A Pictorial Essay of Somatostatin Receptor Imaging in Tumor-Induced Osteomalacia: A Single Institutional Experience

Abstract
Tumor-induced osteomalacia (TIO) is a rare cause of severe debilitating osteomalacia, due to hypophosphatemia. A strong clinical suspicion based on biochemical parameters can lead to the search for a culprit tumor in the body. The disease entity is more commonly caused by benign mesenchymal tumors. While many imaging modalities have been tried, it is now known that these tumors show high somatostatin receptor (SSTR) expression. Hence SSTR receptor imaging has emerged as a useful diagnostic tool. Here we present a series of TIO cases with clinical presentation and imaging characteristics.

Keywords: Fibroblast growth factor 23, hypophosphataemia, somatostatin receptor imaging, tumor-induced osteomalacia

Introduction
Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome, characterized by severe osteopenia and persistent hypophosphatemia. Patients may present with morbid symptoms of bone pain or muscle weakness, and clinically associated with insufficiency fractures and moderate to severe hypophosphatemia. Unless suspected, these patients often go through long series of investigations with no definite causative diagnosis, while the osteomalacia progresses. The syndrome is caused by renal phosphate wasting, leading to persistent hypophosphatemia. The basic pathogenesis is due to increased levels of circulating phosphatonin. The well-known phosphatonin is fibroblast growth factor 23 (FGF23), a 32 kDa polypeptide with 251 aminoacids. Other phosphatinons like secreted frizzled protein-4, matrix extracellular phosphoglycoprotein, fibroblast growth factor 7, and certain noncollagenous matrix proteins called SIBLING have also been reported. These phosphatonin causes phosphaturia, as well as inhibit renal 1α-hydroxylase, which mediates the activation of 25-hydroxy Vitamin D to 1,25-dihydroxy Vitamin D. Low levels of active Vitamin D results in impairment of intestinal absorption of phosphate and further deters mineralization of osteoid matrix.

Chong et al. proposed classification of TIO into primary and secondary. Primary TIO is associated with small clinically occult benign tumors of mesenchymal origin, classified as phosphaturic mesenchymal tumors (PMT). The most common of PMTs is PMT MCT (mixed connective tissue variant), others being PMT osteoblastoma-like, ossifying-fibroma-like, and nonossifying-fibroma-like variants. Approximately 53% of reported cases of TIO occur in the bone, 45% in the soft tissue, and 2% in the skin. Tumor localization and removal result in dramatic clinical and biochemical improvement. Secondary TIO is the syndrome of phosphate wasting which is associated with other pathologies such as prostate cancer, neurofibromatosis I, epidermal naevus syndrome, and fibrous dysplasia.

The dilemma in diagnosing and locating the possible culprit lesion in primary TIO is that these PMT are often small, occasionally in unusual locations, and hence difficult to localize with conventional imaging.

On radiological evaluation, X-rays typically show osteopenia. X-rays may reveal Insufficiency fractures or Looser’s zones may appear. Stress fractures are
usually bilateral and symmetrical and tend to occur at specific sites. These are pathognomonic for the presence of osteomalacia.[11-13] However, location of the primary benign tumor causing TIO is very rare on plain X-ray.

On computed tomography (CT) scans, these tumors appear as small, well-defined round or oval lesions which show significant enhancement due to their vascular nature. On magnetic resonance imaging (MRI), these lesions are isointense to muscles on T1-weighted (T1W) imaging and markedly hyperintense on T2-weighted (T2W) imaging. They show marked enhancement on postcontrast T1W fat-suppression imaging. However, these modalities do not have whole-body coverage, leading to missing of lesions at unusual sites. Moreover, the imaging findings on both CT and MRI of these small nodular lesions may be nonspecific, making them difficult to diagnose with high confidence. This precludes the use of whole-body MRI in the routine localization of these tumors.

Molecular imaging techniques have shown better performance in locating these tumors. This is partly due to the innate advantage of whole-body coverage, but mostly now, due to the specific binding of some of the newer ligands. Conventionally, whole-body Tc-99m MDP bone scan was used. The sensitivity of bone scanning is limited, because of the limited resolution of traditional gamma camera imaging for locating small lesions, and because many of these tumors are in soft tissue and hence not localized on bone scintigraphy. Moreover, the bony changes of osteomalacia and associated fractures may cause difficulty in detecting focal tumors. The blood pool phase of the bone scan may occasionally be useful in detecting soft-tissue lesions, if tumors are more than few cm in size.

