Skeletal Radiol (2015) 44:863–868
DOI 10.1007/s00256-014-2067-3

CASE REPORT

# Complementary roles of bone scintigraphy and MR imaging in the detection and long-term follow-up of primary non-Hodgkin's bone lymphoma in a child-case report

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Received: 23 July 2014 / Revised: 9 November 2014 / Accepted: 17 November 2014 / Published online: 30 November 2014


**Abstract** The aim of our report is to demonstrate the complementary roles of bone scintigraphy (BS), magnetic resonance imaging (MR), and positron emission tomography using 2-deoxy-2-[18F]fluoro-D-glucose (F-18-FDG PET/CT) in the diagnosis and treatment monitoring of a child with primary non-Hodgkin's lymphoma of bone (PLB). Increased blood flow, high tissue accumulation, and markedly increased uptake on the late BS pointed toward an active bone process in the left femoral region. Bone marrow infiltration of the left femur and cortical sclerosis, which were both demonstrated by MR imaging, were later confirmed as PLB by bone marrow biopsy. The normalizations of the flow and tissue phases of BS a year after treatment and during the entire follow-up were in keeping with inactive disease and clinical remission. However, even 8 years after treatment and complete remission, MR imaging demonstrated persistent unmodified bone marrow alteration and appreciable cortical involvement. A slightly increased metabolic activity of the left femoral epiphysis demonstrated by F-18-FDG PET/CT and mild activity in the same region on delayed BS were demonstrated in the late follow-up. Our results strongly suggest that BS and MR imaging should be included in the diagnostic algorithm of children with undefined bone symptoms. However, mild metabolic activity on the F-18-FDG PET/CT scan could not reliably differentiate between the presence or absence of disease in a patient with PLB in clinical remission.

**Keywords** Three-phase bone scintigraphy · Primary bone lymphoma · MR imaging · Children · F-18-FDG PET/CT

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## Introduction

Primary non-Hodgkin's lymphoma of bone (PLB) is a rare subtype of non-Hodgkin's lymphoma, which comprises less than 1 % of all lymphomas and 5 % of all extranodal non-Hodgkin's lymphoma [1, 2]. It is a very rare malignancy in children, and only 2–9 % of cases involve the bone/bone marrow as the primary site [3]. Boys appear to be affected more frequently than girls [2]. The most common sites of involvement are the femur, pelvis, and tibia [2].

Because of its diversity, heterogeneity, the presence of unusual symptoms, and rare incidence in children, PLB appears to be quite a diagnostic challenge. The imaging of primary bone lymphoma should, therefore, have a key role in the early diagnosis, detection of the extent of the disease, and follow-up of children after treatment.

Different morphologic and scintigraphic imaging modalities have been used for the detection of malignant bone/bone marrow involvement in children, but none have yielded any general recommendations on an optimal imaging algorithm [4–11]. Correlative imaging modalities, defined as the combined interpretation of different imaging modalities, have been reported as being superior to separate analysis in children because each of the modalities on its own has certain advantages as well as limitations [4].

The aim of our report is to demonstrate the complementary roles of bone scintigraphy (BS), magnetic resonance imaging

(MR), and positron emission tomography using 2-deoxy-2-[18F]fluoro-D-glucose (F-18-FDG PET/CT) in the diagnosis and treatment monitoring of a child with primary non-Hodgkin's lymphoma of bone.

## Case report

In 2006, a 15-year-old girl was admitted to our Pediatric Clinic with a 12-month history of recurrent pain in both lower limbs, especially the left one. One year prior to admission, she had been treated with oral nonsteroidal anti-inflammatory drugs. Due to the worsening of her symptoms, several months before admission the girl had been prescribed corticosteroid medications in order to reduce the inflammation and pain.

On admission, the dominant symptoms included pain in the lower left limb and partial to complete immobility. The left knee was slightly swollen, presenting considerable tenderness and limited mobility. No history of trauma was reported. Physical examination showed no lymphadenopathy, splenomegaly, or any other system abnormality.

Laboratory analysis showed an increased erythrocyte sedimentation rate of 49 mm/h and no other hematological abnormalities or blood disorders. Radiographs of both lower limbs revealed no detectable abnormalities.

