Original Article

Ga-68 DOTATATE Positron Emission Tomography-Computed Tomography Imaging in Oncogenic Osteomalacia: Experience from a Tertiary Level Hospital in South India

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Abstract

Aim: Utility of Ga68 DOTATATE PETCT imaging to localise cause for oncogenic osteomalacia (OOM). **Materials and Methods:** Retrospective analysis between March 2015 to March 2018 of all patients with a clinical diagnosis (based on a combination of clinical history, hypophosphatemia and elevated FGF-23 values) of OOM who underwent Ga-68 DOTATATE PET/CT. **Results:** Total of 27 patients had undergone Ga-68 DOTATATE PET/CT imaging in our centre from March 2015 to March 2018. Of these 16 patients with clinically suspected oncogenic osteomalacia were included in our study. Age range 18-61 years of which 12 were males. Total of 13 (81.25%) patients were found to be positive on imaging for a possible mesenchymal tumour. Most common site of tumour was the lower limb (76%). Most common presenting symptom was bone pain (81%) followed by muscle weakness (19%). Overall, 10 patients underwent surgery, all of whose biopsy was reported as phosphaturic mesenchymal tumour. During the three month follow up, serum phosphorous measured in 15/16, post-surgical/ medical treatment had normalised in all except two patients who had undergone only medical therapy with neutral phosphate. Fall in FGF-23 was more pronounced in surgically treated patients as compared to those who received medical treatment. **Conclusion:** Ga68-DOTATE PET/CT is a useful investigatory modality for localizing cause for oncogenic osteomalacia.

Keywords: *Fibroblast growth factor-23, Ga-68 DOTATATE positron-emission tomography-computed tomography, oncogenic osteomalacia, phosphaturic mesenchymal tumor*

Introduction

Oncogenic osteomalacia (OOM), also known as tumor-induced osteomalacia (TIO), is a paraneoplastic syndrome caused by small mesenchymal tumors. The first case of OOM was described by Robert McCance in 1947.[1] In general, it presents with bone pain, fractures, and muscle weakness associated with persistent hypophosphatemia due to renal phosphate wasting, normal or low 1,25(OH) 2D, and elevated or inappropriately normal fibroblast growth factor-23 (FGF-23).[1,2]

The main factor responsible is FGF-23 that acts at the proximal renal tubule, inhibits phosphate reabsorption and 1α-hydroxylation of 25-hydroxyvitamin D, leading to hypophosphatemia and ultimately osteomalacia.[1,3] Since the symptoms are relatively nonspecific and phosphate levels are not usually included in many routine metabolic panels, hypophosphatemia is often overlooked and patients are misdiagnosed with a variety of skeletal, rheumatologic, or neuropsychiatric diseases.[4]

The tumors can be located anywhere from head to toe in bones as well as soft tissue and are often too small in size to localize. Detecting these occult mesenchymal tumors (OMT) is of utmost importance, as they are completely curable after resection.[1,3] OMT express somatostatin receptors and so functional imagings that utilize somatostatin analogs are the most sensitive.[5,6] The superiority of Ga-68 DOTATATE (Ga-68 $DOTA^0$-Ty^3 octreotate) among the various functional imaging tracers lies in its higher affinity for somatostatin receptors 2 and 5.[7]

On the basis of our experience with various functional imaging modalities, this study aimed to validate the use of Ga-68 DOTATATE positron-emission tomography-computed tomography (PET/CT) in localizing the OMT.

How to cite this article: John JR, Hephzibah J, Oommen R, Shanthly N, Mathew D. Ga-68 DOTATATE positron emission tomography-computed tomography imaging in oncogenic osteomalacia: Experience from a Tertiary Level Hospital in South India. Indian J Nucl Med 2019;34:188-93.

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Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.IJNM_14_19

Quick Response Code:

Subjects and Methods

A total of 27 patients had undergone Ga-68 DOTATATE PET/CT imaging in our center from March 2015 to March 2018.

Inclusion criteria

All patients with a clinical diagnosis (based on a combination of clinical history, hypophosphatemia, and elevated FGF-23 values) of OOM who underwent Ga-68 DOTATATE PET/CT and a minimum follow-up period of 3 months were included in the study.