Whole-body positron emission tomography CT (PET-CT) offers higher sensitivity and specificity with the advantage of whole-body metabolic imaging in addition to a whole-body diagnostic contrast CT. F-18 fluorodeoxyglucose (FDG) PET-CT has been used previously but demonstrated limited accuracy. In recent years with the understanding that these small mesenchymal tumors have somatostatin receptors (SSTRs), targeted imaging with Ga-68 DOTANOC and DOTATATE is emerging as the modality of choice in localizing PMT. El-Maouche et al. conducted a prospective study comparing Ga-68 DOTATATE-PET/CT to Octreoscan-SPECT/CT and F-18 FDG-PET/CT in localization of phosphaturic tumors. The sensitivity and specificity of Ga-68 DOTATATE-PET/CT were 54.5% and 85.7%; Octreoscan-SPECT/CT, 36.3% and 80% and F-18 FDG-PET/CT, 36.3% and 86% respectively.[14] In their series, Zhang et al. showed that Ga-68 DOTATATE PET/CT imaging had a sensitivity of 100% (32/32) and a specificity of 90.9% (10/11) with overall accuracy of 97.7% in the detection of tumors responsible for osteomalacia.[15] At times, tumors are identified on FDG-PET/CT imaging but not on Somatostatin analog imaging. Therefore somatostatin analog imaging and FDG based studies could be complementary.

At our center we now routinely use Ga-DOTATATE whole-body PET-CT for evaluation of suspected TIO. Over the last 9 years, 22 patients with suspected TIO based on clinical and/or biochemical parameters, underwent Ga-68 DOTATATE PET/CT. Primary mesenchymal tumors were localized in these patients at a variety of sites. Most of these as expected, are at clinically undetectable or unsuspected locations, and most are unusual in location, difficult, and unlikely to be seen by conventional techniques. The image series below demonstrates the utility and patterns of findings on Ga-68 DOTATATE PET/CT scan for primary TIO.

Method of scan - 3 to 4 mCi of Ga-68 DOTANOC or DOTATATE was injected intravenously. Whole-body PET-CT images are acquired after 1 h. It is essential to image from vertex to toe.

Case 1

A 49-year-old female, presented with complaints of progressive muscle weakness for 6 months and bilateral hip pain. She underwent multiple radiological and biochemical investigations and was found to have osteomalacia and bilateral femoral stress fractures. Biochemistry showed low serum phosphorus – 2.14 mg/dl. Subsequently, suspicion of TIO was raised, and she was found to have elevated FGF 23 – 206 RU/ml (normal: 0-150). Clinical history and thorough physical examination did not yield any clue about the site of possible tumor. She was referred to us for tumor localization. A Ga68-DOTATATE PET-CT was performed. Scan is shown in Figure 1a-d.

Teaching point

This small maxillary lesion was missed on clinical evaluation, and the patient had no localizing symptoms. This is often the case with these small culprit lesions. The high intensity of focal increased SSTR expression in the lesion, associated with osteolytic bone changes are quite typical of a bony PMT.

This patient underwent segmental maxillectomy. Biopsy [Figure 1e] showed the mesenchymal tumor. There was dramatic improvement in the clinical symptoms within 2 months postsurgery.

Case 2

A 39-year-old male, presented with complaints of multiple bone pains for 2 years and difficulty in walking. After 2 years of multiple radiological and biochemical investigations with multiple specialists including general physicians and orthopedic reference, was evaluated in detail by endocrinologist and found to have low serum phosphorus - 1.9 mg/dl (Normal: 2.5–4.9) and normal calcium 9.2 mg/dl (Normal: 8.5–10.1). A suspicion of
TIO was raised, and FGF-23 was advised. It was found to be significantly elevated – 417.4 (Normal 0–150). The Ga68-DOTATATE scan is shown in Figure 2a-c.

**Teaching point**

This case again demonstrates that these small lesions can be present in unusual locations, that are mostly not clinically detectable. The CT findings alone, as in this case may also appear nondiagnostic – could have been mistaken for the cluster of lymph nodes, or nonspecific soft tissue thickening. The high intensity of SSTR expression in the lesions makes Ga 68 DOTATATE imaging highly sensitive for detection, and this finding in relation to the clinical scenario of high FGF23 is also highly specific for TIO.

The patient underwent excision of the perineal tumor. Biopsy showed mesenchymal tumor. There was the dramatic improvement in the clinical symptoms within 2 months postsurgery. This affirmed the specificity of the SSTR imaging technique.