A three-phase bone scan with Tc-99m-1,1-diphosphono-2,3-propanodicarboxylic acid (Tc-99m-DPD) and MR imaging was performed on 2 consecutive days. Increased blood flow, high tissue accumulation, and higher distal left femoral uptake in the late bone phase strongly supported an infective/inflammatory active bone process (Fig. 1a,b,c). Other parts of the skeletal system showed normal tracer distribution on the delayed whole-body scan. However, bone marrow infiltration of the left femur and cortical sclerosis were demonstrated by MR imaging (Fig. 1d,e), so the child was referred to an orthopedic surgeon for bone marrow biopsy.

Bone marrow biopsy of the distal part of the left femur showed large abnormal cells; immunohistochemical analysis identified them as positive for anti-CD10 and anti-CD20 antibodies, thus confirming the diagnosis of primary non-Hodgkin's B cell lymphoma of bone.

The patient received eight cycles of R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone, and monoclonal antibody retuximab) in 3-week intervals, followed by 20 external beam radiotherapies (36 Gy). The therapy was well tolerated, and 1 year after treatment the patient achieved full remission, complete with full mobility and the absence of pain in the leg. Repeated bone marrow biopsy of the affected bone showed no presence of the disease.

The child was followed up for 8 years by means of BS and MR imaging. Additionaly, 2-deoxy-2-[18F]fluoro-D-glucose (F-18-FDG PET/CT) was performed in the late follow-up period. The control MR imaging done a year (Fig. 2d,e) and 8 years (Fig. 3d,e) after treatment did not show remarkable changes compared with the initial image. Moreover, even 8 years after treatment and complete remission, MR imaging demonstrated persistent unmodified bone marrow alteration and appreciable cortical involvement, with low level signal on the T1-weighted (T1w) sequence and hyperintense signal on the T2-weighted (T2w) images.

On the other hand, the flow (Figs. 2a and 3a) and tissue phases (Figs. 2b and 3b) of a three-phase bone scan normalized after treatment and during the whole observation period, which was in concordance with the clinical course of the disease. The late bone scan changed significantly a year after treatment, reflecting the resolution of the disease (Fig. 2c). However, 8 years after treatment the bone phase did not achieve complete normalization, demonstrating mild increased activity on the epiphyseal portion of the femur (Fig. 3c). A sclerotic lesion of the left femur was demonstrated on the CT portion of the F-18-FDG PET/CT scan (Fig. 4a), accompanied by slightly increased F-18-FDG metabolic activity on the epiphyseal region of the left femur during the last follow-up (Fig. 4b, c).

## Discussion

A review of the literature revealed many cases of PBL patients presenting with mono- or polyarthritis [13]. The most common presenting complaint in PBL is pain without a preceding trauma, which is slight and intermittent in the early phase of the disease and intolerable in the later stages. This was also the case with our patient, whose pain was partially relieved by nonsteroidal antinflamatory drugs at the onset of the disease. Our patient also showed nonspecific clinical presentation of the disease without the symptoms usually associated with a malignant condition, such as weight loss, early morning vomiting, constant tiredness, nausea, paleness, or persistent fever.

Pathological classification of PLB can demonstrate a wide spectrum of histological subtypes, although most are classified as intermediate-grade or aggressive B-cell lymphomas [14]. According to the diagnostic criteria for confirming PLB, imaging plays the most important role in the early diagnosis, assessment of the extent of the disease, and monitoring of therapy in patients with PLB [15].