Exclusion criteria

Patients with incomplete clinical and laboratory data and those referred from other centers for only functional imaging were excluded from the study.

As a result, 16 patients were included in this study, and their detailed history, biochemistry, functional imaging, treatment modality, histopathology, and follow-up data were reviewed retrospectively.

Biochemical analysis

The biochemical parameters estimated were as follows: serum phosphate mg/dL (SP), serum calcium mg/dL (SCa), parathyroid hormones pg/mL (PTH), serum alkaline phosphatase (SAP), FGF-23 (C-terminal) RU/mL, 24-h urine phosphorous in mg/L, Vitamin D levels ng/mL, and tubular maximum for phosphate corrected for glomerular filtration rate (TMPGFR) mmol/L.

Functional imaging

After clinical and biochemical evaluation, patients were subjected to functional imaging, including Ga-68 DOTATATE PET/CT (done in all patients, n = 16), F-18 FDG-PET/CT (2/16), and Tc-99 m methyl diphosphonate (MDP) bone scintigraphy (7/16). Informed consent was obtained in all patients before imaging.

Ga-68 DOTATATE PET/CT imaging: Ga-68 was eluted on site from the $^{68}Ge/^{68}Ga$ generator and labeling done with DOTATATE. Around 75–185 MBq (2–5 mCi) was injected intravenously and imaging was done after 30–45 min. PET/CT was acquired from head to toe for all patients using Siemens Biograph True Point PET-CT. CT with intravenous contrast was used for anatomical characterization. The images were interpreted qualitatively by experienced nuclear medicine physicians. Focal increased uptake on PET with concordant lesions on CT were considered to be the culprit lesions.

All patients with positive Ga-68 DOTATATE PET/CT scans were treated either with surgical excision or medically managed with phosphate and Vitamin D supplements. Resected tumors were subjected to pathological review by experienced pathologist. Treatment response was determined by clinical assessment in terms of symptomatic improvement and normalization of SP and FGF-23 levels.

Statistical analysis

All data were analyzed and frequency distribution was done for categorical variables and presented as number and percentage. Descriptive statistics, such as the mean, standard deviation, and median with interquartile ranges for continuous variables, were calculated. Data were also represented graphically using tables and charts.

Results

A total of 16 patients with a definite clinical diagnosis of OOM (based on a combination of history, hypophosphatemia, and elevated FGF-23 values), underwent Ga-68 DOTATATE PET/CT imaging. Ga-68 DOTATATE PET/CT was positive in 13/16.

The baseline characteristics and imaging details of the 16 patients are given in Table 1.

There were 12 male (75%) and 4 female (25%). The mean duration of symptoms was 3.8 years and the mean age was 45 years (18–61 years). The most common presenting symptom was bone pain (81%), followed by muscle weakness (19%). The mean biochemical parameters were as follows: FGF 23 - 448 RU/mL (normal range: 21.6–91.0 RU/mL), serum phosphorous: 1.4 mg%, serum calcium: 8.9 mg%, serum alkaline phosphatase (ALP): 267 U/l (details not available for one patient), and serum Vitamin D: 33.5 IU (details not available for one patient).

Mean TMPGFR was calculated in 12 patients and was found to be 0.93 mg/dl (normal range 2.5–4.2 mg/dl). Tubular resorption of phosphate was measured from phosphate and creatinine levels in urine and serum samples before starting phosphate supplements. TMPGFR was calculated using the formula SP × (1− [(urine phosphorous/urine creatinine) × (serum creatinine/serum phosphorous)]). TMPGFR provides the most accurate assessment of renal phosphate handling.

Among the positive Ga-68 DOTATATE PET/CT scans (n = 13), 10 were in the lower limb, two in the head and neck (one in the right ethmoid and one in the left side of mandible), and one in the paravertebral soft tissue of D2 vertebra. Bone scintigraphy was done for 7/16, of which four scans showed areas of focal uptake at the site of fractures, two scans were suggestive of metabolic bone disease, and one scan was a normal study. However, OMT was not picked up in any of these patients.

Overall, 10 patients underwent surgery, and the biopsy was reported as phosphaturic mesenchymal tumor (PMT). Fourteen patients were treated with orally administered phosphorous supplements (neutral phosphate), and in eight patients, it was used as a bridging therapy till the suspicious mesenchymal lesion was excised surgically.