**Case 3**

A 53-year-old female had a tibial fracture 1 year back. While being evaluated for the same she was found to have osteomalacia. On biochemistry diagnosed to be a case of hypophosphatemic rickets. Also gave a history of generalized bodyache for 1 year. Underwent multiple investigations, and found to have significantly elevated FGF 23 – 2698.3 RU/ml (normal: 0–150) and low serum phosphorus – 2.13 mg/dl. Was referred for Nuclear Imaging and a Ga-68 DOTATATE PET/CT was performed [Figure 3].

**Teaching point**

Sinonasal region is a rare site for the presence of PMT-causing TIO. In our series, 3 patients had lesions in nasal cavity. It is to be noted that this site of the lesion was clinically occult with no history of epistaxis, nasal block, or pain. Even on CT images it was not likely to be identified with much specificity and could have been
confused with nonspecific findings of mucosal thickening in the nasal region. Kane et al.\(^{[16]}\) reported series of 6 patients with PMT in sinonasal regions and difficulties in identification of these lesions on radiography. Kurien et al.\(^{[17]}\) reported 8 cases, of which only 3 had ENT symptoms.

**Case 4**

A 60-year-old male, a known case of osteomalacia - presented with generalized body ache and difficulty in walking for 2 years. He received symptomatic treatment, but the severity of the symptoms progressed. After undergoing multiple tests, a suspicion of TIO was made based on elevated serum FGF 23 – 272 RU/ml (normal: 0–150) and low serum phosphorus – 2.26 mg/dl [Figure 4].

**Teaching point**

In this case, unlike case 3, the lesion was relatively large, however, there was lack of any localizing clinical symptoms for the nasopharyngeal region. Therefore in 2 years of suffering, the patient did not undergo any radiological imaging of the head and neck. This reaffirms the advantage of PET-CT - being a whole-body imaging technique, it is the investigation of choice for lesion localization in suspected TIO. In our series of 22 cases being evaluated for TIO, we found 3 sinonasal PMTs.

**Case 5**

26-year-old male, presented with body ache, muscle weakness for 3 years, had fracture of neck of left femur 2 years back, MRI – Rugger jersey spine, received a short course of steroids and symptom exacerbations were managed with analgesics, received Teriparatide for 6 months, treated with bisphosphonates, Vitamin D and calcium supplements. His serum PTH – 27.2, ALP – 346 (Normal 40–150). After 3 years of no relief, he was further evaluated biochemically and then FGF 23 was tested - it was found to be elevated and after 3 years of nonspecific treatment, a clinical suspicion of TIO was made. Ga-68 DOTATATE PET/CT was performed [Figure 5].

**Teaching point**

This case demonstrates that these small lesions may be occult on CT images. Though osteolytic changes on CT are typical, early or small lesions such as this case may not show any change on the CT scan. Even though the lesion is small, it is apparent on PET imaging based on the high degree of SSTR expression and tracer binding in the lesion. Though CT scan has higher spatial resolution than PET scan alone, the detectability of lesions on PET scan is based

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**Figure 3:** (a) Ga-68 DOTATATE positron emission tomography-computed tomography (PET/CT) maximum intensity projection image showed focal area of intensely increased tracer uptake in the head. (Focal tracer uptake seen in the left forearm is the injection site), (b and c) axial, coronal, and sagittal sections of CT and PET/CT fusion images localize this uptake to a soft-tissue density lesion between the superior aspect of nasal septum and medial wall of posterior ethmoidal air cells on the left side.

**Figure 4:** (a) Ga-68 DOTATATE positron emission tomography-computed tomography (PET/CT) maximum intensity projection image showed an area of intense heterogeneously increased tracer uptake in the head. (b and c) Axial, coronal, and sagittal sections of CT and PET/CT fusion images localizing the uptake to heterogeneously enhancing soft tissue density mass in the left nasal cavity involving the middle and superior turbinates and superiorly to left ethmoid sinus and left frontal sinus with the destruction of ethmoid air cells.
on the intensity of tracer binding and not on size – hence even morphologically small lesions with intense radiotracer bindings become apparent before obvious radiological changes.

**Case 6**

A 53-year-old woman, postmenopausal, presented with bilateral hip pain and difficulty walking for 2 years. She was initially diagnosed with Vitamin D deficiency and treated with Vitamin D3 supplements. However, there was no improvement in symptoms even after normalization of Vitamin D level. She was labeled as Vitamin D resistant hypophosphatemic osteomalacia. On further investigations, serum Phosphorus was low –1.5 mg/dL (normal range: 2.5–4.5 mg/dL) and Serum FGF 23 was then found to be high – 725 RU/mL (Normal range <180 RU/mL). Hence, a provisional diagnosis of TIO was made. She was referred for PET-CT imaging. Ga-68 DOTATATE PET/CT was performed [Figure 6].

