PICTORIAL ESSAY Musculoskeletal Imaging

Clinical and imaging features of primary bone lymphoma: a pictorial essay

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ABSTRACT

Primary bone lymphoma (PBL) is rare and histologically in most of the cases is non-Hodgkin. Imaging plays a crucial role in early detection, Staging and assessing response to treatment. This pictorial essay presents epidemiological, clinical and imaging features of PBL. Conventional radiographs can appear normal, even in the presence of a large tumour. CT is used primarily for image-guided biopsy. MR imaging is the method of choice for early detection. Positron emission tomography is useful for Staging and reStaging after treatment.

KEY WORDS
Lymphoma/primary bone; MR imaging/diagnosis; Diagnostic Imaging/methods; Bone neoplasms/diagnosis

Introduction

Primary bone lymphoma (PBL) is a malignant lymphoid neoplasm arising from the bone marrow. Non-Hodgkin Lymphoma (NHL) constitutes the majority of PBL cases and includes a variety of histologic types, such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, marginal zone lymphoma, peripheral T-cell lymphoma, small lymphocytic lymphoma, Burkitt lymphoma, lymphoblastic lymphoma, and anaplastic large cell lymphoma [1-3]. DLBCL accounts for the vast majority

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of cases ranging from 68% to 80% worldwide [4-7]. Currently, only cases with a clear osseous origin should be considered as PBL, either with a single osseous lesion, with or without involvement of regional lymph nodes, or with multiple osseous lesions, without nodal or visceral disease [8, 9]. The latter subgroup is usually called multifocal (more than one lesion in the same bone) or polyostotic (lesions in more than one bone) disease, and it remains unclear whether it should be classified as PBL or as stage IV systemic lymphoma. This definition of PBL excludes lymphomas that have disseminated from lymph nodes or extranodal sites to the skeleton. PBL has been considered to show the best prognosis of all primary osseous malignancies [10]. In contrast to adults, PBL in children is regarded as a systemic clinical entity that is distinct from its adult form, with different evolution and prognosis, higher incidence of micrometastasis, and a propensity for spread to the central nervous system [11, 12]. The present pictorial essay summarises current epidemiological and clinical PBL features and emphasises its manifestations on imaging.

Discussion

Classification and incidence

The Ann-Arbor classification is used for Staging of PBL. A solitary osseous lesion corresponds to Stage IE. Stage IIE occurs when a solitary bone lesion with regional nodes is diagnosed. By definition, stage III disease is excluded from the characterisation of PBL due to distal nodal involvement **(Table 1)**. Multifocal bone disease is classified as Stage IV, which has been shown to have a similar prognosis to PBL with localised disease [5, 6, 13]. Most patients present with limited stage disease (stages I and IIE) [14, 15]. However, with increasing use of fluorine-18 fluorodeoxyglycose positron emission tomography/computed tomography (18F-FDG PET/CT), a higher proportion of patients is diagnosed with stage IV disease [5, 16]. Some reports have included only patients with Ann Arbor stage I-II disease, whereas others have included patients with stage IV disease.

Due to complex definition, the exact incidence of PBL is difficult to accurately estimate. Nevertheless, it is considered a rare malignancy, comprising <5% of extranodal lymphomas, <1% of all NHLs, and <7% of all malignant osseous tumours [8, 9, 17]. Most reports suggest almost equal distribution between sexes with a slight male predominance, with a median age at diagnosis between 45 and 60 years old and wide age range (15–99 years) [7, 9, 10, 14, 15].

Location

The most commonly affected site is the femur, which accounts for almost 30% of cases, with tumour cell infiltration along the shaft of the bone longitudinally. Long bones cumulatively (femur, humerus and tibia) account for more than half of cases, especially in patients with unifocal disease, with the pelvis and spine being the affected sites in almost 20% of patients [5, 15, 17-20]. In several recent case series (sample size ranging from 19 to 116 patients), the spine accounted for the majority (ranging from 25% to 50%) of lesions followed by the pelvis and femur, probably because of inclusion of patients with multifocal disease [7, 21-23]. The largest series in literature (1500 patients) showed an association between younger age and appendicular disease location, probably due to the presence of active bone marrow in long bones in younger patients [6].

Clinical findings

Pain at a specific anatomic site in the appendicular or axial skeleton appears to be the main reason for patients to seek medical advice. Other presenting features include a palpable mass in almost half the patients, pathologic fractures, a combination of the above features or even cord compression symptomatology in case of spinal involvement [5, 7, 14, 17, 24, 25]. A minority of patients (1-30%) can demonstrate “B” symptoms (fever, weight loss and night sweats) [5, 10, 15]. Elevated serum levels of lactate dehydrogenase (LDH) are detected in up to 45% of patients [5, 15]. The reported average time between the onset of symptoms and diagnosis ranges from 5 to 8.5 months, but it seems that it has no remote influence on the prognosis [25, 26]. Pathological fractures of long bones affected by PBL are reported in up to 28% of patients [6, 14, 20].

Imaging

Although bone biopsy is mandatory for the establishment of PBL diagnosis, imaging plays a significant role in initial depiction, guiding biopsy, Staging and determining the extent of the lesion, reStaging and monitoring the therapeutic effect.