During the 3-month follow-up, only one patient had repeat Ga-68 DOTATATE PET/CT which showed no evidence of any residual lesion/new lesion.

Table 1: The baseline characteristics and imaging details of the 16 patients

Case	Age (year)	Sex	Symptom duration (year)	Presenting symptom	FGF-23 (RU/mL)	Serum phosphorous (mg) (%)	SCa (mg) (%)	SAP (U/L)	25-hydroxy Vitamin D	Suspicious site of primary tumor	HPE proven	HPE diagnosis
1	45	Male	4	BP	208	1.9	8.4	357	21.9	Head of the left femur	Yes	Consistent with phosphaturic mesenchymal tumor
2	53	Male	2	BP	1500	1.9	8.5	318	70	Left greater trochanter	Yes	Consistent with phosphaturic mesenchymal tumor
3	48	Male	5	BP	112	1.6	9	359	15	Right femur	Yes	Consistent with phosphaturic mesenchymal tumor
4	18	Female	4	BP	202	1.4	9.3	388	27	Right proximal tibia	Yes	Consistent with phosphaturic mesenchymal tumor
5	50	Female	3	BP	206	1.4	8.5	149	50.8	Right femur	Yes	Consistent with phosphaturic mesenchymal tumor
6	61	Male	4	BP	311	1.3	8.8	252	27	Left distal tibia	No	N/A
7	55	Female	5	BP	218	2.2	8.8	104	44	Left distal femur	No	N/A
8	50	Male	5	BP	226	1.7	9.2	423	20	Right ethmoid	No	N/A
9	55	Female	2	BP	1094	1.3	9.0	420	39	Left mandibular body	Yes	Consistent with phosphaturic mesenchymal tumor
10	39	Male	6	MW	152	1.1	9.2	236	14	Medial condyle of the right femur	Yes	Consistent with phosphaturic mesenchymal tumor
11	43	Male	3	BP	594	1.1	9.0	249	48	Neck of the right femur	Yes	Consistent with phosphaturic mesenchymal tumor
12	32	Male	6	MW	1433	0.9	9.5	253	22	Greater trochanter of the right femur	Yes	Consistent with phosphaturic mesenchymal tumor
13	59	Male	4	BP	344	1.0	9.3	386	20	Paravertebral soft tissue at D2 level	Yes	Consistent with phosphaturic mesenchymal tumor
14	36	Male	1	BP	191	2.0	9.3	50	50	Negative scan	No	N/A
15	32	Male	4	BP	206	1.4	8.9	70	ND	Negative scan	No	N/A
16	59	Male	3	MW	170	1.4	8.8	ND	35	Negative scan	No	N/A

BP: Bone pain, MW: Muscle weakness, HPE: Histopathology, ND: Not done, N/A: Not applicable, S.Ca: Serum calcium, SAP: Serum alkaline phosphatase, FGF: Fibroblast growth factor

Serum phosphorous measured in 15 patients, postsurgical/medical treatment had normalized in all except two patients who had undergone only medical therapy with neutral phosphate. Serum FGF-23 was measured in all patients before treatment, but only nine patients had follow-up levels assessed. The mean follow-up FGF-23 levels (postsurgical/medical treatment) were 133 RU/mL. Fall in FGF-23 was more pronounced in surgically treated patients as compared to those who received only medical treatment.

The patients not included in the study (11/27) were due to incomplete clinical and laboratory data or no follow-up.

Representative Ga-68 DOTATATE PET/CT images of three patients are shown in Figure 1.

Discussion

OOM is a rare disorder in which osteomalacia is associated with a benign tumor. In 1959, Prader *et al*. were the first to identify that the disease was the result of a tumor which secreted a "rachitogenic" substance and that resolution of the osteomalacia was noted on complete resection of the tumor.[8] FGF-23, which affects renal phosphate metabolism and bone mineralization,[9] was confirmed to be present at an elevated level in TIO patients in 2001.[10,11] Nearly 500 cases of TIO have been reported in the literature. Mean age of the diagnosis is 40–45 years with a wide age range, including cases reported in children. No significant predilection between sexes has been noted.[12]

In the present study, all 16 patients presented with adult onset, nonspecific bone pain, and muscle weakness which could have been attributed to a wide range of diseases. However, these patients had certain laboratory abnormalities in common such as decreased serum phosphorous and elevated ALP with normal serum calcium levels. All patients were initially treated with calcitriol (Bioactive Vitamin D), calcium, and orally administered phosphorous but with no improvement biochemically. Hence, a diagnosis of PMT was suspected and FGF-23 was done which was found to be elevated in all except three patients. The diagnosis of PMT was based on tumor localization on imaging and confirmed with histopathology reports.