Conventional imaging modalities proved to be indeterminate in cases of PLB [12, 13]. The radiographic appearance of PLB is variable, meaning that bone lesions can appear near normal on radiographs [12], which was the case in our study. Compared to a CT, Ga-67 scintigraphy proved to be highly sensitive and specific, both in the diagnosis and as a predictor of long-term outcome in patients with bone lymphoma [11]. Although CT may yield different patterns of lesions in patients with PLB at presentation,

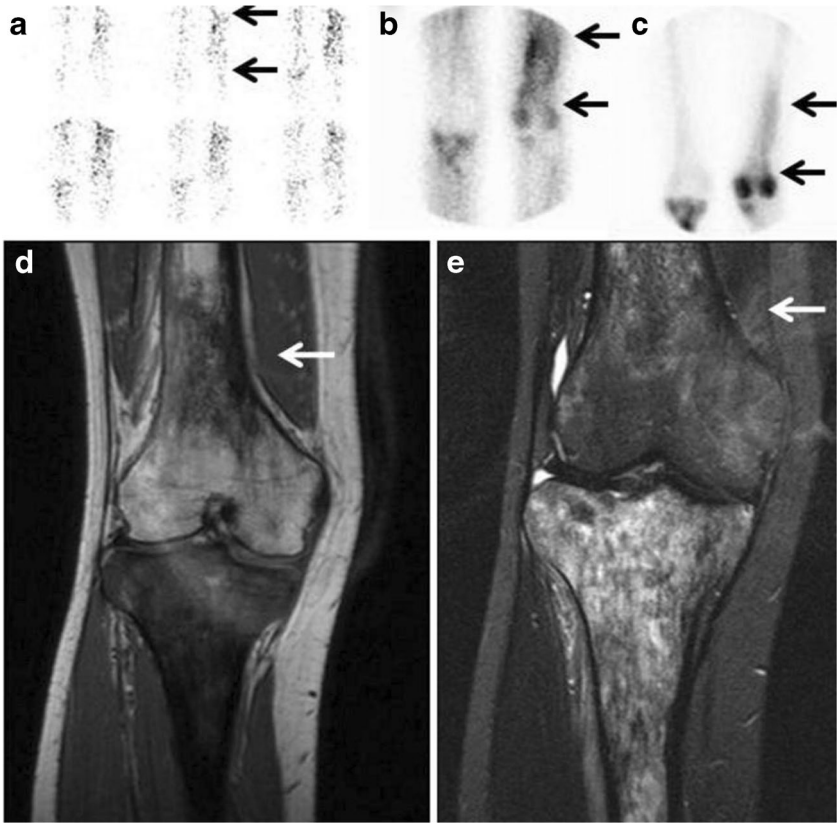


**Fig. 1** A 15-year-old female with primary non-Hodkin's B cell lymphoma of bone. Anterior three-phase bone scan (Tc-99m-DPD) and MR imaging of the left knee. **a** Increased flow, **b** tissue, and **c** delayed bone accumulation of the left knee and distal left femur. Coronal MR imaging of the left femur. **d** T1-weighted image reveals infiltration of the left femur with cortical sclerosis. **e** T2-weighted image shows a hyperintense, pathological signal in the femur

during, and after treatment, this method is not considered reliable enough because it does not show negative results even 1 year after remission [9]. This was confirmed by our case, in which the sclerotic lesion of the left femur was demonstrated on the CT portion of the F-18-FDG PET/CT scan 8 years after treatment.

