

Missed causative tumors in diagnosing tumor-induced osteomalacia with ^{18}F -FDG PET/CT: a potential pitfall of standard-field imaging

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Keywords: Tumor osteomalacia
 -Field of imaging -Pitfall in imaging

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Received:

21 December 2015

Accepted revised:

15 February 2016

Abstract

Objective: We describe herein two tumor-induced osteomalacia (TIO) cases for whom the causative lesions, located in their popliteal fossa, that were not identified in the standard field of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT), which usually images only the head, trunk, and proximal parts of the extremities. **Clinical Presentation and Intervention:** A 47 years old Japanese man with multiple pathological fractures due to osteomalacia, accompanied by muscle weakness, hypophosphatemia, and an elevation of alkaline phosphatase (ALP) was referred to our hospital. A ^{18}F -FDG PET/CT scan was performed, but no ^{18}F -FDG uptake was detected in the standard field of imaging. Magnetic resonance imaging revealed a small subcutaneous tumor (1.9×1.2×0.6cm) of the left posteromedial knee, displaying uniform enhancement on gadolinium-enhanced T1-weighted fat-suppression imaging. The tumor was resected widely and diagnosed as phosphaturic mesenchymal tumor, mixed connective tissue variant (PMTMCT). The other patient was a 31 years old Japanese woman with multiple pathological fractures, hypophosphatemia and elevated ALP and was referred to our hospital on suspicion of TIO. Although the causative lesion was not identified in the standard field of ^{18}F -FDG PET/CT, ^{18}F -FDG uptake (SUVmax 2.9) was detected on the right knee in the additional whole-body ^{18}F -FDG PET/CT. Magnetic resonance imaging revealed a soft-tissue tumor (6.4×4.1×2.9cm) in the right posterior knee. Following biopsy, the tumor was marginally resected, and was pathologically diagnosed as PMTMCT. **Conclusion:** Once patients are suspected to have TIO, a whole-body nuclear imaging study such as ^{18}F -FDG PET/CT should be performed, in order not to miss the hidden causative tumor, especially occurring in the distal extremities.

Hell J Nucl Med 2016; 19(1):46-48

Epub ahead of print: 1 March 2016

Published online: 1 April 2016

Introduction

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic disorder of abnormal phosphate and vitamin D metabolism, caused by secretion of the phosphaturic hormone, fibroblast growth factor 23 (FGF23) by a phosphaturic mesenchymal tumor (PMT) [1-4]. A patient with TIO usually complains of bone pain, myalgia and fatigue [1-3]. Since these symptoms are common and rather unspecific, patients often remain undiagnosed or misdiagnosed for years [3-5]. Complete resection of the causative tumor is the only regimen to cure this disease [1-3, 5-7]. Phosphaturic mesenchymal tumor is known to show intense uptake of fluorine-18-fluorodeoxy glucose (^{18}F -FDG), positron emission tomography/computed tomography (PET/CT) was reported to be a useful tool for seeking the causative lesion [3, 8-10]; however, there is a diagnostic pitfall. We describe herein two TIO cases for whom the causative lesions located in their popliteal fossa were not identified in the standard field of PET/CT, which images only the head, trunk, and proximal parts of the extremities.

Case 1

A 47 years old Japanese man with multiple pathological fractures due to osteomalacia, accompanied by muscle weakness, hypophosphatemia, and an elevation of alkaline phosphatase (ALP) was referred to our hospital. Bone mineral density (BMD) decreased in the lumbar vertebrae (T-score, -3.9), total hip (-0.9), and the femoral neck (-1.3). Since

the patient was suspected to have TIO, venous sampling of FGF23 from the extremities was performed. The values of all samples were higher than normal (85-100pg/mL, normal range 10-50pg/mL), but there were no differences among the samples. In order to detect the causative tumor, a ^{18}F -FDG PET/CT scan was performed, but no ^{18}F -FDG uptake was detected in the standard field of imaging (Figure 1A). We sampled venous blood once again, and this time we found that the sample from the left femoral vein showed the highest value (218pg/mL). Additional MRI revealed a small subcutaneous tumor (1.9×1.2×0.6cm) of the left posteromedial knee, displaying uniform enhancement on gadolinium-enhanced T1-weighted fat-suppression imaging (Figure 1B, C). The tumor was resected widely and diagnosed as PMT, mixed connective tissue variant (PMTMCT). The serum FGF23 value of the patient was undetectable (<10pg/mL) on the morning after the surgery. Pain was relieved quickly, and serum phosphorus recovered to within the normal range. Four months after surgery, BMD were improved in the lumbar vertebrae (T-score, -1.9), total hip (0.5), and the femoral neck (-0.1).