Radiographic manifestation of PBL covers a wide spectrum of non-specific findings and as a rule under-

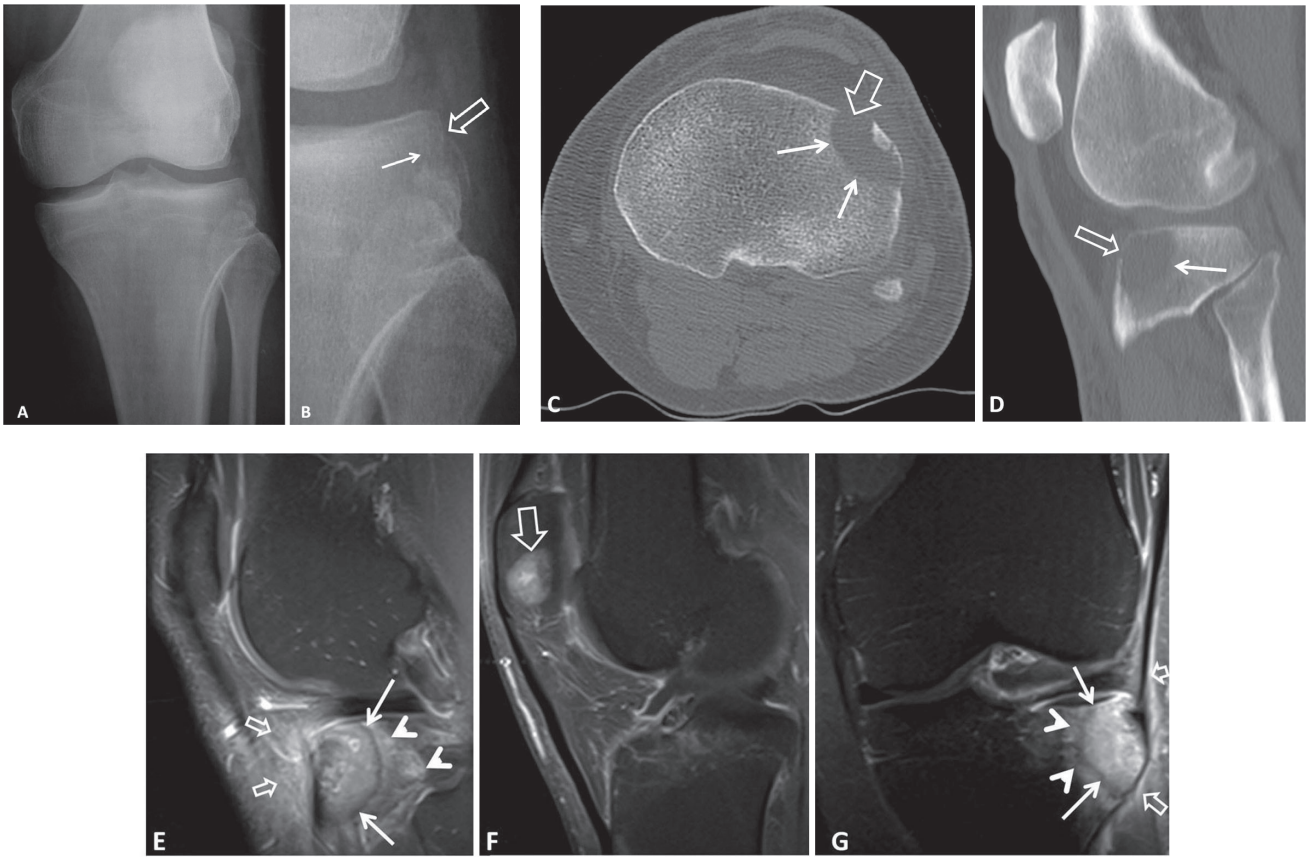

Fig. 1. *A 44-year-old male patient with primary non-Hodgkin lymphoma of bone. AP radiograph of the knee* ***(A)*** *and magnified view* ***(B)****. A subtle lucent area on the lateral proximal tibial epiphysis (thin arrow) and cortical disruption (open arrow) are shown. Axial* ***(C)*** *and sagittal reconstruction* ***(D)*** *CT images showing to better advantage the hypodense osteolysis (thin arrows) and the anterior cortical disruption (open arrows). Fat suppressed contrast enhanced T1w MR images in the sagittal* ***(E, F)*** *and coronal* ***(G)*** *planes showing to better advantage the bone marrow involvement in the lateral tibial metaepiphysis (thin arrows), reactive soft tissue changes (short open arrows) and another asymptomatic focus of involvement in the lower pole of the patella (open arrow). Reactive bone marrow oedema surrounds the malignant lesion (arrowheads).*

estimates the true extent of the osseous infiltration as shown with MRI. As a rule, normal or nearly normal radiographs have a large discrepancy with MRI regarding the extent of the lesion. The radiographs may be totally normal, may show osteolytic lesions with a permeative or "moth-eaten" pattern, osteosclerotic areas or a mixed pattern **(Figs. 1, 2)**. Osteolysis is the most common pattern and may be well or poorly defined, with or without cortical disruption. Aggressive periostitis suggests a poor prognosis [27, 28]. Osteosclerotic appearance of PBL is very rare. According to one study, it occurs in 2% of patients and is seen usually in Hodgkin's variant [17]. Osteosclerosis in the spine has been well known as "ivory vertebra", reflecting the osteoblastic response with reactive osteoid formation, following malignant cell's infiltration **(Fig. 3)** [29]. However, the "ivory vertebra" is not pathognomonic for PBL and indeed it is seen more commonly with spinal involvement in Hodgkin's disease. Osteosclerosis may be associated with cortical thickening and expansion of the bone **(Fig. 4)**. CT is very efficient in depicting bone marrow involvement, assessing cortical disruption and potential soft tissue involvement **(Figs. 1-3)**. In addition, CT-guided biopsies are routinely performed for establishing diagnosis.

