Successful Localization Using ^{68}Ga -DOTATOC PET/CT of a Phosphaturic Mesenchymal Tumor Causing Osteomalacia in a Patient with Concurrent Follicular Lymphoma

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Received: 10 August 2018 / Revised: 29 August 2018 / Accepted: 3 September 2018 / Published online: 12 September 2018
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Abstract

Diagnosing tumor-induced osteomalacia is often challenging because conventional imaging modalities may fail to locate the responsible tumor. This report describes the ability of ^{68}Ga -DOTATOC PET/CT to successfully distinguish between the responsible phosphaturic mesenchymal tumor and concurrent lymphoma lesions. A 52-year-old man with bone pain for several years was diagnosed with a vitamin D-resistant hypophosphatemic osteomalacia. Whole body ^{18}F -FDG PET/CT revealed multiple enlarged hypermetabolic lymph nodes in his bilateral cervical, axillary, mediastinal, abdominal, pelvic, and inguinal regions. Core needle biopsy of the right cervical lymph node confirmed the diagnosis of follicular lymphoma. However, lymphoma was not considered the cause of osteomalacia. ^{68}Ga -DOTATOC PET/CT before chemotherapy showed a small nodule with intensely increased uptake in the right inguinal region, which was distinguished from the other enlarged lymph nodes. The nodule was surgically removed and histopathologically consistent with phosphaturic mesenchymal tumor. After surgery, the patient's serum phosphorus and alkaline phosphatase levels normalized without nutritional supplement.

Keywords PET/CT · ^{68}Ga -DOTATOC · Hypophosphatemia · Oncogenic osteomalacia · Phosphaturic mesenchymal tumor

Introduction

Tumor-induced osteomalacia (TIO) is a type of rare paraneoplastic disease. Early diagnosis and accurate localization of the responsible tumor are important, as its complete surgical resection is the treatment of choice. However, conventional imaging modalities, such as CT and MRI, are ineffective in localizing phosphaturic mesenchymal tumors of mixed connective tissue type. The diagnostic performance of ^{18}F -FDG PET/CT is superior to that of conventional imaging modalities [1], but the sensitivity and specificity of ^{18}F -FDG PET/CT are suboptimal [2, 3]. By contrast, many studies have reported that somatostatin receptor-based functional PET/CT has high sensitivity and specificity, and plays a crucial role in localizing TIO [2, 4, 5]. This report describes a patient with vitamin D-resistant osteomalacia, in whom the responsible phosphaturic mesenchymal tumor (PMT) was successfully distinguished from concurrent lymphomatous lesions using ^{68}Ga -DOTATOC PET/CT.

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Case Report

A 52-year-old man was referred to the oncology clinic of our institution for further evaluation of hypermetabolic lymph nodes found on recently performed ^{18}F -FDG PET/CT. The patient had complained of pain in his neck, back, waist, left hip, and right arm. One and a half years earlier, he had first visited a local hospital for right chest pain. Chest X-rays showed no abnormality, but dual energy X-ray absorptiometry measurements of bone mineral density of the lumbar spine showed osteoporosis (T score -3.4), and laboratory tests showed a low serum phosphorus concentration (1.3 mg/dL ; normal range $2.5\text{--}4.5\text{ mg/dL}$). Initial bone scan showed increased radiotracer uptake by multiple foci, suggesting multiple fractures in bilateral ribs, the sacrum, both ilia, and the left calcaneus (Fig. 1a). The total reabsorption of phosphorus (TRP) was $78.1\text{--}82.1\%$, so it indicated renal phosphate wasting. Following a diagnosis of hypophosphatemic osteomalacia, he was treated with the active form of vitamin D and phosphate, but hypophosphatemia persisted, suggesting a diagnosis of TIO. One month before surgery, ^{18}F -FDG PET/CT was performed to locate the tumor causing his vitamin D-resistant hypophosphatemia. ^{18}F -FDG PET/CT revealed multiple enlarged hypermetabolic lymph nodes in the cervical, axillary, mediastinal, abdominal, pelvic, and inguinal regions, and a diffuse hypermetabolic spleen suggesting lymphomatous involvement (Fig. 2).

Initial laboratory tests showed a decreased serum phosphorus concentration (2.1 mg/dL ; normal range $2.5\text{--}4.5\text{ mg/dL}$), an increased alkaline phosphatase concentration (183 IU/L ; normal range $40\text{--}120\text{ IU/L}$), and slightly elevated concentrations of uric acid (7.5 mg/dL ; normal range $3.0\text{--}7.0\text{ mg/dL}$) and alanine aminotransferase (60 IU/L ; normal range $0\text{--}40\text{ IU/L}$). Other laboratory test results, including serum calcium and intact parathyroid hormone levels, were within the normal range.

