Tumor-Induced Osteomalacia: Experience From Three Tertiary Care Centres In India


¹Department of Endocrinology, Post Graduate Institute of Medical Education and Research.
²Department of Endocrinology, P D Hinduja Hospital and Medical Research Centre.
³Department of Endocrinology, Jawaharlal Institute of Post Graduate Medical Education and Research.
⁴Department of Nuclear Medicine, Post Graduate Institute of Medical Education and Research.
⁵Division of Endocrinology, Rabindranath Tagore Medical College.
⁶Department of Histopathology, Post Graduate Institute of Medical Education and Research.
⁷Department of Orthopaedics, P D Hinduja Hospital and Medical Research Centre.

Corresponding author: Professor Dr. Sanjay Kumar Bhadada

Department of Endocrinology, Post Graduate Institute Of Medical Education and Research, Chandigarh – 160012

Phone number +91 9876602448, Email ID – bhadadask@rediffmail.com

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Abstract

Tumour-induced osteomalacia (TIO) is a rare para-neoplastic syndrome characterized by recalcitrant hypophosphatemia. Reports from the Indian subcontinent are scarce, with most being single center experiences involving few patients. Herein, we conducted a retrospective analysis of 30 patients of TIO diagnosed at three tertiary care hospitals in India. Patients with persistent hypophosphatemia (despite correction of hypovitaminosis D), normocalcemia, elevated alkaline phosphatase, low TmP/GFR and elevated or “inappropriately normal” FGF23 levels were labeled as having TIO. They were sequentially subjected to functional followed by anatomical imaging. Patients with a well-localized tumor underwent excision; others were put on phosphorous and calcitriol supplementation. The mean age at presentation was 39.6 years with female:male ratio of 3:2. Bone pain (83.3%) and proximal myopathy (70%) were the chief complaints; 40% of cases had fractures. The mean delay in diagnosis was 3.8 years. Tumors were clinically detectable in 4 patients (13.3%). The mean serum phosphate was 0.50 mmol/L with a median serum FGF23 level of 518 RU/ml. Somatostatin-receptor based scintigraphy was found to be superior to FDG-PET in tumor localization. Lower extremities were the most common site of the tumor (72%). Tumor size was positively correlated with serum FGF23 levels. Twenty-two patients underwent tumor resection and 16 of them had phosphaturic mesenchymal tumors. Surgical excision led to cure in 72.7% of patients whereas disease persistence and disease recurrence were seen in 18.2% and 9.1% of cases, respectively. At the last follow-up, serum phosphate in the surgically treated group was significantly higher than in the medically managed group.
Introduction

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome characterized by persistent hypophosphatemia. The basic pathophysiology of underlying hypophosphatemia is increased renal phosphate wasting consequent to raised levels of circulating phosphatonin. The best characterized phosphatonin is fibroblast growth factor 23 (FGF23), a 32 kDa polypeptide consisting of 251 amino acids (Liu and Quarles 2007). In addition, other phosphatonin such as secreted frizzled protein-4, matrix extracellular phosphoglycoprotein (MEPE), FGF 7 and certain noncollagenous matrix proteins called SIBLING have also been implicated (Bhadada et al. 2013; Carpenter et al. 2005; Rowe et al. 2004; Schiavi and Moe 2002; Shaikh et al. 2008; Berndt et al. 2003). In most cases, small, benign, mesenchymal soft tissue tumors are responsible for the increased FGF23 production (Alonso and Varsavsky 2016; Weidner 1991). Besides causing phosphaturia, FGF23 inhibits renal 1α-hydroxylase, the enzyme that converts 25-hydroxy vitamin D to its active form, 1, 25-dihydroxy vitamin D (Perwad and Portale 2011). Low levels of active vitamin D further impairs intestinal absorption of phosphate and deters mineralization of the osteoid matrix. Chronic hypophosphatemia leads to skeletal manifestations of osteomalacia in adults and rickets in children (Minisola et al. 2017). Adults complain of bone pains, fatigue, proximal myopathy and fragility fractures (Chong et al. 2011). Untreated TIO leads to significant morbidity and can be debilitating (Tarasova et al. 2013). Fortunately, complete tumoral excision leads to rapid normalization of biochemical parameters and resolution of symptoms (Sun et al. 2015). Around 300 cases of TIO have been reported worldwide, however reports from the Indian subcontinent are limited (Bhadada et al. 2013; Jagtap et al. 2011; Sahoo et al. 2014; Bhatt et al. 2014; Ashish
et al. 2014; Verma et al. 2017; Dutta et al. 2018; Annamalai et al. 2016). Herein, we describe the clinical features, biochemical parameters, imaging modalities and the treatment outcome in 30 patients of TIO diagnosed at three tertiary care hospitals in India.

**Materials and Methods**

A retrospective analysis of the medical records of TIO cases diagnosed at three tertiary care hospitals from January 2011 to December 2017 was conducted.