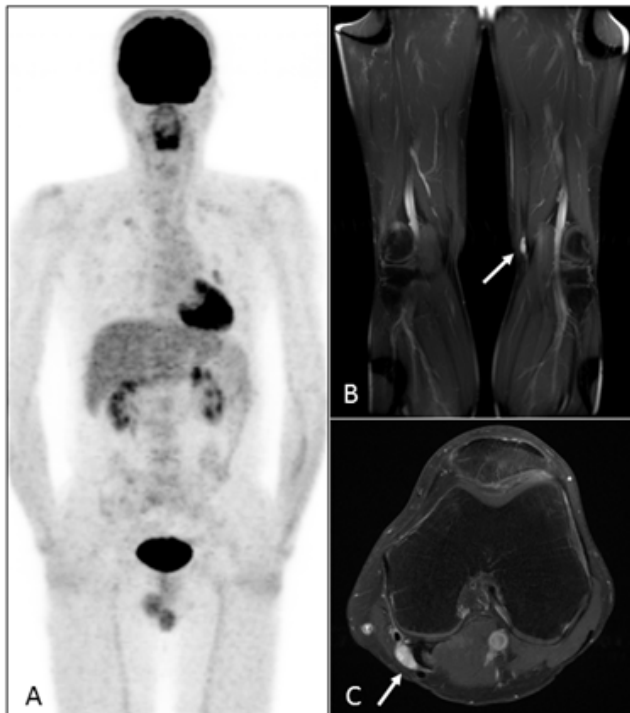


Figure 1. The planar image of the standard field of ^{18}F -FDG PET/CT showed no abnormal ^{18}F -FDG uptake in Case 1 (A). Coronal (B) and axial (C) MRI revealed a small tumor on the left posterior knee, displaying uniform enhancement on gadolinium-enhanced T1-weighted fat-suppression imaging.

Case 2

A 31 years old Japanese woman with multiple pathological fractures, hypophosphatemia and elevated of ALP, was referred to our hospital on suspicion of TIO. ^{18}F -FDG PET/CT with standard imaging field had been taken at the primary hospital, but abnormal uptake was not detected (Figure 2A).

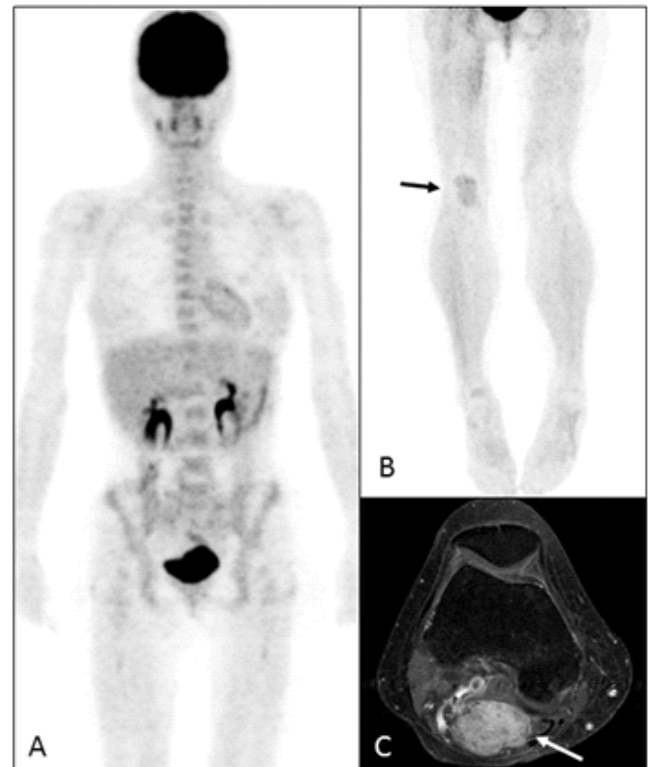


Figure 2. There was no abnormal ^{18}F -FDG uptake in the standard field of the ^{18}F -FDG PET/CT scan of Case 2 (A). Whole-body ^{18}F -FDG PET/CT (B) demonstrated ^{18}F -FDG uptake in the right knee. MRI showed a tumor in the popliteal fossa that displayed heterogeneous enhancement on gadolinium-enhanced T1-weighted fat-suppression imaging (C).