All cases of hypophosphatemia should be evaluated to determine if it is the result of renal phosphate wasting, and this is done by calculating TMPGFR. Acquired hypophosphatemia due to renal phosphate wasting is most likely because of PMT, in which case small, benign PMT would be producing excess FGF-23.

Bone scintigraphy is a sensitive imaging modality for detecting osteoblastic lesions. Bone scan findings of TIO have been reported before with the patterns of abnormality not significantly different from osteomalacia caused by other etiologies, including malabsorption, renal failure, and Vitamin D deficiency. This can mislead the effort to localize the tumor and also should not be misread as features of metastatic tumor.[13] This study too shared the experience with previous authors that bone scintigraphy has not proven to be useful for localizing OOM.[14] Other functional imaging modalities are whole-body Tc-99m methoxyisobutylisonitrile scan and single-photon emission computed tomography, Tc-99m blood pool scintigraphy, Tl-201 scintigraphy and Somatostatin Receptor Scintigraphy (SSRS) with Tc-99 m hydrazinonicotinyl-Tyr3-Octreotide, In-111 octreotide, F-18 FDG-PET/CT, and Ga-68 DOTATATE PET/CT. Studies comparing conventional nuclear imaging and PET/CT showed that PET/CT scan is far better owing to its better spatial resolution and rapid whole-body tomographic imaging.[15]

Some studies promote the use of F-18 FDG-PET/CT for localizing PMT. FDG-PET/CT may be sensitive but is highly nonspecific and can identify areas of increased metabolism that are not related to the tumor such as areas of active fracture healing. Furthermore because of the low proliferative rate of PMT, the level of uptake of FDG can be altered.[16] Tumors associated with osteomalacia express somatostatin receptors, predominantly SSTR-2 subtype. Ga-68 DOTATATE, like octreotide is an antagonist of SSTR, which on receptor binding is internalized and results in the accumulation of radiotracer in the tumor cells.[17] A study done by Zhang *et al*. showed that Ga-68 DOTATATE PET/CT had a sensitivity of 100% and specificity of 90.9% with overall accuracy of 97.7% in the detection of OOM.[18] Another study by El-Maouche *et al*., in 2016, found that the sensitivity and specificity of Ga-68 DOTATATE PET/CT in localizing tumors was 54.5% and 85.7%, respectively.[2]

Histopathologically, OOM is classified as PMT by Weidner and subdivided into mixed connective tissue (MCT) variant, ossifying fibroma-like variant, nonossifying fibroma-like variant, and osteoblastoma-like variant. The most common variant (approximately 70%–80%) reported in the literature is PMT MCT.[19] PMT's are characterized by neoplastic cells that are spindle to stellate in shape, normochromatic with small nuclei and indistinct nucleoli. The nuclear grade is low, and mitotic activity is usually absent or very low.[1]

Following localization of PMT, definitive treatment is surgical resection with a wide margin to avoid the risk of disease relapse. Postoperative radiotherapy for margin positive tumors has been proposed, but data are limited.[3,20] Following resection, there is a rapid clinical recovery, with serum phosphorus and intact FGF-23 returning to normal within the first week in most patients, as was seen in this study as well.[21] An upcoming alternative is an image-guided ablation with radiofrequency or cryoablation in patients for whom surgery is not an option due to poor tumor accessibility. Although surgery remains the treatment of choice, image-guided ablation may be an effective alternative, less invasive, and safe treatment associated with short hospital stays.[22]

For patients without confirmed evidence of causative tumors, medical therapy with phosphorous supplementation and calcitriol is essential, with the goal of improving symptoms and healing osteomalacia, while maintaining phosphatemia in the lower end of the normal range, and PTH and ALP in the normal range.[1] Medical supplementation can also be used in the initial periods of assessment as a bridge therapy till surgery.

