Bone 64 (2014) 222–227

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

^{68}Ga DOTA-TATE PET/CT allows tumor localization in patients with tumor-induced osteomalacia but negative ^{111}In-octreotide SPECT/CT

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ARTICLE INFO

Article history:
Received 23 December 2013
Revised 27 March 2014
Accepted 14 April 2014
Available online 24 April 2014

Edited by Sharmila Majumdar

Keywords:
Tumor-induced osteomalacia
Oncogenic osteomalacia
Octreotide scintigraphy
Hypophosphatemia
^{68}Ga DOTA-TATE PET/CT
FGF23

ABSTRACT

Tumor-induced osteomalacia (TIO) is a paraneoplastic syndrome characterized by renal phosphate wasting, hypophosphatemia and low calcitriol levels as well as clinical symptoms like diffuse bone and muscle pain, fatigue fractures or increased fracture risk. Conventional imaging methods, however, often fail to detect the small tumors. Lately, tumor localization clearly improved by somatostatin-receptor (SSTR) imaging, such as octreotide scintigraphy or octreotide SPECT/CT. However, recent studies revealed that still a large number of tumors remained undetected by octreotide imaging. Hence, studies focused on different SSTR imaging methods such as ^{68}Ga DOTA-NOC, ^{68}Ga DOTA-TOC and ^{68}Ga DOTA-TATE PET/CT with promising first results. Studies comparing different SSTR imaging methods for tumor localization in TIO are rare and thus little is known about diagnostic alternatives once a particular method failed to detect a tumor in patients with TIO.
Here, we report the data of 5 consecutive patients suffering from TIO, who underwent both ^{111}Indium-octreotide scintigraphy (^{111}In-OCT) SPECT/CT as well as ^{68}Ga DOTA-TATE PET/CT for tumor detection. While ^{111}In-OCT SPECT/CT allowed tumor detection in only 1 of 5 patients, ^{68}Ga DOTA-TATE PET/CT was able to localize the tumor in all patients. Afterwards, anatomical imaging of the region of interest was performed with CT and MRI. Thus, successful surgical resection of the tumor was achieved in all patients. Serum phosphate levels returned to normal and all patients reported relief of symptoms within weeks. Moreover, an iliac crest biopsy was obtained from every patient and revealed marked osteomalacia in all cases. Follow-up DXA revealed an increase in BMD of up to 34.5% 1-year postoperative, indicating remineralization. No recurrence was observed.
In conclusion our data indicates that ^{68}Ga DOTA-TATE PET/CT is an effective and promising diagnostic tool in the diagnosis of TIO, even in patients in whom ^{111}In-OCT prior failed to detect a tumor.

Introduction

Tumor-induced osteomalacia (TIO) – synonymously known as oncogenic osteomalacia (OOM) – is a rarely occurring paraneoplastic syndrome caused by phosphaturic mesenchymal tumors leading to renal phosphate wasting. TIO is often caused by small benign tumors that can occur almost anywhere in the body and cause no significant symptoms itself due to their small size [1,2]. Patients suffering from TIO complain about sudden onset of myalgia, skeletal pain, recent history of fatigue fractures and increased fracture risk [3]. Blood and urine analyses are characterized by an absolute or relative reduction of calcitriol (1,25(OH)2D3), elevated alkaline phosphatase (AP) levels and, most notably, by hyperphosphaturia and subsequent hypophosphatemia [4–6]. At the end, the combination of renal phosphate wasting and calcitriol deficiency leads to osteomalacia, generalized disturbances in skeletal mineralization and thus to an increased fracture risk in patients with TIO [7]. This is caused by factors secreted by the tumors, so-called phosphatonins [8]. The most commonly found and best-characterized phosphatonin in TIO is FGF23 [5,9].

TIO can be cured completely by surgical removal of the tumor. However, the major problem in treating TIO is still to localize the small, slow growing and clinically silent tumors and thus often months or even years pass from the first onset of symptoms to the successful treatment of TIO [7,10–12]. Due to the fact that these tumors can occur almost

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http://dx.doi.org/10.1016/j.bone.2014.04.016
8756-3282/

anywhere in the skeleton as well as the soft tissue, conventional radiological methods such as X-ray, computed tomography (CT) or magnetic resonance imaging (MRI) are limited in the primary detection of the causative tumors [5,11,13,14].

Tumors in TIO are known to express somatostatin receptors (SSTR); in particular, SSTR2/2A has been found to be the predominant subtype in TIO causing tumors [7,15,16]. Thus, recent studies reported improved tumor localization in patients with TIO by using somatostatin receptor imaging methods such as ^{111}Indium-octreotide scintigraphy (^{111}In-OCT), ^{99m}Tc-octreotide scintigraphy (^{99m}Tc-OCT), and ^{111}In-OCT with single photon emission computed tomography (SPECT/CT) [7,11,14,17–19]. However, a large number of suspected tumors still remained undetectable. Preclinical studies showed a pharmacological superiority of ^{68}Ga-octapeptides in imaging of SSTR2-expressing cells and hence SSTR positive tumors compared with ^{111}In-labeled peptides [20] Thus, recent studies focused on other SSTR imaging methods such as ^{68}Ga DOTA-NOC, ^{68}Ga DOTA-TOC and ^{68}Ga DOTA-TATE Positron Emission Tomography/Computed Tomography (PET/CT) [21–25]. Whereas first results appear promising, most studies focused on just one particular method. Studies comparing the effectiveness of octreotide SPECT/CT to DOTA-TATE, DOTA-NOC or DOTA-TOC PET/CT in the diagnostic of TIO are, however, rare and thus little is known about diagnostic alternatives once tumor localization by a particular method in patients with TIO was not successful.