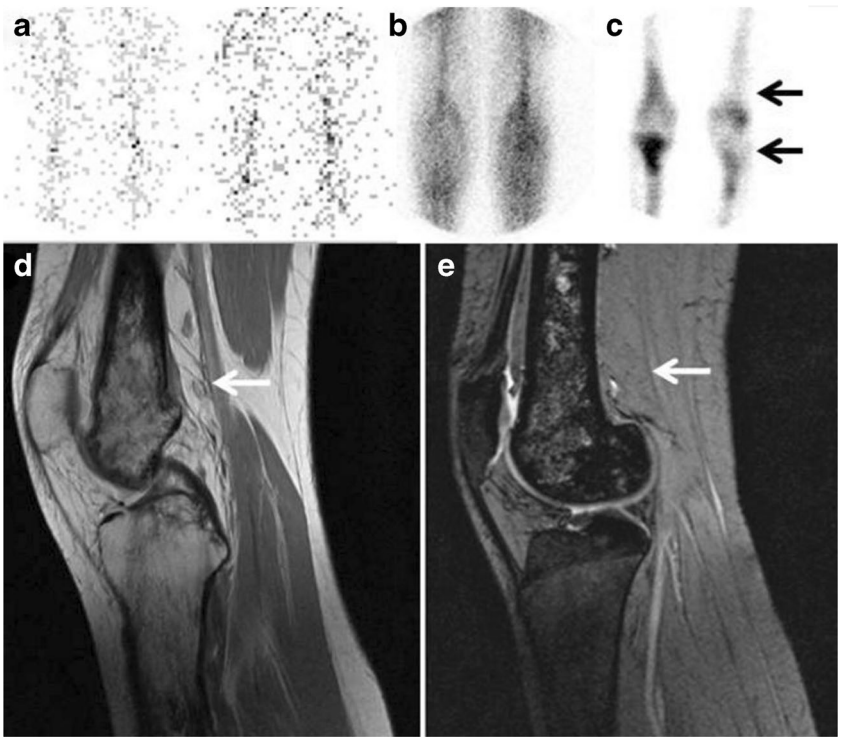


**Fig. 2** A 15-year-old female with primary non-Hodkin's B cell lymphoma of bone a year after treatment. Anterior three-phase bone scan (Tc-99m-DPD) and MR imaging of the left knee. **a** Normal flow, **b** normal tissue accumulation, and **c** mild focal accumulation of the left knee; slightly decreased tracer accumulation in the distal left femur and proximal tibia. Sagittal MR imaging of the left knee. **d** T1w image reveals neoplastic infiltration of bone marrow of the left femur with cortical sclerosis with low level signal. **e** T2w image shows femoral deformation with infiltration

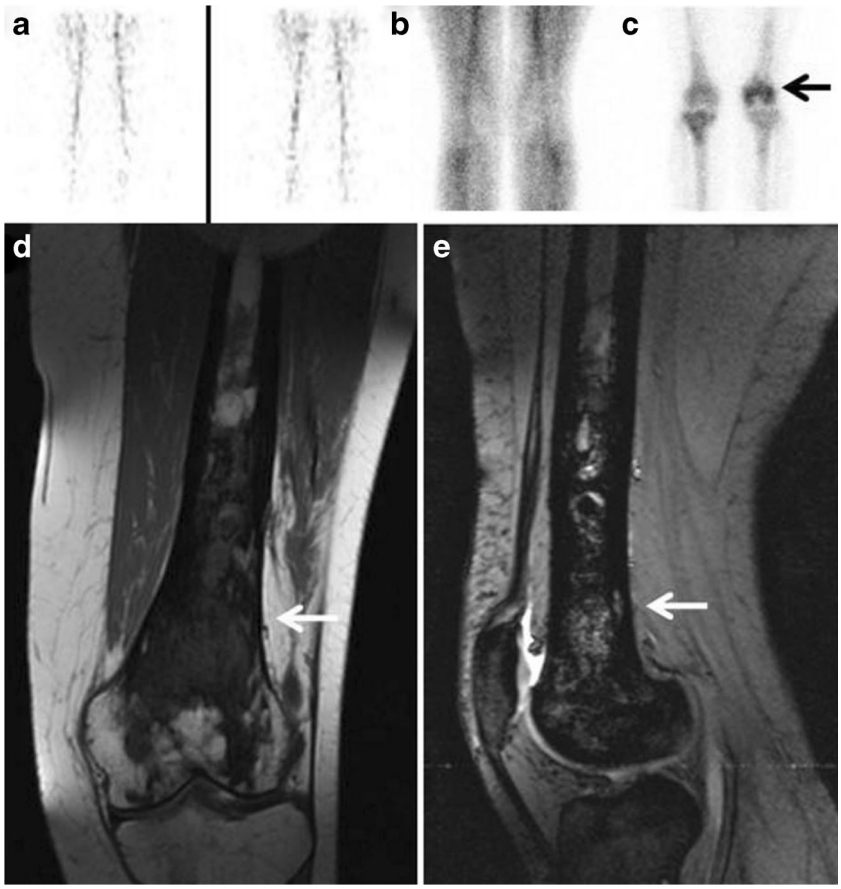


**Fig. 3** A 15-year-old female with primary non-Hodkin's B cell lymphoma of bone 8 years after treatment. Anterior three-phase bone scan (Tc-99m-DPD) and MR imaging of the left knee. **a** Normal flow, **b** normal tissue accumulation, and **c** slightly increased tracer accumulation in the distal left femur. **d** Coronal T1w MR imaging of the left femur reveals neoplastic infiltration of bone marrow of the left femur with cortical sclerosis. **e** Sagittal T2w MR image shows femoral deformation with infiltration