MRI is the method of choice for assessing bone marrow disorders. PBL is demonstrated with low signal intensity on T1w, and with high signal intensity on fluid sensitive sequences. A similar to muscles signal on T1w MR images is caused by replacement of the high signal fatty bone marrow by neoplastic tissue showing a long

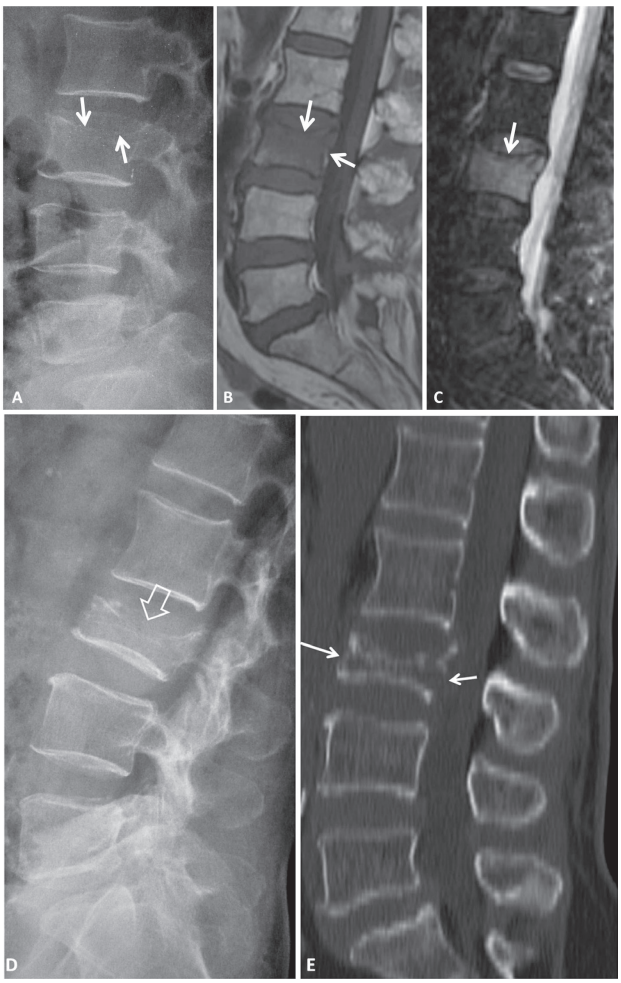

Fig. 2. *A 67-year-old female patient with primary spinal non Hodgkin lymphoma, presenting with low back pain. The lateral radiograph* ***(A)*** *shows mild osteopenia in the upper L3 vertebral body, with suspicion of mild collapse of the upper epiphyseal plate (arrows). The sagittal T1w* ***(B)*** *and STIR* ***(C)*** *MR images show to better advantage the almost complete infiltration of the bone marrow of L3 vertebral body and collapse of the superior epiphyseal plate (arrows). Two weeks after the initial imaging investigation, a non traumatic pathologic fracture is shown on plain radiograph (arrow)* ***(D)****. Sagittal reconstruction CT* ***(E)*** *shows to better advantage the compressive pathologic fracture (arrows).*

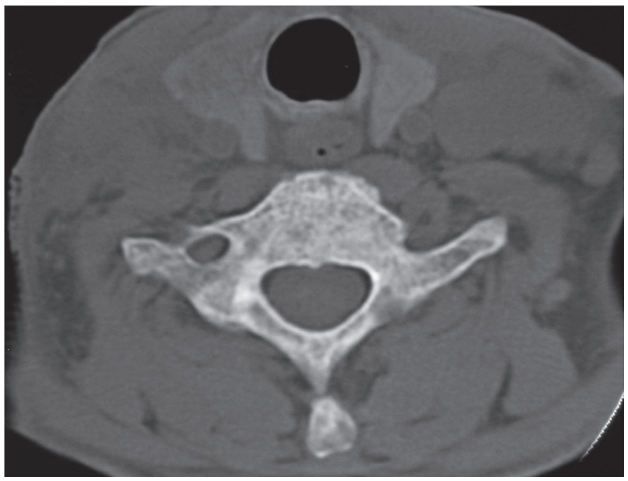

Fig. 3. *A 37-year-old male patient with primary spinal non-Hodgkin lymphoma. Axial CT shows the osteosclerotic (ivory) appearance of C7 vertebra.*

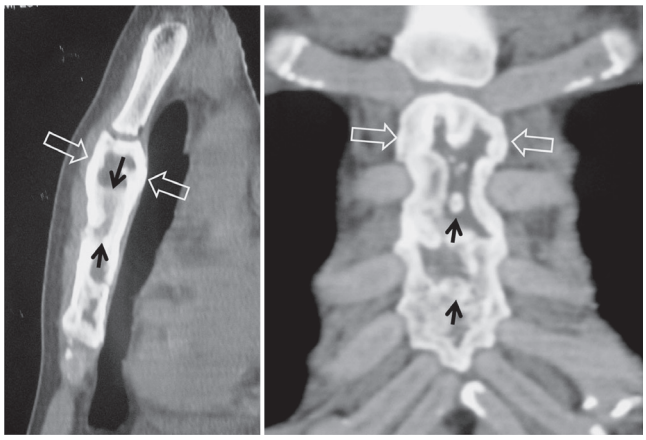

Fig. 4. *A 23-year-old male patient with primary non-Hodgkin lymphoma of the sternum. Sagittal (left) and oblique coronal (right) CT reconstructions showing bone expansion (open white arrows), cortical thickening and sclerosis in the bone marrow (black arrows).*

T1 relaxation time [30]. Hyperintense signal on fluid sensitive sequences is the result of a long T2 relaxation time of the neoplastic tissue, due to high intra- and extracellular water content [31].