All patients (more than 18 years of age) who presented to us with symptoms suggestive of osteomalacia (namely bone pain, proximal muscle weakness and/or fragility fractures) underwent a detailed historical evaluation with special emphasis on duration of symptoms and similar family history. All patients who had a similar family history were excluded as they were more likely to be hereditary causes of hypophosphatemic osteomalacia rather than TIO. A thorough physical examination, concentrating on any ‘lumps or bumps’ present on the body, was performed in all patients.

Blood samples for biochemical investigations were collected after 8 hours of the overnight fast. Serum calcium [reference range (RR) 2.15-2.55 mmol/L], inorganic phosphate (RR 0.87-1.45 mmol/L), albumin (RR 4.93-6.96 μmol/L), alkaline phosphatase (RR 40-129 IU/L) and creatinine (RR 35.36-106.06 μmol/L) were measured by auto-analyzer (Roche diagnostics, Modular P 800, Germany). Calcium values were corrected for respective serum albumin levels. Serum iPTH (RR 1.6-6.9 pmol/L) and 25(OH)D (RR 27.1-107 nmol/L) were measured by electrochemiluminescence assay using commercially available kits (Elecsys 2010 system, Roche diagnostic, Germany). Those having hypovitaminosis D at the time of presentation were parenterally supplemented with 6 lakhs IU of cholecalciferol and a
biochemical panel was repeated after 4 weeks. Patients who remained symptomatic and continued to have hypophosphatemia even after correction of serum vitamin D levels were suspected of having hypophosphatemic osteomalacia. In them, subsequently, TmP/GFR was calculated with the help of the standard nomogram (Walton and Bijvoet 1975). Finally, those patients having refractory hypophosphatemia, normocalcemia, elevated ALP and low TmP/GFR underwent estimation of serum FGF23 levels, using a two-site enzyme-linked immunosorbent assay [Human FGF 23 (C-Term) ELISA, Quidel Immutopics, RR 0-150 RU/ml, the coefficient of variation < 10%]. Patients with the above biochemical profile and elevated or “inappropriately normal” FGF23 levels were labeled as having TIO. Written informed consent for publication of their clinical details and/or clinical images was obtained from all the patients. Ethical clearance for the study was obtained from the Institutional Ethical Committee, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

Biochemical confirmation was followed by imaging studies in an attempt to localize a culprit tumour. Functional imaging was carried out in most cases using somatostatin receptor-based scintigraphy (\(^{68}\text{Ga-DOTATATE/DOTANOC}, \(^{99}\text{mTc-HYNIC-TOC scintigraphy}\)), although\(^{18}\text{F-FDG PET/CT scan}\) was used in some of the patients. Anatomical tumor localization was done using contrast-enhanced computed tomography (CT) or magnetic-resonance imaging (MRI) depending upon the nature of the suspected lesion with CT being preferred for bony lesions and MRI being preferred for soft tissue lesions. A thorough skeletal survey was performed in all patients including radiographs of the skull, cervical, thoracic, lumbosacral spine (antero-posterior/lateral), bilateral shoulders with proximal humerii, both bones of forearm, hands, rib cage, pelvis, proximal femur and both bones of the leg.
Patients with a well-localized tumor underwent excision, and post-surgery serum phosphate level was monitored daily till it got normalized. Serum FGF23 level was repeated 2 months after tumor resection. Patients with no tumor localization or surgically inaccessible tumors were medically managed with oral phosphate and calcitriol supplementation. Phosphate was supplemented in the form of sodium phosphate granules at a starting dose of 20 mg/kg/day in 4-5 divided doses which was gradually hiked up to a dose of 50 mg/kg/day in an attempt to achieve serum phosphate in the low normal range. Calcitriol was supplemented at a starting dose of 20 ng/kg/day in three divided doses and was titrated based on serum iPTH and urinary calcium levels. A baseline ultrasonography of the kidneys was done in all medically treated patients to rule out nephrolithiasis/nephrocalcinosis and was repeated every 6 monthly. Surgically treated patients presenting with recurrence or persistence of symptoms underwent repeat imaging in an attempt to localize any residual or recurrent lesion. Subsequently, they either were re-operated or put on medical management. Serum phosphate levels at the last follow-up were compared between the surgically treated and the medically managed groups.

