Review Article

PET/CT in Evaluation Bone Marrow Infiltration in Malignant Lymphoma

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The bone marrow is found within the central cavities of axial and long bones. It consists of hematopoietic tissue islands and adipose cells surrounded by vascular sinuses interspersed within a meshwork of trabecular bone. It accounts for approximately 5% in humans [(1)].

Bone marrow consists of a hematopoietic component (parenchyma) and a vascular component (stroma). The parenchyma includes hematopoietic stem cells (HSCs) and hematopoietic progenitor cells, which are not randomly distributed in the bone marrow but rather are localized close to the endosteum of the bone and more around blood vessels [(1)]. Bone marrow stroma contains multi-potential non-hematopoietic progenitor cells capable of differentiating into various tissues of mesenchymal origin, including osteoblasts, endothelial cells, reticular cells, fibroblasts and adipocytes. The bone marrow's microvasculature with a single layer endothelium forms sinusoid, which radically distributes around the draining central sinus. The vasculature provides the barrier between the bone marrow compartment as a functional and spatial entity from extra lymphoid organ and the peripheral circulation [(2)].

Bone marrow displays structural and functional features resembling a secondary lymphoid organ, and contains follicle-like structures similar to lymph nodes or spleen, although it lacks the organized T- and B-cell areas .Bone marrow microenvironment provides appropriate support for T cells to develop in the absence of the thymus [(3)].

Approximately 8%–20% of bone marrow mononuclear cells are lymphocytes, with a T cell/B cell ratio of 5:1 [(4, 5)] Bone marrow lymphocytes are distributed throughout stroma and parenchyma, and condensed in lymphoid follicles. Approximately 1% of the bone marrow mononuclear population represents plasma cells, which can produce antibodies [(4, 5)].

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The hematopoietic tissue consists of a variety of cell types including, the blood cells and their precursors, adventitial/barrier cells, adipocytes, and macrophages. The hematopoietic tissue cells are not randomly arranged but demonstrate a particular organization within the tissue. For hematopoiesis to occur it must be supported by a microenvironment that is able to recognize and retain hematopoietic stem cells and provide the factors (e.g., cytokines) required to support proliferation, differentiation and maturation of stem cells along committed lineages. The hematopoietic microenvironment consists of adventitial reticular cells (e.g., barrier cells), endothelial cells, macrophages, adipocytes, possibly, bone lining cells (e.g., osteoblasts) and elements of the extracellular [6].

Pathogenesis of bone marrow infiltration in lymphoma:

Lymphomas may involve the bone marrow or the cortical bone. HD infiltrates the bone by direct extension; thus, the thoracic and lumbar spines are most frequently affected. Unlike in NHLs, HD may be more often sclerotic or mixed sclerotic and lytic. Primary cortical bone infiltration is almost always caused by NHLs, with a permeative osteolytic pattern in about 75% of cases. Primary NHLs most frequently involve the appendicular skeleton, in particular the metaphysis of the femur, humorous, or tibia, whereas secondary bone lymphoma more frequently involves the spine. There are 5 major patterns of bone marrow infiltration in patients with non-Hodgkin lymphoma: focal non Para trabecular, focal Para trabecular, intra sinusoidal, diffuse interstitial and diffuse solid [7].

There has been increasing recognition that lymphomas of follicle origin, including follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma, may manifest in the marrow as typical or atypical follicle formation [8].

Bone involvement in lymphoma:

Bone marrow involvement in Hodgkin's disease (HD) or aggressive non-Hodgkin's lymphoma (NHL) indicates advanced stage of disease and also poor prognosis. However, bone marrow infiltration (BMI) is not uncommon and can occur in patients at seemly early stage of disease. The incidence of lymphoma bone marrow involvement ranges approximately 5–21% in HD patient [9] 30–50% in NHL patients [10] and as high as 50–80% in low-grade NHL [10, 11].

Bone marrow biopsy: Marrow involvement confers a poorer prognosis than involvement of liver, lung or osseous bone. Infiltration of bone marrow is often

Patchy, particularly in higher grade lymphomas, this explains the increased diagnostic yield from bilateral as compared to with unilateral iliac crest bone marrow biopsies. Bone marrow biopsy commonly changes the pathological state, usually from stage III to stage IV [12].

Magnetic Resonance Imaging (MRI)

MRI is sensitive imaging modality for detection of **bone marrow disease** with affected areas having low T1 signal and high STIR signal. MRI can result in upstaging in as many as 33% of patients with negative iliac crest biopsies. Occasional false-negative studies are seen, usually where there is microscopic infiltration (less than 5%) with low-grade lymphoma. Focal deposits as small as 3-5 mm can be identified. This has some clinical significance, patients with a positive.