The high sensitivity of MRI may show additional lesions modifying thus the pattern of involvement to multifocal **(Fig. 1)**. The abnormal bone marrow areas enhance following contrast medium administration **(Figs. 5, 6)**. The findings are not specific though and can simulate other disorders, such as primary bone tumour or metastatic disease. The osteosclerotic pattern may show only subtle findings **(Fig. 7)**. MRI is the preferred modality for assessing the extraosseous soft tissue involvement. Of particular interest is the finding that in PBL, like other small round cell tumours, the soft-tissue mass and marrow changes are associated with surprisingly little cortical destruction [28, 32]. Furthermore,

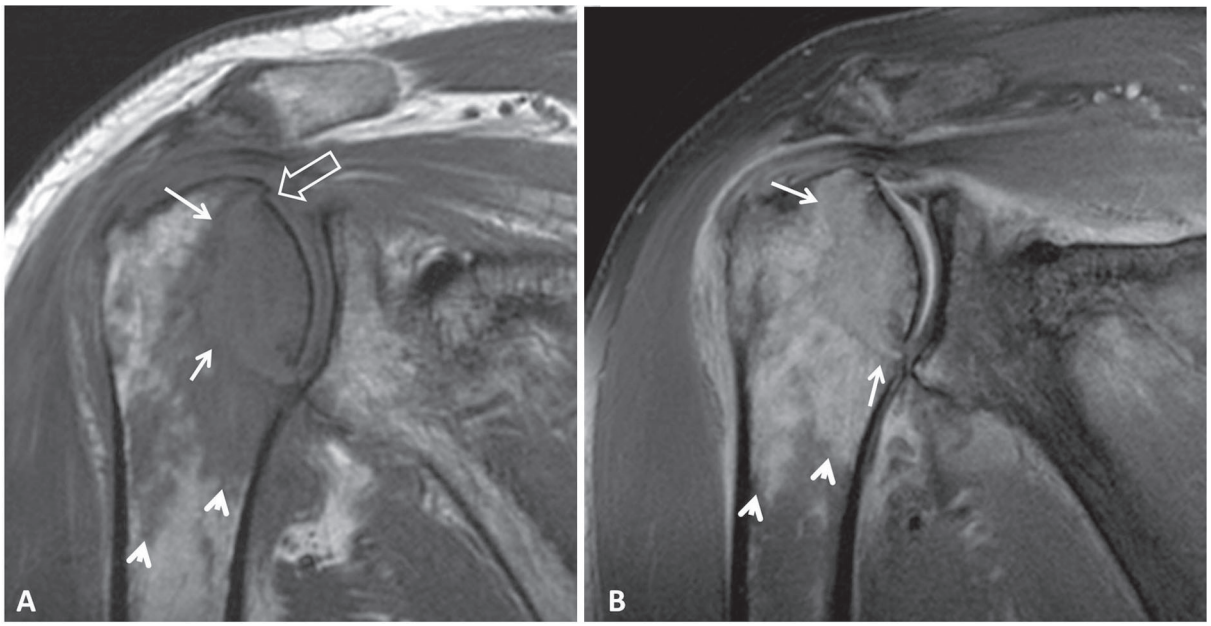

Fig. 5. *A 67-year-old male patient with pain of the right shoulder over the last month. Oblique coronal T1w* ***(A)*** *and fat suppressed PDw* ***(B)*** *MR images showing the lymphomatous lesion (arrows), reactive bone marrow oedema (arrowheads) and articular collapse (open arrow).*

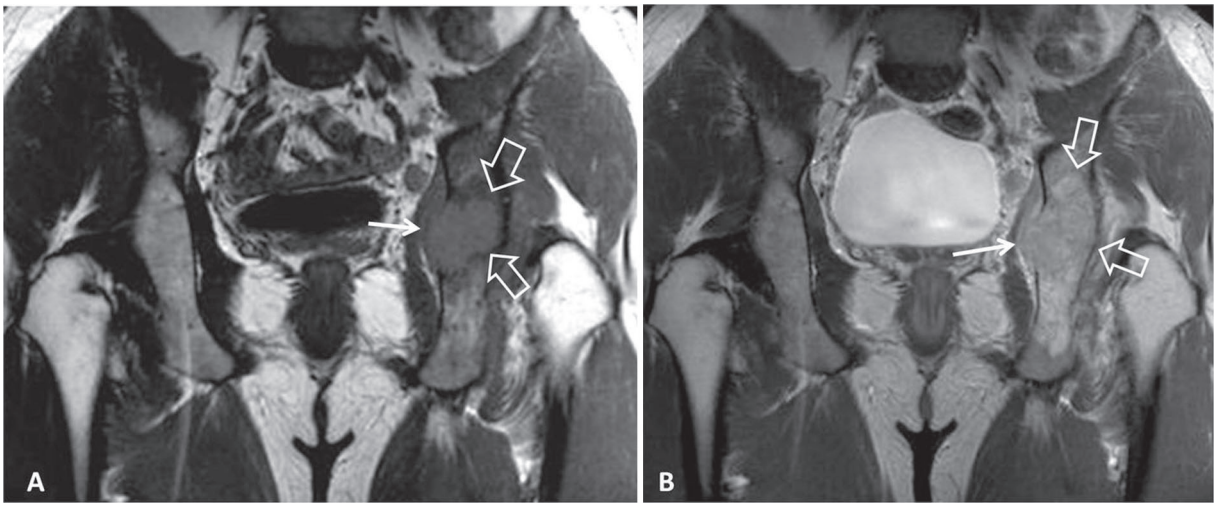

Fig. 6. A *25-year-old male patient with primary bone non-Hodgkin lymphoma of the acetabulum. Coronal T1W* ***(A)*** *and contrast-enhanced T1w* ***(B)*** *MR images showing a large, low-signal intensity and enhancing lesion of the left ischial bone (open arrows). The lesion is expansile and there is extension through the disrupted cortex to the soft tissues medially (arrows).*

