



# Functional and Anatomical Imaging for Early Diagnosis of Tumor Induced Osteomalacia

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## Abstract

Oncogenic osteomalacia, or tumor-induced osteomalacia (TIO), is an acquired paraneoplastic syndrome being associated with benign or in rare cases malignant mesenchymal. Patients with TIO often present with many years of nonspecific but progressive symptoms commonly with bone pain, muscle weakness, reduced height, and multiple fractures. Due to this nonspecificity, patients are often misdiagnosed with a variety of musculoskeletal, rheumatologic diseases and sometimes even having psychiatric disorders. Not only that these tumors are rare but also finding the tumor can be a major diagnostic challenge and may need total body magnetic resonance imaging, computed tomography and scintigraphy using radio labelled somatostatin analogue and sometimes even venous sampling. Majority of clinicians, radiologists and pathologists are not aware of this rare disease because mostly the cases are described in rheumatology practice. We provide mini review of the current literature by having looked at the different studies done including case reports to conclude the best practice for the diagnosis and treatment of this rare entity.

**Keywords:** Magnetic Resonance Imaging; Positron Emission Tomography; Computed Tomography; Venous Sampling

## Introduction

Tumors that can lead to this syndrome are classified on the basis of histology as phosphaturic mesenchymal tumors mostly mixed connective tissue PMTMCT, but also other morphology like osteoblastoma like tumors, ossifying fibrous like tumors, or nonossifying fibrous like tumors. Weidner N. Reviewed 16 tumours to establish four different morphologic patterns with further subgroups mostly the first group with ten sub types [1]. Decades after the discovery of fibroblast growth factor mesenchymal tumor were found to be related to fibroblast growth factor 23 (FGF23), which is responsible for hypophosphataemia and phosphaturia occurring in this paraneoplastic syndrome [2]. Hypophosphataemia, phosphaturia and elevated alkaline phosphatase are the important laboratory readings that may guide to more precise investigations and better diagnosis [3,4]. Regardless of tumour morphology, the hallmark of the diagnosis which forms the basis of all diagnostic modalities is the association of the tumor with the clinical syndrome of TIO, which includes an elevation in plasma FGF23 and its disappearance after tumor resection. As tumours are typically very small in size and slow-growing, detecting and locating these tumors is quite challenging [5].

Clunie GP et al. studied four cases confirming that slow recognition of acquired hypophosphataemic osteomalacia and TIO resulting in unnecessary and prolonged morbidity. These cases emphasize that osteomalacia may precede the discovery of a tumor and illustrate that the site and nature of tumors and their complete resection is often difficult to assess [6,7]. As a result, the time from osteomalacia to identifying the associated tumour averages a period of 5 years and in some studies 7 years. An added problem is that tumor behavior varies from case to case. Seijas R et al. reported two cases with surprisingly different outcomes one showing complete cure while other resulted in incomplete resection and later on recurrence with multiplicity [8].

## Discussion

TIO was first described in 1947 by Robert McCance, who treated a patient having low phosphorous levels, bone pain, with high doses of vitamin D but the symptoms did not completely resolve until a tumor in femur bone was removed. In 1959, Andrea Prader treated rickets in an 11-year-old girl who had decreased tubular phosphate reabsorption however normal kidney function. A tumour, giant cell granuloma, was diagnosed

in a rib and removed resulting in healing of rickets. More than 300 cases of TIO have been reported in the literature [9,10].

The first evidence of a circulating factor that could cause phosphate wasting in phosphaturic disorders was set by Meyer et al. and Nesbitt et al. in mice and by Miyauchi et al. who induced hypophosphatemia in mice by transplanting a tumour removed from a patient [2,11]. FGF23 binds to target proximal tubule cells via FGF receptor and inhibits renal phosphate reabsorption. FGF23 is also a regulatory hormone for 1,25-vitamin D and leads to a decreased concentration of the vitamin in blood under physiological conditions, FGF23 is secreted predominantly by bone and undergoes degradation by proteolytic enzymes. By contrast, tumours secrete FGF23 several hundred-fold higher than normal levels, leading to dysregulation of FGF23 degradation pathway [12,13].