**Teaching point**

On biochemical evaluation for metabolic bone disease, the Phosphorus level should be closely considered in addition to calcium levels, for possible diagnosis. If Calcium and Phosphorus are both low, it could be due to Vitamin D deficiency. In hyperparathyroidism, Phosphate can be low with high Calcium. If on normalization of Vitamin D deficiency and ruling out hyperparathyroidism, the Phosphorus is still low, the possibility of phosphaturia should be considered and FGF23 level checked.

**Case 7**

A 62-year-old male, with a history bone pains and fracture of the right femur - diagnosed with osteomalacia 1 year back. Was investigated and found to have elevated FGF 23 levels. The patient was referred for FDG PET-CT. It showed no focal area of abnormal increased metabolic activity and the whole-body CT images did not reveal any suspicious abnormality. Sclerotic changes were seen in the neck of the right femur – likely due to the old healed fracture. Hence Ga-68 DOTATATE PET-CT was performed [Figure 7a-d].

**Teaching point**

As seen in this case, as well as in Figure 1a, whole-body scan can sometimes show multiple focal areas of increased...
tracer uptake. These areas are due to stress fractures in the osteopenic bones. Sites of fractures are known to show increased SSTR expression. However, in this case the culprit lesion is the one in Figure 7b. There is almost always very intense tracer uptake in PMT lesions, which helps differentiate it from areas of fracture.

**Case 8**

A 38-year-old male, clinical details are lost since this scan was done 7–8 years back, with clinical suspicion of TIO, underwent Ga-68 DOTATATE PET/CT [Figure 8].

**Teaching point**

This case again demonstrates the very unusual sites for these tumors, and hence the importance of covering head to toe in the scan. PET CT imaging has advantage of easy whole-body coverage of bone as well as soft tissue, which is not easy even with whole-body MRI with its lengthy acquisition time and need for multiple sequences. This case also highlights the extent of metabolic changes that are caused in the bones, in this case, a young male, leading to severe symptoms for the patient – all caused by a small innocuous appearing benign lesion. High degree of clinical suspicion and early reference for sensitive and specific techniques like Ga68-DOTATATE PET-CT is needed for their detection.

**Case 9**

A 48-year-old female - initially presented with pain in lower back for 2 years - later progressed to involve upper back with radiation to bilateral legs. MRI scan showed diffuse patchy edema in sacral body and both ala with no fracture line, a nondisplaced fracture surrounded by mild edema in L5 transverse vertebra. FDG PET/CT scan was performed twice in an interval of 4 months – showed mild rarefaction of sacral ala and revealed no abnormal metabolically active lesion. She was further investigated - Serum phosphorus – 1.9 (Normal: 2.7–4.5); FGF 23: 233 RU/ml (Normal: 0–150); Urine creatinine: 59.70, Urine phosphorus was elevated: 220.6, Fractional
excretion of phosphate (FEPO₄) - 12.5%. A provisional diagnosis of TIO was made. Ga-68 DOTATATE PET/CT was performed [Figure 9].

Teaching point
Mostly in the presence of localizing site for pain, the radiological investigation is limited to the site of pain – in this case low back – and as in this case, only regional MRI could be nondiagnostic for the actual pathology. This case reiterates the importance of a high degree of clinical suspicion for metabolic abnormalities in young patients with bone pain, and thereafter the importance of whole-body imaging technique. This case also demonstrated higher sensitivity of SSTR imaging with Ga68-DOTATATE as compared to FDG PET-CT.

Conclusion
DOTATATE PET/CT demonstrated high-grade SSTR expression and localized PMT with confidence in each case. In our series of 22 cases, tumors were localized in the following regions - 9 patients had lesions in lower extremities, 10 were in the head and neck location, 2 had lesions in the pelvic region (1 perineum, 1 acetabulum), and 1 patient had lesion in the breast.

Osteomalacia associated with hypophosphatemia and phosphaturia should raise a strong suspicion of TIO if other causes are not found based on biochemical or endocrinological workup. Laboratory measurement of FGF-23 is an easily available parameter to lead to this suspicion. A whole-body imaging modality from vertex to toe is essential for the diagnostic survey. At our center, SSTR imaging is now the first-line imaging modality for evaluating suspected TIO.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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