Several staging investigations following the diagnosis of Ewing's sarcoma (ES) and osteosarcoma compared F-18-FDG PET/CT, BS, and other conventional imaging modalities [5–12, 16]. Numerous primary bone tumors are found to be FDG avid, but the degree of FDG uptake in bone tumors does not necessarily reflect the malignant potential [5]. Many benign sources of FDG uptake in the musculoskeletal system can be mistaken for aggressive or malignant processes in the bone. Benign bone and soft-tissue lesions can simulate malignancy, particularly if they are highly avid, whereas low-grade malignancies with low FDG uptake can be mistaken for benign lesions [7]. Ulaner et al. compared F-18-FDG PET/

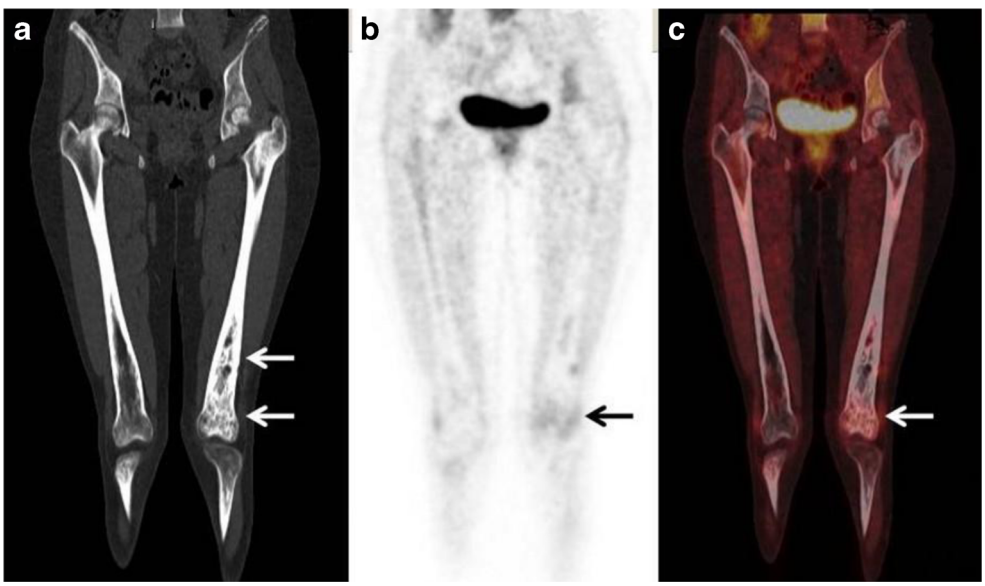


**Fig. 4** A 15-year-old female with primary non-Hodkin's B cell lymphoma of bone 8 years after treatment. Coronal F-18-FDG PET/CT of both legs. **a** Sclerotic lesion of the left femur on CT and **b**, **c** slightly increased tracer uptake in the distal left femur on F-18-FDG PET/CT

CT scans and BS in patients with ES and concluded that BS does not add to staging performed by F-18-FDG PET/CT when ES is lytic, but in the cases when ES is sclerotic, a bone scan may detect osseous metastases not otherwise detected by FDG PET/CT [7]. Franzius et al. found that the sensitivity, specificity, and accuracy of F-18-FDG PET in the detection of osseous metastases from Ewing's sarcomas are superior to those of BS. However, in the detection of osseous metastases from osteosarcoma, FDG PET seems to be less sensitive than BS [10]. Newman et al. conducted staging investigations following the diagnosis of ES using a chest CT, BS, F-18-FDG PET/CT scan, and bone marrow biopsy [16]. These authors pointed out that each of these staging investigations provides complementary prognostic information, but the optimal combination of staging investigations was not clearly defined [16].

