) demonstrated a new lesion of similar characteristics in the subcutaneous tissue of the ipsilateral femur (oval outline). Coronal CT images of the lower limb (c) depicted associated soft-tissue muscular masses within the medial compartment of the femur (arrow) and bone-marrow hyperdensity of the distal femoral bone (rectangular outline), suggestive of infiltration. On the contrary, there is recession of the iliac fossa lesion, as depicted in image (d). This was a case of primary NHL muscular lymphoma.

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Fig. 12: 40-year-old male presented with subtle pelvic pain and "B-symptoms". Initial work-up with CT (a) demonstrated bone abnormalities in body of the right ilium and adjacent part of the sacrum, with diffuse mixed sclerotic-lytic pattern (oval outline). Less profound findings could be seen on the left side of the sacrum. There was no body expansion and no evidence of sacroiliac joint deformity. Further imaging with MRI (b,c) depicted a diffusely low signal on T1-WI (b) in the right iliac body and the sacrum, more prominent on the right side (asterisks), while on T2-WI (c) the corresponding areas appeared inhomogeneous with multiple foci of increased signal. Differential diagnosis mainly included metastases (especially from prostatic/testicular carcinoma), osseous lymphoma and Paget disease of the bone. Despite the demographics, there was no bony enlargement and no markers suggestive of Paget's disease. Since the blastic-sclerotic pattern is the less common type of bone lymphoma, biopsy was conducted to determine the disease. Histopathological results showed DL-BCL of the bone and patient was subjected to combined chemoradiotherapy. Follow-up CT imaging 6 months later (d), portrayed intensification of the cortical sclerosis and the sclerotic areas within the lesions, more prominent in the posterior part of the ilium (oval outline), possibly owing to radiation treatment. MRI depicted the affected regions as diffusely inhomogeneous on both T1-WI (e) and T2-WI (f), showing excessive areas of high signal, more pronounced on the left part of the sacrum (arrows) compared to the initial study, an indication of post-treatment fatty bone-marrow conversion.

Fig. 13: 19-year-old male with palpable gluteal mass. CT imaging (a,b) revealed a space-consuming mass arising in the right piriformis muscle (asterisks, a) and extending both into the perineum, effacing the obturator internus and levator ani (mostly the puborectalis) ipsilaterally, and externally to the gluteus medius and gluteus maximus (asterisks, b). The mass appeared inhomogeneous, showing areas of enhancement, especially in the gluteal area. CT also depicted rectum displacement with rectal wall thickening (arrow, a), suggesting infiltration, as well as subcutaneous fat stranding in
the right gluteal area (arrow, b). There was no associated bony lesion. Findings were indicative of soft-tissue malignancy, most likely sarcoma, due to the invasive character of the mass. Further imaging with MRI (c,d,e), depicted the lesion as inhomogeneous, slightly hyperintense to normal muscle on T1-WI (asterisk, c) and isointense to muscle on T2-WI (asterisk, d), showing heterogeneous, mostly marginal-septal enhancement, especially in the most medial part, on contrast-enhanced T1-WI (arrow, e). Involvement of more than one muscle compartments and extension along the neurovascular bundle with adjacent subcutaneous fat stranding, were imaging characteristics more indicative of muscle lymphoma, rather than sarcoma, as confirmed with biopsy (see also Fig. 14).

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Fig. 14: Same patient as in Fig. 13: Post-treatment follow-up MRI demonstrated prominent decrease in tumour size, particularly in the gluteal area, as seen on axial T1-WI (arrow, a) and STIR image (arrow, b). STIR image depicts a remaining small linear high-signal area within the right obturator internus muscle. Sagittal STIR image (c) further demonstrates normal wall thickness of the colon. Contrast-enhanced T1-WI (d) shows peripheral enhancement at the medial part of the obturator internus and the gluteus maximus, as well as enhancement of the perirectal fat tissue (oval outline), with no evidence of rectal wall infiltration. Findings were suggestive of response to therapy.

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Conclusion

PBL/PML are malignant neoplasms with varied radiographic appearance, often non-specific. A high index of suspicion is required to minimize delayed diagnosis and misdiagnosis.

Osseous lymphoma might appear normal or demonstrate subtle findings on radiographs but may have a sonorous appearance on other studies. Further imaging is necessary to unmask underlying marrow disease. MRI remains the key imaging technique, both in the diagnostic and differential-diagnostic procedure. We should always consider lymphoma when encountering a poorly-defined sclerotic or mixed sclerotic/lytic bone lesion, demonstrating locally aggressive behavior.

Imaging also plays an important role in assessing response to treatment and planning further therapeutic management in both PBL and PML.

As primary musculoskeletal lymphoma remains a rare entity, though highly curable, it is important to be differentiated from other causes of lytic or sclerotic bone lesions, such as other primary bone tumors, metastases and infectious disease.
References