MRI study having a significantly poorer prognosis regardless of bone marrow biopsy findings. In follow-up of previously infiltrated bone marrow areas, MRI is useful as it can differentiate sclerosis, fat and edema from tumor; however, there may be false positives in those patients who have received radiotherapy [13].

PET/CT in Diagnosing Bone Marrow Infiltration:

FDG PET-CT was recently evaluated as a supplementary lymphoma staging method for BM involvement in several studies.

However, the question of whether it can reduce the need for BM biopsies at the iliac crest is still not approved [9, 14].

Early studies with FDG PET reported a high discrepancy and variable effectiveness of FDG PET for identifying BM infiltration .However, more recent studies have indicated that FDG PET is highly specific (specificity of 91–100%) for detection of BM involvement by lymphoma and has 100% PPV for BM involvement as confirmed by post FDG PET biopsy [9,15]**.**

Chen-Liang et al, in retrospective study done of 372 patients (140 patient has HL and the other 232 has high grade B-NHL) comparing PET/CT and BMB regarding bone marrow infiltration demonstrated that PET/CT has a high accuracy for the evaluation of BM involvement in HL but it is not as compliant in HG B- NHL. In HL PET/CT resulted in upstaging of 21 patients to stage IV while one patient was under staged. Where in NHL using PET CT alone in diagnosing BM infiltration resulted in upstaging of 47 patients to stage IV while 25 patients were under staged [16].

Diffuse Bone Marrow Uptake:

Diffuse homogeneous FDG uptake in the axial and appendicular skeletons often reflects benign enhancement owing to inflammation or cytokine release; however, bone marrow involvement cannot be entirely excluded [7].

Figure 1; showed a case of HD with diffuse bone marrow uptake likely hyperplasia.

Salaun et al 2009, [17] perform study with total number of 106 patients underwent 18F-FDG PET/CT for initial staging of HL. Bone marrow uptake level was assessed visually according to liver uptake and semi-quantitatively using the maximum standardized uptake value (SUV max) measured in the sacral area. They concluded that diffuse BMU at initial staging of HL could be due to bone marrow involvement but more likely to bone marrow inflammatory change [17].

In patients with chemotherapy followed by bone marrow stimulants such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, the bone marrow will have diffuse, increased FDG accumulation. Therefore, diffuse bone marrow FDG uptake is commonly attributable to the effect of hematopoietic cytokines.

However, diffuse bone marrow FDG uptake can also be caused by bone marrow involvement by malignancy [18].

Figure 2; showed a patient with solitary focal FDG bone marrow uptake likely infiltration.

The sensitivity of FDG PET CT differs greatly according to the pathological subtype of lymphoma. It showed better sensitivity in patients with Hodgkin's disease and in aggressive histologic types of non-Hodgkin's lymphoma than in patients with less aggressive histologic types [14].

Fuster et al [19] investigated the role of FDG-PET *vs* bone marrow disease in detecting bone marrow disease in patients with HL and NHL and found out that FDG-PET was more sensitive than BMB in HL and NHL with the exception of Grade 1 and 2 follicular lymphomas. Their findings were consistent with those of Pakos et al regarding the overall accuracy and high sensitivity of PET compared with BMB.

Whereas, bone marrow biopsy (BMB) showed better sensitivity in HL (76%) and in aggressive NHL, while FDG-PET gave false negative results in two-thirds of patients with bone marrow involvement in more indolent histological forms of NHL [17].