In our case study, a combined MR imaging and three-phase bone scan were performed both initially and during the follow-up. Bone scintigraphy is a well-established imaging modality, and although it is not specific, its exquisite sensitivity makes it a helpful procedure in many pathological conditions [17,18]. Moreover, a three-phase bone scan adds important information about the vascularization of the bone lesion, differentiating between malignant tumors, which tend to be more vascularized and have an increased uptake in all three phases of the scan, and benign bone tumors, which often do not show changes in the flow and tissue phases of the scan [5].

Magnetic resonance imaging is the standard method of choice when it comes to diagnosing malignant lesions that involve bone marrow. A typical MR imaging pattern of the PLB lesion demonstrates low signal intensity on T1-weighted images and a hyperintense appearance on T2-weighted images, as it is more sensitive than CT when it comes to detecting soft-tissue mass [12]. This is why MR imaging should be routinely used in the initial workup of these lesions [12]. In our PLB case study, T1-weighted pulse sequences were found to be most useful in demonstrating the marrow changes, as T1-weighted images reveal areas of low signal intensity within the marrow. Also, in the case of our patient, T2-weighted images showed high signal intensity due to peritumoral edema and reactive marrow changes. However, control MR imaging done a year and 8 years after treatment did not show remarkable changes compared with the pretreatment image. Even 8 years after treatment and a clinically complete remission, MR imaging demonstrated persistent unmodified bone marrow alteration and appreciable cortical involvement, with a low-level signal on the T1w sequence and a hyperintense signal on T2w images. On the other hand, the findings obtained from a three-phase bone scan at the time of the diagnosis were consistent with the active phase of the disease, and the normalization of the flow and tissue phases a year after treatment and during follow-up was in keeping with inactive disease and clinical remission. Initially increased delayed bone uptake can be explained by the spreading of tumor cells from the marrow through small vascular channels that run through the cortex [19]. Decreased activity of the affected bone on a late scan, a year after treatment, was the consequence of radiation osteitis, characterized by a uniformly decreased uptake within the radiation region. This pattern, which can be identified up to 6 months after treatment, can persist for a long time, although the osseous uptake may on occasion return to pretreatment levels [12]. However, even 8 years after treatment complete normalization of the bone uptake was not achieved. However, although the presence of minimal FDG uptake on the PET/CT scan did not provide any useful information in our study case, its utility in the follow-up period could be important, especially when the clinical picture is not clear and when the findings of increased F-18-FDG uptake could encourage clinicians to perform another biopsy. Establishing complete or partial treatment response using imaging can sometimes be difficult, mainly because it is not always possible to differentiate between residual tumor and the repair process. These difficulties are particularly relevant when using imaging modalities that detect malignant bone involvement based on the presence of bone destruction or reactive bone remodeling, such as CT, delayed BS, or the type of imaging that visualizes bone marrow alteration, such as MR. Even when complete clinical remission has been achieved, as was the case in our study, normal appearance of bone on imaging may be absent, and the bone may remain morphologically abnormal despite the disease being "burnt out" [20]. All these imaging modalities were found unreliable in the treatment monitoring of our study case of PLB. Also, metabolic imaging using F-18-FDG PET/CT scans was found useless in our case, since mild metabolic activity could not reliably differentiate between the presence or absence of disease in a patient in clinical remission. Jones et al. described decreased FDG accumulation in soft-tissue and musculoskeletal sarcomas after neoadjuvant therapies, but not the complete absence of FDG uptake. They speculated that the remaining FDG uptake seems to correspond to a pseudocapsule or infiltrating granulation tissues and fibrosis [20].

More studies are necessary to assess the exact role of this imaging modality in the diagnosis, staging, and treatment monitoring of primary bone malignancies, especially the rare types like PLB.

## Conclusion

Our results strongly suggest that BS and MR imaging should be included in the diagnostic algorithm of children with undefined bone symptoms. However, mild metabolic activity on F-18-FDG PET/CT scans could not reliably differentiate between the presence or absence of disease in a patient with PLB in clinical remission.

**Acknowledgments** This work was supported by the Ministry of Science and Technology Development of the Republic of Serbia under project no. 43011.

**Conflict of interest** The authors declare that they have no conflict of interest.

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