

Enhanced 2-deoxy-2- (¹⁸F) fluoro-D-glucose (FDG) Uptake on PET-CT Due to a Benign Condition and Hodgkin's Lymphoma

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Abstract

The utility of FDG PET-CT in documenting malignant disease has been demonstrated for many disease processes. However, non-malignant causes for FDG PET-CT enhancement exist. Here we present an example of a 12 year-old male diagnosed with Hodgkin's lymphoma that underwent an FDG PET-CT for evaluation and initial staging. The scan demonstrated disease in the chest and abdomen in addition to focal uptake in the left distal tibia that was considered to represent a focus of disease. Unexpectedly, as the disease was treated, the focal uptake in the leg did not decrease prompting additional CT and conventional radiograph imaging, which found that the lesion was consistent with Non-Ossifying Fibroma (NOF). This case illustrates that FDG PET-CT can identify both malignant disease and benign bone lesions that may masquerade as metastatic disease.

Keywords: Non-ossifying fibroma; Hodgkin's lymphoma; FDG PET-CT; Tibia

Non-standard Abbreviations: FDG: 2-deoxy-2- (¹⁸F) fluoro-D-glucose; GLUT: Glucose transporter; NOF: Non-ossifying fibroma; PET: Positron emission tomography

The use of 2-deoxy-2- (¹⁸F) fluoro-D-glucose (FDG) PET-CT as a tumor imaging modality was first proposed by Som et al. [1] and originally demonstrated in cerebral gliomas [2]. Its use was based on the principle that more aggressive malignancies have increased glucose uptake. This enhanced uptake is due to the increased expression of GLUT-1 transporters on the cell surface, facilitating the enhanced movement of glucose into the cell. Malignant cells commonly have increased levels of hexokinase as well resulting in increased glycolysis [3]. Increased hexokinase also enhances the phosphorylation of glucose tagged with FDG to trap it within the cell [3]. It has been proposed that degree of FDG activity should correlate with the grade of the musculoskeletal tumor [4,5].

Studies suggest that FDG PET demonstrates a clear distinction between benign and malignant lesions [3]; however, a clear correlation between the degree of FDG uptake and malignant potential of osseous lesions has been questioned. While SUVs (standardized uptake values) may correlate with the aggressiveness of tumors, there is significant overlap between benign and malignant tumors [6]. For example, it has been reported that inflammatory lesions including rheumatoid arthritis, chronic osteomyelitis and sarcoidosis exhibit significant hypermetabolic activity (enhanced 2-FDG activity) [7]. The mechanism of this enhanced uptake is attributed to the activity of macrophages and granulation tissue [8]. The cellular components of primary bone tumors are heterogeneous, often composed of giant and histiocytic cells. The presence of these cell types, derived from the monocyte-macrophage cell lineage, may contribute to the FDG avidity of these lesions [6]. NOF is one of several types of benign lesions including giant cell tumors, chondroblastoma, Langerhans cell histiocytosis, fibrous dysplasia, enchondroma, osteoid osteoma, and hemangioma that may be also be FDG avid on FDG PET-CT [6]. Several studies have noted increased FDG uptake in NOF lesions [9-13] (Figure 1).

A. The initial whole body PET-CT scans demonstrated multiple areas of FDG uptake within the mediastinum, right hilum extending

into the lower neck, and the right supraclavicular region. Additional sites of a bulky hypermetabolic conglomerate of lymph nodes were noted in the portahepatic and portocaval regions. A focus of FDG uptake was also identified in the lower third of the left tibia that correlated (corresponded to) with the activity identified on the bone

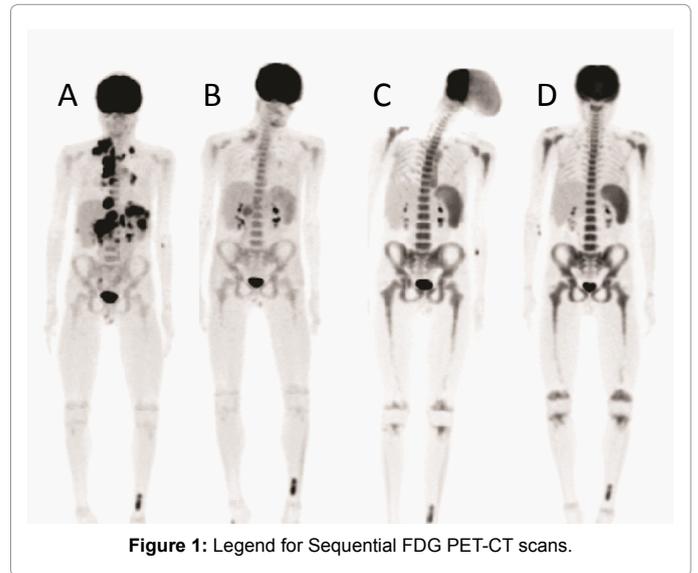


Figure 1: Legend for Sequential FDG PET-CT scans.