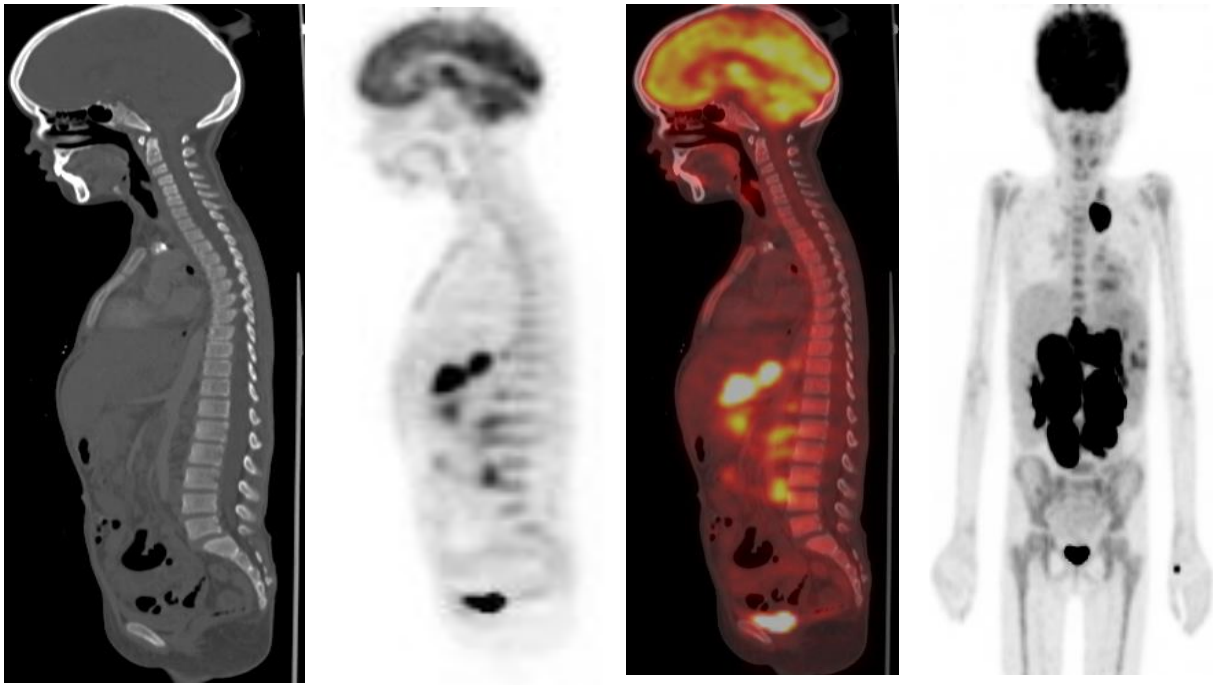

Figure (1): PET CT of known case of HD with diffuse FDG bone marrow uptake likely due to hyperplasia.

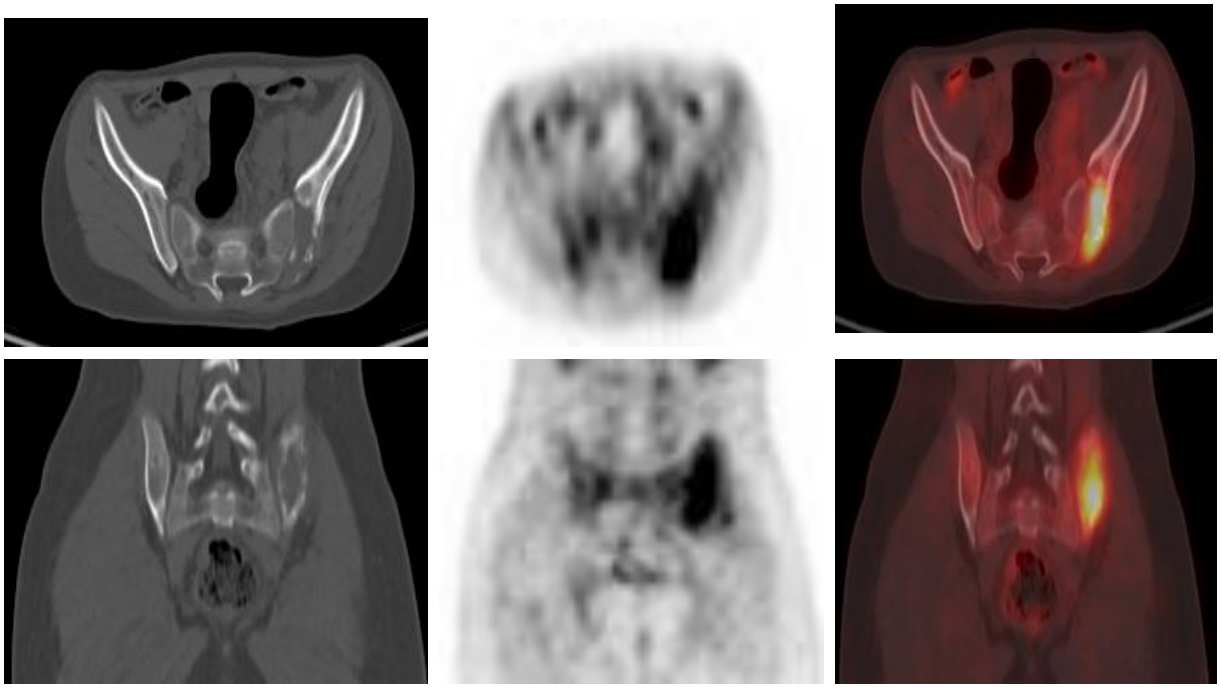

Figure (2): Initial pretreatment PET/CT revealed metabolically solitary active FDG avid destructive osseous lesion at the left iliac bone.

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