Fig. 1 **a** Anterior (left) and posterior (right) views of initial $^{99\text{m}}\text{Tc}$ HDP whole body bone scans in this patient, showing multiple foci of increased uptake in the bilateral ribs, sacrum, both ilia, and the right calcaneus. **b** Follow-up $^{99\text{m}}\text{Tc}$ HDP whole body bone scan images after 18 months of vitamin D and phosphate supplementation show more foci of increased uptake in bilateral ribs, L-spine, sacrum, both ilia, and both calcanei

Follow-up bone scan showed multiple new fractures in his bilateral ribs, L-spine, and left calcaneus (Fig. 1b). Contrast-enhanced computed tomography (CT) of the neck, chest, abdomen, and pelvis revealed multiple enlarged lymph nodes with homogeneous enhancement in the cervical, axillary, mediastinal, abdominal, pelvic, and inguinal regions. Immunohistochemical staining of a core needle biopsy sample of his right cervical level IV lymph node resulted in a diagnosis of follicular lymphoma. However, the lymphoma was not considered the cause of osteomalacia.

To identify the tumor that induced osteomalacia, ^{68}Ga -DOTATOC PET/CT was performed. This modality showed a 1-cm-sized nodule with intensely increased ^{68}Ga -DOTATOC uptake in the right inguinal region, distinguishing this lesion from the low uptake of ^{68}Ga -DOTATOC in the cervical, axillary, mediastinal, abdominal, pelvic, and inguinal lymph nodes (Fig. 3). Retrospective review of the abdominal and pelvic CT scans of this patient showed a 1-cm-sized round, homogeneously enhanced nodule in the right inguinal region, adjacent to multiple enlarged lymph nodes (Fig. 4). The right inguinal nodule was surgically removed. Immunohistochemical examination of a biopsy sample revealed a low-grade oval to spindle cell tumor with collagenized to myxoid matrix, osteoclast-like multinucleated giant cells, and typical staghorn-like hemangiopericytic vessels (Fig. 5). These findings were consistent with PMT.

After surgical excision, the patient's serum phosphorus level increased to 4.4 mg/dL , and his alkaline phosphatase level normalized to 95 U/L within 1 month. All laboratory test results were within the normal range, except that his uric acid concentration was 7.6 mg/dL . The patient received 4 cycles of bendamustine and rituximab chemotherapy for the treatment of follicular lymphoma, with follow-up ^{18}F -FDG PET/CT after chemotherapy showing a complete metabolic response.

Discussion

This report describes the successful use of ^{68}Ga -DOTATOC PET/CT to localize the responsible tumor causing osteomalacia in a patient with concurrent multiple lymphomatous lesions throughout his entire body. Variable imaging modalities were performed to localize his PMT, but ^{18}F -FDG PET/CT failed to localize PMT due to the presence of concurrent follicular lymphoma. By contrast, ^{68}Ga -DOTATOC PET/CT was able to distinguish PMT from concurrent multiple follicular lymphoma lesions. Although contrast-enhanced CT showed the PMT as a small, homogeneously enhanced nodule, this modality failed to recognize this lesion because of the concurrent presence of multiple enlarged lymph node lesions.

Although the rate of hypophosphatemia is not low, most patients can be treated successfully with vitamin D or phosphate replacement therapy [6, 7]. Rarely, hypophosphatemia may be resistant to vitamin D or phosphate replacement

Fig. 2 **a** Anterior maximum intensity projection (MIP) ^{18}F -FDG PET/CT image, showing multiple enlarged lymph nodes with increased areas of FDG uptake in the cervical, axillary, mediastinal, abdominal, pelvic, and inguinal regions, and diffusely increased FDG uptake in the spleen, which were interpreted as lymphomatous involvement. Scanning also showed multiple fractures of the bilateral ribs and both calcanei, with mildly increased FDG uptake. **b** Fused ^{18}F -FDG PET/CT axial images, showing multiple lesions with increased FDG uptake in both inguinal regions. A small nodule with moderately increased FDG uptake, finally confirmed as a PMT (white arrow), could not be distinguished from lymphomatous lesions with increased FDG uptake (yellow arrow)

Fig. 3 **a** Anterior maximum intensity projection (MIP) ^{68}Ga -DOTATOC PET/CT imaging, showing a focus of intensely increased ^{68}Ga -DOTATOC uptake in the right inguinal region (red arrow), and multiple foci of low ^{68}Ga -DOTATOC uptake in multiple fractures of the bilateral ribs, L-spine, sacrum, and bilateral calcanei. Lymph nodes of the cervical, axillary, mediastinal, abdominal, pelvic, and inguinal regions showed no or weak ^{68}Ga -DOTATOC uptake. **b** Fused ^{68}Ga -DOTATOC PET/CT axial images of the inguinal region, showing a focus of intensely increased DOTATOC uptake (white arrow, SUVmax = 24.0), which could be distinguished from the lymphomatous lesions with weak ^{68}Ga -DOTATOC uptake in adjacent lymph nodes (yellow arrow, SUVmax = 3.4)

Fig. 4 Abdominal and pelvic computed tomography, showing a small, round, homogeneously enhanced nodule (white arrow), distinguished from other enlarged lymph nodes (yellow arrow), in the right inguinal region

therapy. However, the exact prevalence of TIO remains unclear because of its low prevalence and difficulties in diagnosing this condition.