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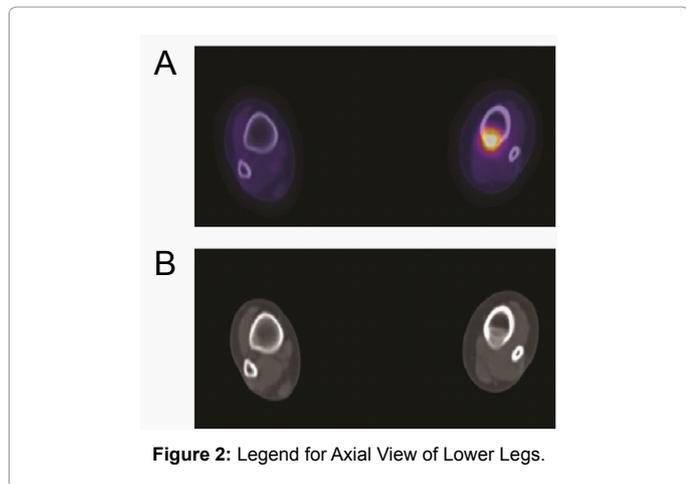
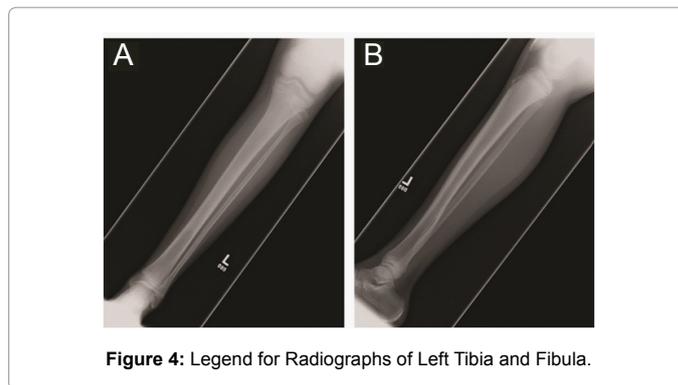
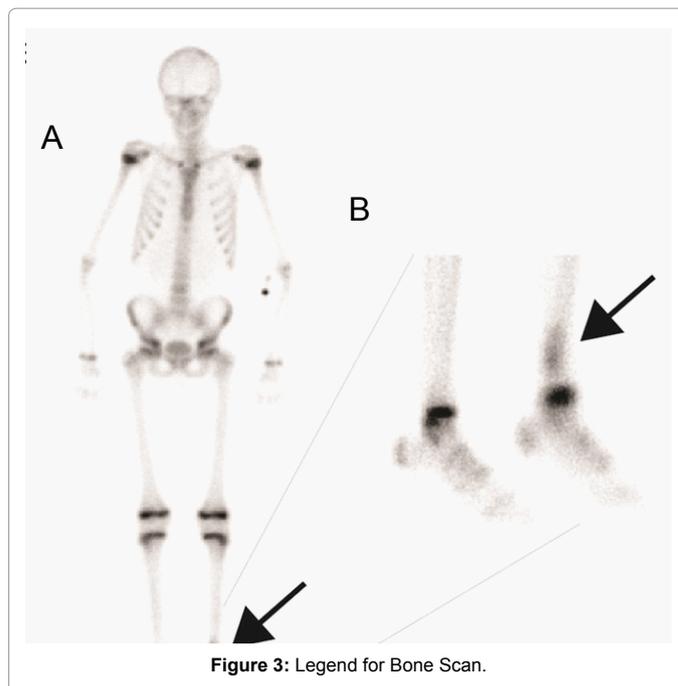
scan. B, C. Subsequent PET-CT scans were performed after initiation of R-CHOP chemotherapy with resolution of uptake in the chest and abdomen with persistent uptake in the lower left leg. Increased areas of uptake in the upper humeri, femora, epiphyseal joints of the bilateral legs and along the length of the spine are compatible with increased marrow activity in response to chemotherapy, best appreciated on the PET-CT scans from 1 month (B) and 2 ½ months after the initiation of chemotherapy (C). D. The PET-CT scan performed 4 months after the initiation of chemotherapy (10 days after the end of his 4th cycle of chemotherapy) showed no residual FDG activity consistent with regression of the Hodgkin's lymphoma. PET-CT detected complete restoration of FDG activity in areas of previous hematopoiesis marrow activation (Figure 2).

A. An axial section of the lower legs demonstrate localized hypermetabolic (2-FDG) activity by PET-CT in the medioposterior aspect of the left tibia. B. The corresponding co-registered CT image demonstrates an osteolytic lesion (lower right) with subtle cortical thinning at the posterior margin of the femur that extends into the medullary cavity (Figure 3).