Fibroblast growth factor 23 measurement of selective venous samples from her extremities found the highest values (319pg/mL) from her right femoral vein. Since the causative tumor was suspected to exist in her right lower extremity, whole-body ^{18}F -FDG PET/CT was performed additionally and ^{18}F -FDG uptake (SUVmax 2.9) was detected on the right knee (Figure 2B). Additional MRI revealed a soft-tissue tumor (6.4×4.1×2.9cm) in the right posterior knee displaying heterogeneous enhancement on gadolinium-enhanced T1-weighted fat-suppression imaging (Figure 2C). Following biopsy, the tumor was marginally resected, and was pathologically diagnosed as PMTMCT. Two days after the surgery her serum FGF23 value decreased to within normal range (13-22pg/mL). The patient recovered from hypophosphatemia and multiple bone pain within a month. Seventeen months after the operation, she had no signs of recurrence.

Discussion

In the histopathological classification of PMT as a causative tumor of TIO, mixed connective tissue variant is the most common subtype (70%-80%) so as the present cases, and the other subtypes, osteoblastoma-like, ossifying fibroma-like or nonossifying fibroma-like variants are less common [11].

For detecting the causative tumor of TIO, various conventional imaging studies, such as MRI [12], ¹⁸F-FDG PET/CT [3, 8-10], thallium-201 scintigraphy [13], technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) single-photon emission tomography (SPET) [13], and ^{99m}Tc bone scintigraphy [2] have been used. Recently, the expression of various somatostatin receptors (SSTR1-5), particularly SSTR2, in the causative tumors of TIO have been reported [14-16]. Therefore, somatostatin-based functional scans, ¹¹¹In-pentetreotide or octreotide scintigraphy [15-17], ^{99m}Tc-HYNIC-TOC SPET/CT [18,19], ⁶⁸Ga-DOTATATE PET/CT [19], ⁶⁸Ga-DOTANOC PET/CT [20-23] are useful for seeking the causative tumor of TIO, especially, ⁶⁸Ga-DOTANOC is recognized as a highly sensitive and specific tracer for imaging of SSTR overexpression [21-23]. Although widely used standard peptides such as ¹¹¹In-DOTATOC has sole affinity for SSTR2, ⁶⁸Ga-DOTANOC has a high affinity for SSTR5 as well as SSTR2 [22, 23]. Jadhav et al. (2014) reported that ⁶⁸Ga-DOTATATE and ^{99m}Tc-HYNIC TOC SPET/CT are more sensitive than ¹⁸F-FDG PET/CT [19]. In Japan, however, since somatostatin-based functional scans are uncovered by the national health insurance, we usually use ¹⁸F-FDG PET/CT for detecting the causative tumors of TIO.

Since the causative tumor of TIO can occur in nearly every part of the body [2-4, 6, 19], and it may be small or obscure [19], a causative tumor occurring in the distal extremities may be missed in the standard field of nuclear imaging, which usually covers the cranium to the proximal thigh [24]. Unfortunately, it is hard to say that the necessity of whole-body field in seeking the causative tumors of TIO is widely known among the clinicians including the radiologists. In daily clinical practice, whose common aim is seeking the visceral cancers, we usually check only in the standard field in order to reduce the inspection time and radiation exposure level of our personnel. In the present case 1, though the values of venous FGF23 from the extremities were high, only standard field imaging of PET/CT was examined. In case 2, a young female underwent full-dose ¹⁸F-FDG PET/CT twice for seeking the causative tumor whose radiation exposure could be reduced by single PET/CT with whole-body field.

In conclusion, this report suggests that once patients are suspected to have TIO, a whole-body nuclear imaging study such as ¹⁸F-FDG PET/CT should be performed, in order not to miss the hidden causative tumor, especially occurring in the distal extremities.

The authors declare that they have no conflicts of interest

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