Late relapse due to local recurrence or distant metastasis is uncommon and is seen in <5% of patients with PMT. Hence, long-term follow-up is recommended with FGF-23 being used as a marker for the early detection of recurrences.[12,23] A benign PMT may occasionally progress to high-grade osteosarcoma.[24]

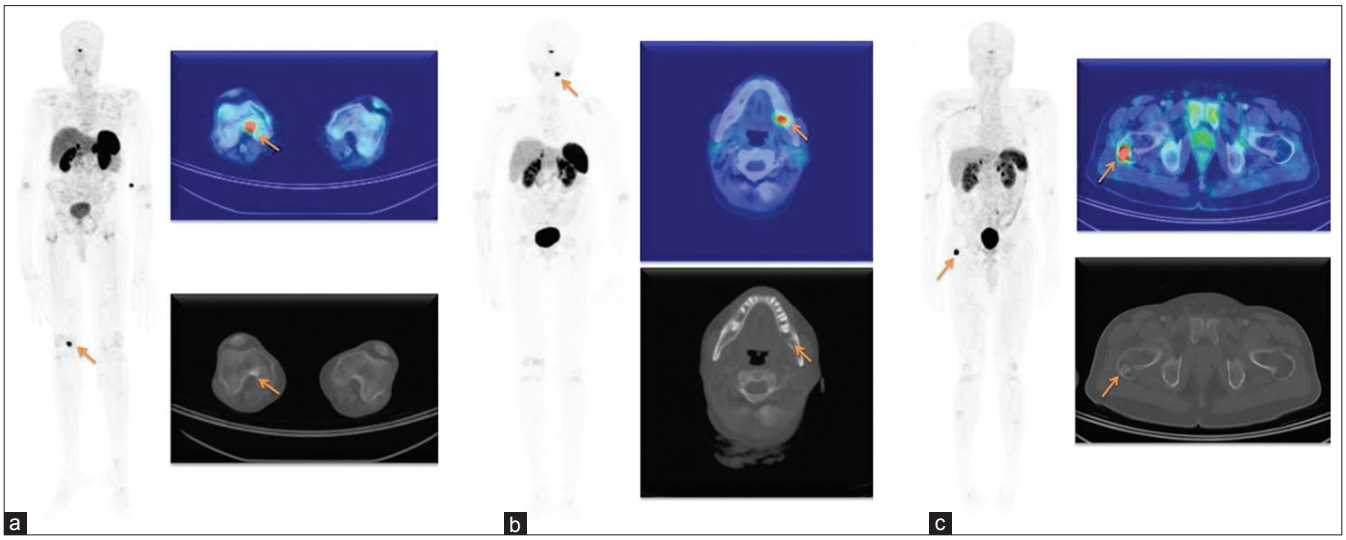

Figure 1: 68 Ga-DOTATATE positron-emission tomography-computed tomography anterior maximum intensity projection and cross-sectional images. All cases demonstrate intense focal radiotracer uptake in (a) Medial condyle of the right femur, (b) Left side of the mandible, and (c) Trochanter of the right femur. Physiological uptake noted in the pituitary, salivary glands, liver, spleen, and adrenals

The limitations of this study were the relatively small number of patients and that the follow-up periods were not long enough to detect probable recurrence. The fact that these tumors show avid tracer uptake in somatostatin-based tracer imaging suggests a probable role in the use of peptide receptor-based radionuclide therapy (PRRT) with Lu-177 DOTATATE in the management of patients with PMT. There has been one case report regarding PRRT in the management of PMT, but larger studies are still required to assess its usefulness further.[25]

Conclusion

Clinical diligence and perseverance are vital in the management of this rare but potentially debilitating entity, and hence, a systematic approach to hypophosphatemia helps in the early diagnosis and management of OOM. In patients presenting with musculoskeletal pain and severe muscle weakness, OOM should be considered as a possible cause. Assessment of serum phosphorous and FGF-23 levels in patients with probable PMT is vital. Ga-68 DOTATATE PET/CT plays a significant role in localizing the tumor and should be used early in the diagnostic workup. Surgical treatment is effective and results in good prognosis with normalization of biochemical parameters.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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