A. Whole body bone scans and B. Spot view of the lower legs revealed mildly increased linear radiotracer uptake in the distal third of the left tibia (arrow). No other areas of abnormal uptake were noted. Increased radiotracer activity is seen bilaterally at the epiphyseal growth plates of the shoulders, elbows, wrists, knees, pelvis, and ankles. The uptake on bone scintigraphy reflects increased blood flow and increased osteoblastic activity of the bone at sites of osteoclastic bone resorption [14] (Figure 4).

Bone scintigraphy is a sensitive but nonspecific modality for the diagnosis and evaluation of bone tumors [15]. It is beneficial in evaluation of multiple lesions within the same bone. Typically NOF lesions are inactive or minimally active on Tc-99m bone scans in children [16]. Lesions in a healing or involuted stage of development demonstrate faint to moderate uptake on delayed images on a three-phase bone scan [17]. It has been documented that NOF can show increased radiotracer uptake on bone scans related to the stage of development of the lesion [17]. Markedly increased radiotracer uptake can be seen in lesions that ossify [18,19]. During the healing phase, mild uptake can be seen on blood pool images on a three-phase bone scan [17]. The increased radionuclide uptake reflects underlying osteoblastic activity.

Non-ossifying fibromas are typically solitary, however, multiple



lesions in a single patient have been described [20,21]. A small percentage of patients with multifocal NOF have associated underlying neurofibromatosis [20,22,23]. In cases of disseminated NOF associated with extra-skeletal abnormalities that include ocular anomalies, cardiovascular defects, mental retardation, café-au-lait spots, cryptorchidism or hypogonadism, the constellation of findings has been recognized as the Jaffe-Campanacci syndrome [24,25].

Given the concern of possible malignant involvement of the left tibia, a radiograph of the left lower leg was performed. A. AP and B. lateral radiographs of the left lower leg demonstrate a similar appearance to that seen on the CT portion of the FDG PET-CT exam. A cortical based lucent lesion in the lower third of the left tibia was identified without associated periosteal reaction or bone destruction. No fracture was identified. The margins of the lesion are indistinct without sclerosis. The findings were consistent with NOF.

The term NOF were first coined by Jaffe and Lichenstein in 1942 after showing that these lesions were of fibrous tissue origin [26]. NOF is a common benign osseous lesion of the skeletal system with an estimated incidence of 30% of the normal population during the first 2 decades of life; it has a male predominance (2:1) and is rarely

seen after the age of 20 [27]. The terms non-ossifying fibroma (NOF), fibrous cortical defect, and metaphyseal fibrous defect are applied to the same metaphyseal fibrohistiocytic process [28]. NOF are typically found in the long tubular bones, the majority of lesions present in the distal femur followed by the tibia [28,29]. Fifty percent of lesions are bilateral or multiple [30], most commonly in the distal femur and tibia [28,29,31]. NOF is uncommonly found in the upper extremity, however can occur in the proximal humerus and distal radius [28,29]. Rare occurrences of NOF may occur in the hands and ulna [32]. During periods of growth and remodeling, the lesion can "migrate" into the diaphysis and fill in with fibro-osseous growth becoming radiopaque [33].

Disappearance of the lesions is noted in the long bones as they grow in length traveling away from the metaphyseal region. Over time, NOF typically undergo spontaneous regression and consolidate with sclerosis along the periphery combined with ossification within the interior of the lesion [25]. However, a small number of cases can persist and proliferate into the medullary cavity [30,34]. The uncommon occurrence of NOF in adults is indirect evidence that lesions are characterized by spontaneous regression over time [35].

NOFs demonstrate a unique radiographic appearance that is typically diagnostic. In the long tubular bones, lesions are located eccentrically, emanating from the cortex, with bulging of the overlying cortex that can be thinned over the lesion [36]. Lesions are most commonly located in the metaphysis near or adjacent to the epiphysis. A scalloped line of sclerosis may demarcate the inner border of the lesion. NOF are eccentric cortical-based lesions that frequently have thin, sclerotic border that is scalloped. The greatest length of the lesion is parallel to the long axis of bone [28,29]. The clinical course of NOF lesions are variable and typically asymptomatic, often identified by happenstance on radiography taken for unrelated reasons as was the case for this patient. Clinically, lesions are typically silent, however patients may present with pain in cases of pathologic fractures. Pathologic fractures can occur in lesions that measure more than 33 mm in length and involve more than 50% of the transverse diameter of bone are at increased risk for fracture [35]. Lesions in the fibula typically involve the entire width of the bone [35].

In summary, FDG PET is known to be able to help classify many radiographic findings as malignancies, but at the same time is also non-specific, and can have increased tracer uptake in many benign lesions, especially in bone tumors such as NOF. In such cases, it is the radiographic findings that help differentiate abnormal uptake as being that of a benign versus a malignant etiology. There are no universal parameters for PET to define malignancies from benign lesions, but within a histologic group PET appears to correlate well with further defining a lesion. Functional imaging additionally assists in classifying the histologic activity in the bone. Thus, in bone lesions, both the functional and anatomic imaging is used to complement each other to help separate benign from malignant findings, as well as the histopathologic activity of the tumor.

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