PMT tumours usually occur in bones or soft tissues. The most common diagnosis for these tumours has been hemangiopericytoma [14], but it has also included hemangioma, sarcomas, ossifying fibromas, granulomas, giant cell tumours and osteoblastomas. Most of them are believed to be benign, although histopathologically malignant have been also described and also while typically benign, malignant presentation and metastases can occur. While metastases are rare, infiltration of surrounding connective tissue is typically present, which has significant implications for surgical management and recurrence. It also emphasises importance for wide surgical margins to avoid persistence or reoccurrence [3,7]. Uramoto N. et al, reported a case of a recurrent malignant PMT variant which arose in the tongue. In accordance with the tumor recurrence and resection, the hypophosphatemia progressed and didn't improve. However, hypophosphatemia did not progress after receiving radiation therapy at the second recurrence even though the recurrent tumor gradually increased its size. These results suggest clinical feature of malignant PMT could be changed by radiation therapy. Thus, this report could add an insight to the nature of PMT [13,15].

Quoting Jiang et al. review showed, tumors originate in bones (40 %) and soft tissues (55 %) most common limbs and craniofacial [16] and less common locations are the vertebra, knee, hand, chest, abdomen, groin, perineum and gluteal region even in organs such as the liver, tongue, thyroid and lungs. Folpe AL, described osteomalacia-associated mesenchymal tumors of 32 cases and describing craniofacial origin [17]. Quoting Jiang et al. who reviewed 308 tumour-induced osteomalacia cases reported in English literature between 1987 and 2011, about 46 % of reported cases of TIO have occurred in females and 56 % in males, with a mean age of 45 years when definitive diagnosis was made. Patients with TIO often present with bone pain, muscle weakness, reduced height, and multiple fractures, primarily in the ribs, vertebral bodies, and femoral neck. Bumard H and co workers presented a case with bilateral insufficiency fractures of the proximal femur often have a pathological basis of

hemangiopericytoma. Diagnosis of rare causes of insufficiency fractures can be challenging when the causative factor is a tumour [18].

A systematic approach to hypophosphatemia helps in the early recognition and treatment of TIO. Impaired renal phosphate reabsorption is the biochemical hallmark of the disease with normal or low levels of 1,25-dihydroxyvitamin D, elevated levels of alkaline phosphatase and normal circulating levels of calcium and mostly normal or high parathormone [5,6]. When testing antigen expression, FGF23 is positive in about 70 % of all the cases studied, and the proliferating cells within the tumour are usually the source of FGF23 [6]. Somatostatin receptors have also been found to be present in many TIO tumors [19]. Localization of FGF23-producing tumors can be challenging and a step-wise approach, including functional imaging, followed by anatomical imaging, and if necessary selective venous sampling may significantly improve success in tumor localization [6].

Establishing the diagnosis of an FGF23-producing phosphaturic mesenchymal tumor requires an adequate integration of the clinical picture in correlation with radiology and histology in a multidisciplinary setting, since radiology and histology show considerable overlap with other entities that need different treatment and harbor other clinical outcomes. A stepwise approach is advocated, first performing functional tests that include scintigraphy using radiolabelled somatostatin analogue (such as <sup>99m</sup>Tc-Tektrotyd). Tumors associated with osteomalacia variably express five somatostatin receptors (SSTR1-5), allowing SSTR-based functional imaging by somatostatin analogue scintigraphy or positron emission tomography [19-21].

Octreotide is somatostatin analogue that can be radiolabelled in an attempt to detect tumours that express somatostatin receptors [20]. Octreotide scanning is commonly performed with <sup>111</sup>In-labelled pentetreotide. Octreotide scintigraphy is successfully used to locate tumors in up to 95 % of patients with TIO. A study in china by Yang et al, diagnosing and managing 39 cases of TIO, suggesting that the syndrome is an important cause of adult-onset hypophosphatemic osteomalacia and <sup>99m</sup>Tc<sup>m</sup>-OCT scintigraphy is an effective method to detect the tumors that cause TIO [22]. Jan de Beur SM and co workers did Indium-111 labeled pentetreotide imaging in seven patients with oncogenic osteomalacia. In five patients, it was identified a mesenchymal tumour, and clinical improvement occurred after tumour resection suggesting that <sup>111</sup>In-pentetreotide imaging effectively detects occult mesenchymal tumours and facilitates surgical treatment of oncogenic osteomalacia [23].