Heyning et al. observed that 76% of cases with large B-cell type of PBL showed tumour extension into the soft tissues as a result of the permeative nature of the disease [32]. The presence of a soft-tissue swelling has been suggested to indicate an increased risk of relapse with unfavourable prognosis [33].

MRI can differentiate in theory viable from non-viable tumour with the use of diffusion weighted imaging. However, to the best of our knowledge, no large series have been published on the topic. In addition, MRI is capable of assessing complications related to treatment, such as epidural lipomatosis, insufficiency fractures and myeloid depletion **(Fig. 8)**. The main drawback of MRI remains its low specificity when reStaging.

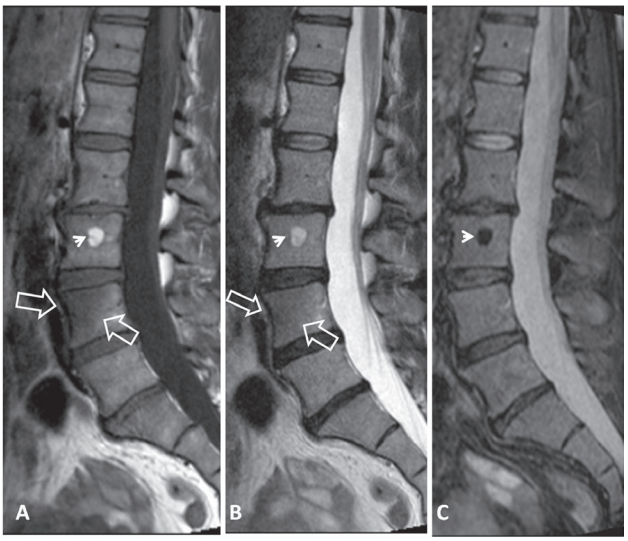

Fig. 7. *A 47-year-old female patient with primary hon-Hodgkin lymphoma of the spine. Sagittal MRI shows a low signal intensity lesion in the L4 vertebral body (open arrows) on the T1w image* ***(A)****. The lesion returns a low signal on the corresponding T2w image (open arrows)* ***(B)*** *and remains occult on the STIR image* ***(C)****. A fatty island of no clinical significance is shown in the L3 vertebral body (arrowheads).*

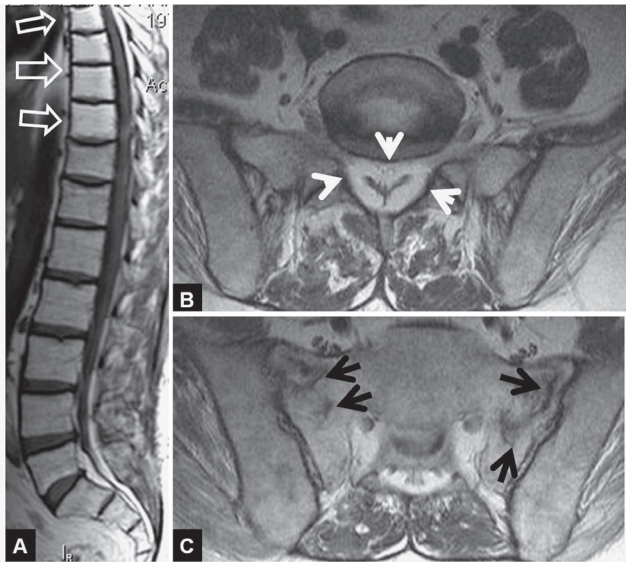

Fig. 8. *A 32-year-old patient with a history of advanced low grade non-Hodgkin lymphoma involving the T-spine. Treatment included radiotherapy and steroid administration. Sagittal T1w* ***(A)*** *and axial T1w* ***(B, C)*** *MR images showing myeloid depletion and fatty replacement at the level of the irradiation (white open arrows), epidural lipomatosis with the typical "Y" configuration of the dural sac at L5/S1 (white arrowheads) and insufficiency sacral fractures (black arrows).*

Following treatment, CT and MRI can show significant reduction in the size and extent of the lesion [34, 35]. Conventional radiographs and CT may show transformation of the osseous changes from lytic to sclerotic or increased sclerosis [29]. The latter does not quantify therapeutic response. Conventional radiographs or CT may also show calcified deposits within the soft tissue component [29]. CT or MRI may not be able to show at all any residual tumour following treatment [35, 36]. 18F-FDG PET/CT depicts the metabolic and functional status of the lesions, which can be semiquantified by the addition of maximum standardised uptake value (SUVmax). SUVmax of 2.5 has been used as a cutoff for differentiating residual lymphoma from metabolically inactive disease, with 100% negative prognostic value and 100% sensitivity in showing residual disease [25]. Indeed, FDG-PET often shows nearly normal activity [37]. A high rate of false positive results compared to consequent biopsy reports has been observed, with post-therapeutic osteonecrosis as a major potential cause [25].