Four types of mesenchymal tumors can cause osteomalacia: (1) PMTs of mixed connective tissue type, (2) osteoblastoma-like tumors, (3) ossifying fibrous-like tumors, and (4) nonossifying fibrous-like tumors [8]. PMT of mixed connective tissue type is the most common type. Most PMTs secrete fibroblast growth factor 23 (FGF23) and cause renal phosphate wasting [9]. This leads to reductions in serum phosphorus and serum 1,25-dihydroxyvitamin D3 (calcitriol) levels [10], and the occurrence of osteomalacia. The sensitivity of serum FGF23 for detection of PMTs has been reported to be ~70–100% [11–13], and it has recently been used to detect PMTs and to monitor recurrence after surgery [5, 14–17].

Despite serum FGF23 levels being a marker for TIO, locating the causative tumor is challenging. About 50% of PMTs occur in the bones and about 50% occur in the soft tissue, with occurrence in the skin being rare [18–21]. PMTs are usually found in the pelvis and lower extremities but may also be found in the sinonasal tract [3, 19, 22, 23]. PMTs are usually small in size, with these small PMTs being round or oval in shape, as well as being well-defined, isodense or hypodense, and homogeneously enhanced on CT. MRI showed that these lesions were isointense compared with the muscles, hyperintense on T2-weighted images, and homogeneously enhancing on contrast-enhanced T1 weighted images. However, it is difficult to localize PMT with CT or MRI because of their small size [18] and nonspecific findings [24].

Because of the limitations of conventional imaging modalities, various combinations of functional and anatomical imaging are often used diagnostically, with many studies recommending ^{18}F -FDG PET to locate PMTs [25–27]. Because PMTs usually express somatostatin receptor type 2A [5, 28], somatostatin receptor PET/CT, such as ^{68}Ga -DOTATATE, ^{68}Ga -DOTATOC, or ^{68}Ga -DOTANOC PET/CT, has been used to detect

Fig. 5 **a** Pathologic examination, showing that the tumor had a variegated appearance. **b** The tumor consisted of low-grade oval to spindle tumor cells embedded in a collagenized to myxoid matrix. Also observed were osteoclast-like multinucleated giant cells and typical staghorn-like hemangiopericytic vessels. Hematoxylin and eosin staining; original magnification **a** $\times 40$ and **b** $\times 100$

PMTs [29]. Immunohistopathological expression of somatostatin receptor type 2 correlated well with ^{68}Ga -DOTATOC uptake [30]. The sensitivities of ^{18}F -FDG PET/CT and somatostatin receptor PET/CT have been reported to be ~36–100% [4, 14, 15, 17, 31] and ~41–100% [2, 4, 5, 16, 17, 31, 32], respectively. Studies directly comparing ^{18}F -FDG PET/CT with somatostatin receptor PET/CT [4, 17, 31] found that somatostatin receptor PET/CT performed better. The sensitivities of somatostatin receptor PET/CT were variable in different studies because some responsible tumors causing osteomalacia do not express SSTR receptors. In addition, pitfalls of somatostatin analogs including osteoblastic reaction and inflammatory processes may mask responsible tumors [32, 33]. The sensitivity of ^{18}F -FDG PET/CT was not high, probably because of the benign nature of PMT. Moreover, nonspecific uptake of FDG led to the low specificity of ^{18}F -FDG PET/CT, especially when PMT was located in the head [4]. The present study showed increased uptake of ^{18}F -FDG by variable malignant tumors, suggesting that this modality may have low specificity. Taken together, these findings suggest that somatostatin receptor PET/CT should be the first-line imaging tool to locate the tumor responsible for TIO.

Compliance with Ethical Standards

Conflict of Interest Sejin Ha, Sujin Park, Hyunji Kim, Heounjeong Go, Seung Hun Lee, Ji Yoon Choi, Jung Yong Hong, and Jin-Sook Ryu declare that they have no conflicts of interest.

Ethical Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the respective institutional research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent The study protocol was approved by the institutional review board of our institute, which waived the requirement for informed consent due to the retrospective nature of the study (IRB no. 2018-1391-0001).

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