Despite this success, there are several limitations of this imaging technology. Inflammatory reactions or a fracture will be associated with a false-positive scan. Somatostatin analogues scintigraphy is also limited by planar two-dimensional imaging and relatively poor spatial resolution, which is particularly

problematic given that TIO tumours are often very small. Single-photon emission tomography (SPECT) or hybrid SPECT/CT enables three-dimensional imaging and better tumour contrast but is time-consuming and therefore limited to areas of suspected abnormality rather than a whole body survey. Somatostatin analogue positron emission tomography can dramatically improve the spatial resolution and lesion detectability. <sup>68</sup>Ga-octreotide PET/CT may have an important role in localization of the culprit lesion, and may potentially reduce significant delay in establishing the diagnosis of TIO [24,25].

FDG-PET/CT can confirm a lesion or identify a lesion that was not initially seen on octreotide scintigraphy. FDG-PET/CT has been proven to be sensitive but not a specific method of identifying FGF23-producing tumors. PET/CT using <sup>68</sup>-gallium is expected to be much more specific and informative for this kind of tumors but is often not available in many centers. Agarwal et al. compared the utility of F-FDG PET/CT and Ga DOTATATE PET/CT to detect the site of primary tumor in patients with suspicion of TIO in 6 patients in which former could detect 3 cases while latter could detect 5 cases [24]. In another study on 54 patients Zhang J and co workers observed (<sup>68</sup>) Ga DOTATATE PET/CT scans were positive in 44 patients, among which, 33 had surgery to remove the lesions and their symptoms diminished promptly, and the serum phosphate levels became normal, which confirmed the diagnoses of TIO [22,25].

There are certain circumstances in which more certainty and testing are indicated. When multiple suspicious lesions are identified on functional imaging, particularly FGD-PET, each with a reasonable degree of suspicion or the suspicious lesion is located in an area where the indicated operation is associated with a high level of potential morbidity. In these cases, additional certainty and testing are indicated. Of particular utility is selective venous sampling with measurement of FGF23 [5].

Venous sampling has been attempted in localizing tumors in the absence of any suspicious lesions identified on either functional or anatomical imaging [26]. In a trial to test to localize tumors by venous sampling without a 'target' lesion which was suggested by anatomical or functional imaging, it was concluded to be not a useful approach [26]. Van Boekel et al. (2008) advocated a two step approach to venous sampling. They suggested that if a suspected tumor cannot be localized by imaging, whole body venous sampling can be performed with assessment of the average values for samples from different anatomical regions. If the average values in samples from a region appear to be higher, more detailed sampling is performed in the smaller branches of the veins in that region. In one patient studied by this approach, it appeared to suggest a particular region. However, in retrospect, the tumor was evident on an MRI that had been performed prior to venous sampling, so the utility of this approach is not clear. An additional approach that can be used for confirmation that a suspicious lesion identified on functional or anatomical imaging

is the culprit tumor is aspiration of the lesion. Elevated FGF23 in the aspirate is diagnostic of a causative lesion. Inspection of cellular morphology consistent with that of a phosphaturic mesenchymal tumor, further supporting that the aspirated lesion represents the culprit lesion Scuibba et al. (2009)

Anatomic imaging (radiography, CT and MRI) should be performed to confirm the location of the tumor after suspicious lesions had been identified by functional imaging]. CT indicates deformations in skeletal bones, rib, bones, thoracic vertebrae and pelvic bone due to osteomalacia or stress fractures, compressive with pathologic kyphosis, stress fractures in both femoral heads and osteosclerotic tumour. Total body magnetic resonance imaging (MRI) is the accurate method to confirm the location of the tumour. It is important to scan the whole body, including extremities [4] as tumours can occur anywhere in the body. Despite all of the advances in imaging that are available today, tumour localization may not be successful. If this is the case, imaging studies should be repeated every 1-2 years.

### Treatment

The treatment of choice for TIO is resection of a tumour with a wide margin, as recurrences of these tumours have been reported [13,26]. Tumour removal is always curative [24], and the recovery and improvement of the patients is relatively quick, FGF23 disappears rapidly from the circulation, and serum phosphate returns to normal by day 5 post operation. The prognosis depends on detecting the tumour and possibility to remove it widely. Nevertheless, the follow-up should be continued because the delayed metastasis can occur as it was described in few cases.

### Conclusion

The diagnosis of TIO is a challenge and is commonly delayed for years due to the nonspecific nature of the presenting symptoms, failure to include serum phosphorus levels in blood chemistry and difficulty in identifying the responsible tumour. The professional evaluation of whole body images, including single-photon emission tomography enables identification and better tumour contrast which can be found in skeletal structures of whatever region of the human body. FGF23 may be of help to understand the underlying mechanisms of TIO and a measurement to follow up the disease course.

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