Staging

Typical Staging workups include a bone scan, CT of the chest, abdomen, and pelvis, bone marrow biopsy, and PET/CT. 18F-FDG PET/CT has been standard care for Staging, reStaging, surveillance of recurrence, and monitoring of treatment response [38]. 18F-FDG PET/CT has sensitivity close to 100% in showing 18F-FDG-avid PBL lesions, due to common B-cell derivation [39, 40]. CT demonstrates less than 50% sensitivity in diagnosing these lesions [40]. 18F-FDG PET/CT can also detect soft tissue involvement beyond the bone lesion, similar to MRI **(Fig. 9)**. In contrast to CT and MRI, the main advantage of 18F-FDG PET/CT in Staging is its ability to detect additional unknown bone lesions with the protocol of whole-body acquisition, with a significant impact on treatment, patient care, and follow-up. In two recent studies, in almost 50% of cases, 18F-FDG PET/CT detected more, previously unsuspected lesions [38, 39]. However, with evolving technology, whole body MRI is competing PET/CT in assessing additional bone lesions.

Differential diagnosis and imaging

Given that PBL generally has an excellent prognosis compared to primary bone sarcoma, and that the treat-

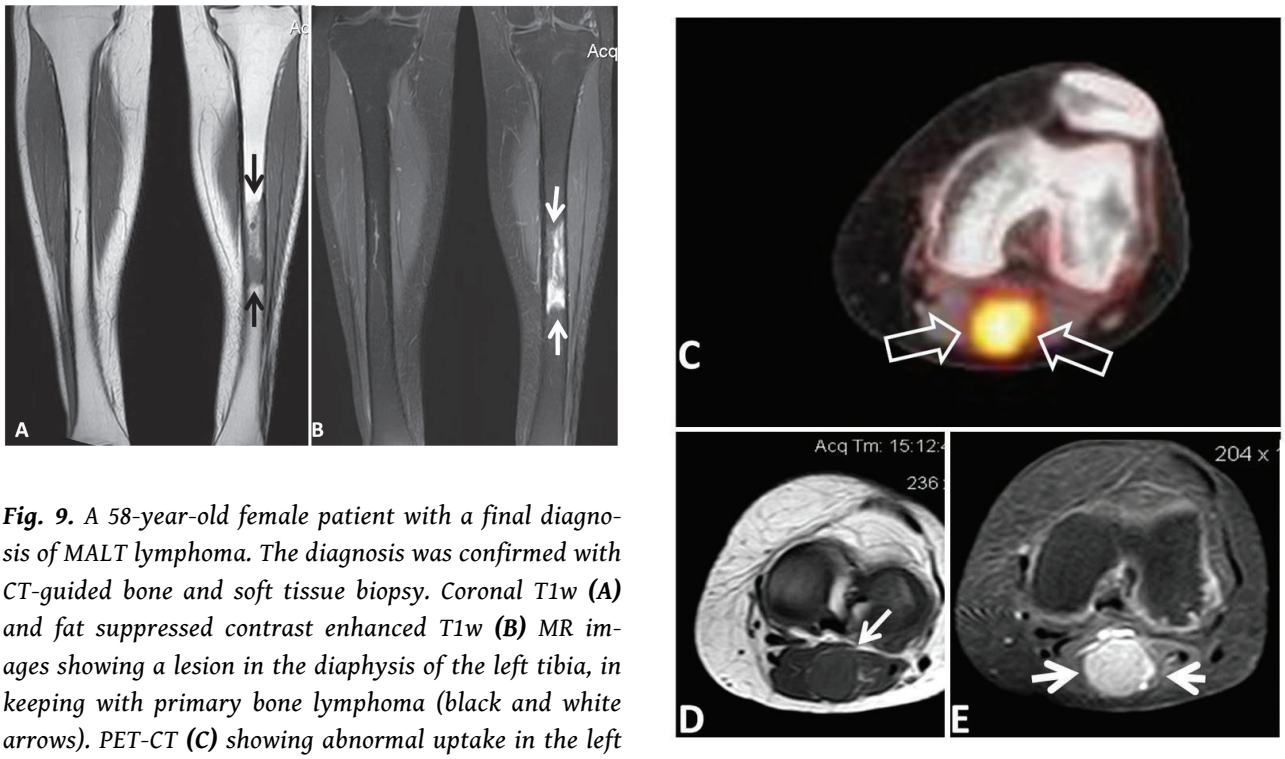

Fig. 9. *A 58-year-old female patient with a final diagnosis of MALT lymphoma. The diagnosis was confirmed with CT-guided bone and soft tissue biopsy. Coronal T1w* ***(A)*** *and fat suppressed contrast enhanced T1w* ***(B)*** *MR images showing a lesion in the diaphysis of the left tibia, in keeping with primary bone lymphoma (black and white arrows). PET-CT* ***(C)*** *showing abnormal uptake in the left popliteal fossa in the absence of any symptoms in this area (white open arrows). Axial T1w MR image* ***(D)*** *shows a iso- to hypointense lesion (white arrow) which is avidly enhancing following GD-DTPA intravascular injection (white arrows in* ***E****).*

