Non-Specific Disease Mimicking Malignancy: Two Cases of FDG Uptake in the Extremities

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Abstract FDG PET is an imaging technique used to assess regional differences in glucose metabolism. A variety of diseases, including malignancy, can show abnormal FDG uptake in bone marrow. PET/CT demonstrated non-specific uptake in the extremities of two patients with fever of unknown origin (FUO). Both patients showed focal and symmetric FDG uptake in the bone marrow of the arms and legs. Although the results of these cases were not diagnostic, the unique uptake pattern of PET/CT should be considered a non-specific reactive change as well as malignancy or other possibilities in the initial differential diagnosis.

Keywords FDG-PET · FUO · Bone marrow

Introduction

F-18 fluorodeoxyglucose (FDG) accumulates in neoplastic cells and activated inflammatory cells. FDG positron emission tomography (PET) can be considered for diagnostic workup of fever of unknown origin (FUO) as well as for cancer evaluation [1, 2]. In previous studies, FDG PET was reported to be helpful for diagnosis in 25–69% of FUO cases [1–3]. The common causes of FUO detected by FDG PET include a variety of malignancies, most notably: colon cancer, sarcoma, Hodgkin's disease and non-Hodgkin's lymphoma. Several infectious diseases such as atypical

pneumonia, spondylitis, infected prosthesis and occult abscess were also associated with FUO as detected by FDG PET. In addition, noninfectious inflammatory diseases such as vasculitis were also successfully diagnosed using FDG PET [1, 4, 5].

We report two cases of malignancy mimicking non-specific changes, as detected by FDG PET, in the bone marrow of the extremities of patients experiencing FUO.

Case Report

Case 1

A 28-year-old female, married and employed as a nurse, was admitted to the hospital after experiencing intermittent high fever for 4 months. The patient also had arthralgia in both hands and feet without swelling or tenderness. Cardiovascular, pulmonary-respiratory, alimentary tract, skin and neurological evaluations were all unremarkable. A fever of up to 39°C persisted but was tolerable. The laboratory findings showed a WBC count of 2,040/l (normal range 4,000–10,000/l) with 46.1% lymphocytes (normal range 20–44%), 11.9 g/dl Hgb (normal range 12–16 g/dl), 162 k/l platelets (normal range 140–440 k/l), 61 mm/h ESR (normal range 0–25 mm/h), 128 U/l AST (normal range 10–35 U/l), 107 U/l ALT (normal range 0–40 U/l) and 424 U/l LDH (normal range 15–550 U/l). CRP was reactive by qualitative analysis. Tuberculin test was negative. Urinalysis, blood culture, autoantibody and serologic tests for viral infection showed non-specific results. Peripheral blood smear revealed no morphological changes. Serum PEP (protein electrophoresis) showed a mild chronic inflammatory condition. The chest X-ray, abdominal USG and the echocardiography were all normal.

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Fig. 1 **a** FDG PET/CT whole body image showed abnormal uptake in elbow, wrist and lower extremities. SUVmax was 5.9 in the left calcaneus. **b** MRI (T2-weighted) image of the left foot showed diffuse and abnormally increased signal intensity in the calcaneus and distal tibia. No evidence of mass or abscess formation, and no evidence of

arthritic findings suggestive of leukemia or lymphoma were observed. **c** Biopsy was also done in the left calcaneus showing lymphocyte infiltration. This observation is more consistent with a reactive or inflammatory process

The patient underwent FDG PET/CT to better identify the cause of her fever. F-18 FDG was injected and imaged 1 h later with Discovery ST (GE Medical Systems, Milwaukee, WI). FDG PET/CT whole body images showed abnormal uptake in the elbow, hand and lower extremities. The focal and symmetric uptake pattern was consistent with the arthralgia sites (Fig. 1). MRI was done 2 days after PET/CT in the sites of abnormal uptake (hand and foot), and a biopsy was also taken 3 days after PET/CT in the left calcaneus. PET/CT and MRI led to the suspicion of malignancy, but the biopsy result was more consistent with a reactive or inflammatory process. During hospitalization, the patient received conservative treatment with broad-

spectrum antibiotics. After 1 week of hospitalization, the fever subsided, and the arthralgia resolved.