Therefore, we present the data from 5 patients with suspected TIO who underwent both, ^{111}In-OCT SPECT/CT, as well as ^{68}Ga DOTA-TATE PET/CT for tumor localization.

Material and methods

Study cohort

Five patients (3 women and 2 men) with an average age of 50.2 ± 8.9 years (range 41–62 years) were referred to our clinic between 2008 and 2012 with a history of bone and muscle pain of unknown cause, depression, fatigue, increased frequency of fatigue fractures and abnormal laboratory findings. A male patient (case I) presented with a recent history of bilateral, atraumatic, femoral neck fractures. None of the patients had any history of cancer or kidney disease. Two patients had already been treated for TIO by administration of oral phosphate supplements and calcitriol. However, the phosphate as well as the calcitriol serum levels remained decreased and no clinical improvement was observed.

A detailed medical history and physical examination (PE) was obtained from every patient. All patients were subsequently subjected to a detailed laboratory analysis of bone metabolism, including blood and urine samples, as well as a 24-hour urine analysis (Table 1). Written informed consent was obtained from all patients to participate in this study. If vitamin D deficiency was detected and no contraindications to a high-dose vitamin D therapy were present, patients were given oral high-dose cholecalciferol therapy (Dekristol 20000 IU; mibe GmbH Arzneimittel, Germany) once a week. After normalization of vitamin D metabolism, supplementation was reduced to 1000 IU cholecalciferol daily (Vigantoletten, Merck, Darmstadt, Germany).

Moreover, following the guidelines of the German Society of Osteology (DVO), [26] bone mineral density (BMD) was determined for the lumbar spine and both proximal femur using dual-energy X-ray absorptiometry (DXA) bone densitometry (Lunar Prodigy, Lunar Corporation, Madison, WI, USA) before and 1 year after surgical removal of the tumor.

Imaging

Once TIO was suspected, all patients underwent whole body somatostatin receptor scintigraphy after intravenous (i.v.) injection of ^{111}In-OCT. The administered dose of ^{111}In-OCT was 150 MBq. Anterior and posterior whole-body planar images were obtained 4 and 24 h after injection. If a high focal uptake was observed, an immediate single photon emission computed tomography (SPECT/CT) scan of the region of interest was obtained. The acquisition was performed in a Symbia-T SPECT Camera (Siemens) with a FOV (Field-of-View) of 53.3 × 38.7 cm, or on an e.cam variable angle SPECT camera with a FOV of 53.3 × 38.7 cm.

Moreover, all patients underwent further investigation by ^{68}Ga DOTA-TATE PET/CT. Imaging was performed using a full ring PET/CT scanner (Biograph LSO DUO; Siemens, Erlangen, Germany) with a reconstructed image resolution of 6-mm full-width at half maximum (FWHM) and a 16-cm axial FOV. A mean of 78 MBq (58–110 MBq) ^{68}Ga DOTA-TATE was injected intravenously and the acquisition was started 20 min post-injection (p.i.) [27]. The whole body scan comprised up to 14 bed positions with an emission time of 4 min per bed position (Fig. 1). The examination lasted for 56 min. The attenuation correction was performed using the two-slice low-dose-whole-body spiral-CT (Somatom Emotion duo) integrated in the PET/CT-scanner. A maximum-likelihood algorithm (OSEM, two iterations, and eight subsets) was used for iterative reconstruction. All analyses were done from head to toe, however, due to technical reasons the whole body PET maximum intensity projection (MIP) were subdivided into two overlapping parts: the trunk and the lower extremities. The pathological accumulations were compared with the low-dose-CT and standard uptake values (SUVmax) were determined for the tumor-like skeletal or soft tissue lesions (Fig. 1). PET images were read by experienced nuclear medicine physicians without knowledge of the ^{111}In-OCT findings; CT scans were read by trained radiologists (knowing the PET findings) (Fig. 1). Once, focal uptake was observed by ^{68}Ga DOTA-TATE PET/CT, all patients underwent anatomical imaging of the identified region of interest by CT and MRI.

Histopathological analysis

The resected specimens were fixed in buffered formalin. Tumor tissue samples were laminated, embedded in paraffin way and stained with hematoxylin and eosin (Fig. 2A). All slides were reviewed, and representative sections from the formalin-fixed, paraffin-embedded tissue blocks were examined using automated immunohistochemistry systems. The freshly cut sections were loaded into a PT Link module (Dako, Glostrup Denmark) and subjected to an antigen retrieval/dewaxing protocol with the Dako EnVision FLEX Target Retrieval Solution, high pH, and then transferred to the Dako Autostainer Link 48 instrument. Immunostainings were performed using the primary antibody SSTR2A (ZYTOMED, Ref. RBK046-05, dilution 1:100) and the Dako EnVision Flex detection system (Fig. 2B). Microscopic analyses

Table 1
Characterization of patients, imaging and histopathological results.

Case	Age	Sex	^{111}In-OCT scintigraphy	^{68}Ga DOTA-TATE PET/CT	Tumor localization	Histopathological diagnosis	SSTR 2A
I	41	Male	Negative	Positive	Right lateral foot	PMTMCT	+
II	57	Female	Negative	Positive	Left maxilla	Odontogenic tumor	+
III	44	Female	Negative	Positive	Cervical vertebra	PMTMCT	+
IV	48	Male	Negative	Positive	Right mandible	Odontogenic tumor	+
V	62	Female	Positive	Positive	Right forearm	PMTMCT	+