ment pathways for these two diseases differ dramatically, it is very important to distinguish PBL from other bone primary malignancies, secondary bone lymphoma or osteomyelitis. Tumour may spread to adjacent bone by invading joint or vertebral spaces, and when present, helps to narrow the differential diagnosis [41, 42]. There is a wide spectrum of findings related to the radiographic appearance of PBL, but no pathognomonic sign is reliable. Nevertheless, a lytic destructive appearance with a "moth-eaten" wide zone of transition, located in the diametaphysis of a long bone, with layered periosteal reaction and little cortical destruction on conventional radiographs together with a soft-tissue mass on CT and MR images are highly suggestive of PBL. When the lesion borders are well defined, the appearance may mimick multiple myeloma. In younger patients, the differential diagnosis of PBL includes osteosarcoma, Ewing's sarcoma and osteomyelitis. The presence of an "ivory vertebra" is not pathognomonic and may correspond to a benign lesion **(Fig. 10)**. In older patients, bone metastasis should be considered. Rarely, bone sequestrum is seen and sequestrum formation has to include in the differentials osteomyelitis, osseous tuberculosis, radiation necrosis and eosinophilic granuloma [18, 27, 31, 32, 41-44]. MRI appearance of non-Hodgkin versus Hodgkin's primary lymphoma is quite similar **(Figs. 11, 12)**.

MRI is excellent at demonstrating bone marrow replacement as areas of low signal on T1w images and bright signal on fluid sensitive sequences. However, MR imaging features can be "protean" in patients with PLB and even appear benign [32].

The evolution of specific biomarkers based on molecular imaging, i.e. diffusion weighted MRI, and the information extracted with radiomics, will eventually contribute to better assessment of the initial lesion's aggressiveness and prognosis on the response to treatment and the outcome [45]. No studies, to the best of our knowledge, exist on the use of diffusion weighted MRI for diagnosing and monitoring treatment response in PBL [30, 35].

Therapeutic options and prognosis

Guidelines for the management of PBL are limited. The

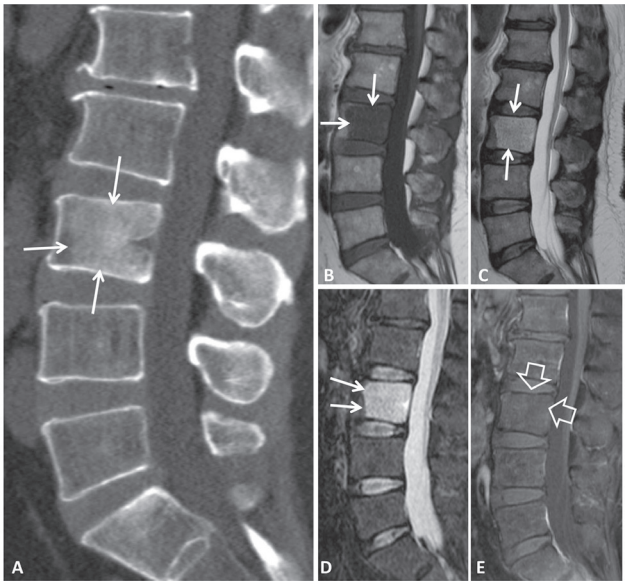

Fig. 10. *A 58-year-old male patient with mechanical low back pain over the last 2 months. Sagittal CT reconstruction* ***(A)*** *showing an osteosclerotic L3 vertebra with diffuse osteosclerosis (arrows). Other causes for this appearance include metastatic deposits from breast or prostatic carcinoma and Paget's disease. Sagittal T1w* ***(B)*** *and T2w* ***(C)*** *MR images show a low and high signal intensity lesion respectively, which might correspond to osseous haemangioma (arrows). The high signal intensity on STIR (arrows in* ***D****) is not compatible with a haemangioma. Sagittal fat suppressed contrast enhanced T1w* ***(E)*** *MR image shows no enhancement (open arrows). The findings are suggestive of a benign notochordal cell tumour which did not show any deterioration within a 5-year imaging follow up.*

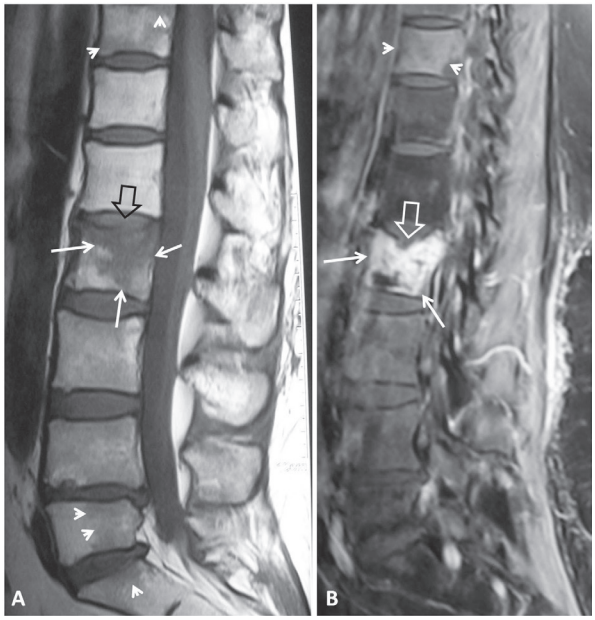

Fig. 11. *A 35-year-old female patient with primary multifocal spinal Hodgkin lymphoma. Sagittal T1w* ***(A)*** *MR image showing infiltration of the bone marrow of the L2 vertebral body (white arrows) along with a pathologic atraumatic fracture of the superior epiphyseal plate (black open arrow). Suspicious lesions are shown in the L5, S1 and T11 vertebrae (white arrowheads). Sagittal fat suppressed contrast-enhanced T1w* ***(B)*** *MR image shows intense enhancement of the abnormal bone marrow in the L2 vertebral body (white arrows), the collapse of the superior epiphyseal plate (white open arrow) and early infiltration of the T11 vertebra (white arrowheads). The suspicious lesions in the L5 and S1 vertebrae correspond to benign hyperplasia.*