Case 2

A 28-year-old woman presented with persistent fever for 3 weeks, occurring most notably at night, newly developed diarrhea, and arthralgia of the left ankle and proximal interphalangeal joints. The patient's history and clinical examinations were non-specific for a fever focus. The laboratory findings showed a WBC count of 4,930/l, 10.9 g/dl Hgb, 281 k/l platelets, 106 mm/h ESR, 6.84 mg/dl CRP (normal range <0.5 mg/dl), 31/48

Fig. 2 **a** FDG PET/CT image showed abnormal uptake in both lower extremities. SUVmax was 5.9 in the right calcaneus. **b** MRI image showed a diffusely increased signal intensity in the marrow of both tibiae and right medial femoral condyle; no evidence of soft tissue abscess, cystic or other mass formation was observed

U/I AST/ALT and 563 U/I LDH. Serum PEP suggested an acute inflammatory condition. The urinalysis, peripheral blood and serologic tests for infection and autoimmune disease were all negative. The blood culture produced no growth, and the tuberculin test was also negative. Chest X-ray, abdominal CT and echocardiography were all normal.

The patient underwent FDG PET/CT to identify the cause of her persistent fever. The FDG PET/CT demonstrated focal FDG uptake in the marrow of the long bones of both lower legs (Fig. 2). MRI was done to assess lesions identified on the PET/CT 3 days later and showed increased signal intensity in the marrow of both tibiae as well as the right medial femoral condyle, suggestive of diffuse marrow disease such as leukemia or lymphoma. However, tissue biopsy was not performed, and the symptoms ultimately resolved spontaneously.

Discussion

FUO can be caused by a variety of disorders including infection, neoplasm and noninfectious inflammatory diseases [6–10]. The diagnostic approach in FUO includes repeated physical examination and thorough history as well as standardized laboratory tests and simple imaging procedures. Nevertheless, there is still a need for more complex or invasive techniques to improve diagnosis. FDG PET/CT can play a role in the diagnostic workup. This technique utilizes radioactive tracers that can accumulate in focal disease processes and guide additional specific testing. It is usually performed as a whole-body procedure allowing delineation of both the location and the number of foci, including the identification of sites that are not clinically suspected. The percentage of FDG PET scans helpful in the diagnostic process of patients with FUO, as reported in the literature, varies between 25% and 69%, reflecting the wide range of possible causes of fever [1, 11–14]. Noninfectious inflammatory diseases encompass 15%–30% of all causes of FUO [7], and the clinical value of FDG PET in noninfectious inflammatory diseases is relatively well established in large-vessel vasculitis. There are also case reports of adult-onset Still's disease, Crohn's disease, sarcoidosis and subacute thyroiditis detected by FDG PET.

In this report, we observed focal and symmetric FDG uptake in the bone marrow of the extremities of two patients with reactive or non-specific inflammation, which may have been associated with lymphocyte infiltration. The clinical diagnosis was not confirmed. Activated lymphocytes showing an increased FDG uptake may explain and identify the fever focus. However, possible alternative explanations for why the fever focus is not at the sites of increased FDG uptake have to be considered. It is quite possible that proliferation of bone marrow might occur

from osteoporotic processes as a result of severe inflammatory reactions [15, 16]. In this situation, the bone formation might be related to the increased uptake. In the present cases, the uptakes of the bone marrow were focal and symmetric in periarticular sites of both extremities and not diffuse as demonstrated in other reactive marrow uptake patterns [17]. We therefore speculate these other explanations are not plausible for our cases. However, there are no reference standards to compare the FDG uptake identified in the long bones of these patients with FUO. When FDG-PET demonstrates a focal and symmetrical uptake in periarticular sites of both extremities in patients with FUO, non-specific reactive changes as well as other explanations should be considered in the initial differential diagnosis.

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