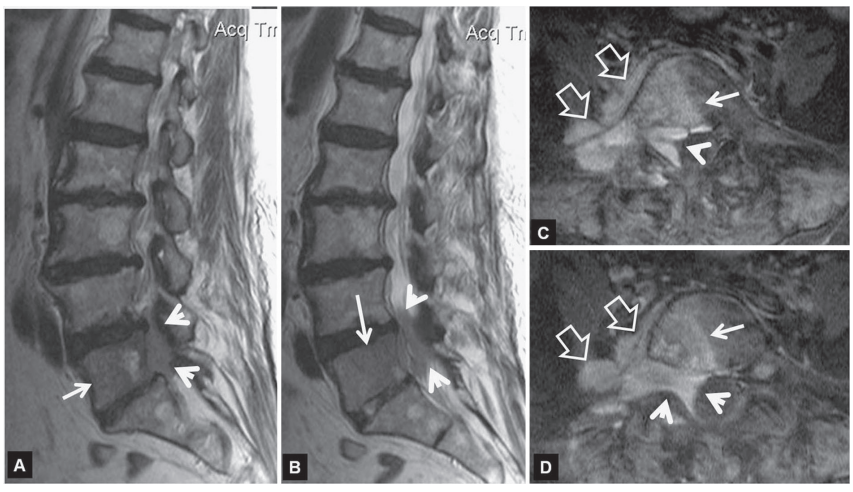

Fig. 12. *MR imaging study including sagittal T2w* ***(A, B)*** *and contrast-enhanced fat-suppressed T1w* ***(C, D)*** *pulse sequences of a 78-year-old female patient with a final diagnosis of non-Hodgkin lymphoma. There is bone marrow involvement (arrows in* ***A-D****), epidural space involvement (arrowheads), and paraspinal small lymph node involvement (open arrows in* ***C, D****).*

level of evidence supporting therapeutic decisions in PBL is very low as no prospective trials have been published. Optimal survival therapy regimens are difficult to suggest, due to lack of homogeneity of inclusion criteria of the disease, and continuous improvement in pharmacologic agents and diagnostic means. Results of earlier studies cannot be compared to each other or to current treatment strategies, since they comprise of small series with histological heterogeneity of PBL. Nevertheless, there is definite trend towards significant improvement in the outcome of patients with PBL with the incorporation of rituximab into standard chemotherapeutic regimens [5, 46-49], although results after its very recent addition have not been fully reflected into recent research. In early stage disease, 5-year overall survival (OS) ranges between 70% and 90% in most studies [20, 22, 25, 49, 50]. Chemotherapy comprising of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) has been the first-choice regimen in primary bone DLBCL, with the recent addition of rituximab (R-CHOP). The additional therapeutic role of radiation, which includes timing, volume and site, is open to interpretation [5, 9, 22, 23, 49, 51].

Indications for surgical treatment include impending or actual pathologic fracture, segmental defects in long bones, and articular or skeletal collapse resulting from avascular necrosis following treatment. Some of these complications can arise following treatment or in cases of disease unresponsive to conservative treatment. Specific criteria have been established to help the treating team decide whether an untreated primary lesion at great fracture risk should be prophylactically fixed [52]. Early surgical treatment of a pathologic fracture in the lower limb, before chemotherapy, allows better quality of life for the patient to endure subsequent treatment and/or hospitalisation. In the upper limb, considering the minor disability induced by using a brace, delayed surgical treatment can be adopted, allowing prompt onset of chemotherapy and radiotherapy. It is necessary sometimes to achieve a significant shrinking of the lesion after preoperative chemotherapy and radiation treatment, and then elect for surgery under safer circumstances. Specific considerations should be devoted to lymphomas involving the spine for the risk of neurological deficits due to a vertebral collapse. Timing of surgery is another controversial issue. In general, surgery is advised following medical treatment wherever applicable. In this concept, treating pathological fractures can be delayed after chemotherapy and radiotherapy if fracture location and patient conditions make it possible. Some authors report an increased incidence of fractures after radiotherapy and this could lead to a preference for early stabilisation of the affected bones [25, 53, 54].

An effort has been made to isolate independent prognostic factors predisposing to a good outcome, although they have not been well and uniformly established. Younger age at diagnosis (<60 years) has been proven consistently to be a statistically significant independent favourable predictor for survival [6, 7, 10, 14, 25]. Complete response to treatment appears to be another important predictive factor for good outcome [14, 55]. The survival of patients with primary bone DLBCL is significantly related to disease stage, with the 5-year OS varying from 82% for patients with stage IE disease to 38% for patients with disseminated DLBCL and skeleton involvement [9]. Multifocality in PBL is another unfavourable prognostic factor for both progression-free survival and OS [7, 10]. Radiotherapy of fractured bone as initial treatment is associated with poorer survival [3]. Finally, a high International Prognostic Index score and soft tissue extension have been recognised by some authors as important prognostic factors that affect survival [5, 7].

Conclusion

PBL has a better prognosis than many other osseous malignancies and thus early depiction allows early treatment. In cases of discrepant findings between radiographs and MRI or CT, the suspicion of lymphoma should be raised. MRI has superb accuracy for assessing bone marrow involvement, is capable of early identification, depicts the extent of soft-tissue involvement and can be used to assess the outcome of treatment. **R**

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Conflict of interest

The authors declared no conflicts of interest.

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