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) 23.0 software program (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to check normality of data. Normally distributed variables were expressed as mean ± SD. Correlations between serum phosphorous, FGF23, tumor size and SUVmax were calculated using Spearman correlation. Student t-test (independent samples) was used to compare serum phosphate levels at initial presentation and the last follow-up as well as pre- and post-operative serum FGF23 levels.
Results

Over a period of seven years from 2011 to 2017, a total of 30 cases of TIO were diagnosed at the three tertiary care hospitals of India. The demographic data and the biochemical investigations of all the 30 TIO patients have been summarized in table 1. The chief presenting complaints were bone pain (83.3%), followed by proximal muscle weakness (70%). Pathological fractures were seen in 12 patients (40%); the most common site being the neck of femur, however none had vertebral fractures. The mean age of patients with and without fractures was comparable (40.0 years vs. 40.4 years). Physical examination could locate the culprit tumors in 4 (13.3%) patients. Three of them were visible to the naked eye [patient 8 (over the right leg just below the knee), patient 11 (over the back) and patient 17 (over the lateral aspect of the left leg)] (figure 1). Patient 9, a 40 years old female, had a palpable firm, globular mass in the right gluteal region that was picked up on dedicated physical examination.

Functional localization of the lesion was undertaken in all but one patient (patient 17, who had a visible lump over the lateral aspect of the left leg, in whom only a contrast-enhanced computerized tomography was performed). Whole-body somatostatin receptor (SSTR) based scintigraphy was performed in most patients, namely, $^{68}$Ga-DOTATATE/DOTANOC scintigraphy in 20 patients and $^{99m}$Tc-HYNIC-TOC scan in 2 patients (figure 2). $^{18}$F-FDG PET was performed in 6 patients while both SSTR-based scintigraphy and FDG PET was done in one patient (and both had failed to localize any tracer-avid lesion). Subsequently, a definite anatomical lesion could be localized in 25 patients (83.3%). The most common site of tumor localization was the lower extremity (72%) followed by the nasal cavity and paranasal sinues (16%). One patient had a subcutaneous lesion over the back and two patients had in the body of the mandible (patients 2 and 28). Most of the lesions were soft tissue tumors (60%).
while the rest (40%) were seen to arise from bones. There was a statistically significant positive correlation between tumor size and FGF23 levels, while there was no significant correlation between SUVmax (maximum standardized uptake volume obtained from SSTR-based scintigraphy) and serum FGF23 levels.

Out of the 25 patients in whom a definite tumor could be localized, 22 of them subsequently underwent surgery (patients 1 to 22). The most common histopathology was that of a phosphaturic mesenchymal tumor (16 patients, 72.7%) (figure 3) followed by hemangiopericytoma (3 patients, 13.6%). Two patients had giant cell tumors (patients 3 and 14), while one had an arteriovenous hemangioma of the left nasal cavity (patient 4). Post-operatively, serum phosphorous normalized in 18 patients, two of them (9.1%) had a local recurrence and required re-operation (patients 12 and 16). Serum phosphorous did not normalize in 4 patients (18.2%) with persistent disease (patients 2, 3, 14 and 19). They were subsequently put on oral phosphorous and calcitriol supplementation. Post-operative serum FGF23 levels were available in 17 patients and there was a statistically significant decline in FGF23 levels compared to baseline ($p=0.002$). Patient 2 had persistent disease and post-operative FGF23 levels showed a rise (307 RU/ml vs 201 RU/ml at baseline). In another patient with persistent disease (patient 14), FGF23 remained high (1216 RU/ml vs. 3990 RU/ml at baseline).

Surgery could not be done in 8 patients; five of them did not have tumor localization (patients 23, 25, 26, 28, 29), one had a surgically inaccessible tumor (patient 27) and two patients were not willing for surgery (patients 24, 30). They were put on medical management. Baseline mean serum phosphate in the medically and surgically managed groups was almost similar (0.45 mmol/L vs. 0.55 mmol/L, $p=0.217$). At
their last follow-up, the mean serum phosphorous in the surgically treated group was higher than the medically treated group (1.00 mmol/L vs. 0.80 mmol/L, $p = 0.006$).

Discussion

We have herein presented a retrospective series of 30 cases of tumor-induced osteomalacia diagnosed at three tertiary care institutes of the country over a period of 7 years. Our patients had a relatively younger age at presentation. Bone pain and proximal myopathy were the principal presenting complaints; fractures were seen in only 40% of the patients. The detailed physical examination was rewarding in four patients for detecting the primary lesion. SSTR-based scintigraphy proved superior to conventional FDG-PET in localizing the culprit tumors. Soft tissue tumors were more commonly encountered than bony tumors with thighs being the predominant site. The most common histological tumor subtype was phosphaturic mesenchymal tumor-mixed connective tissue type. Surgical excision led to cure in 72.7% of patients; disease persistence and disease recurrence were seen in 18.2% and 9.1% of cases, respectively.

The mean age of our patients at the time of initial presentation was 39.6 years which is about half a decade earlier than what has been reported in world literature (Yu et al. 2017; Jiang et al. 2012; Dadoniene et al. 2016). It is however in congruence with an earlier report from India (Jagtap et al. 2011), possibly implying that TIO tends to present somewhat earlier in our population. There was a female:male ratio of 3:2. Usually, TIO shows no gender predilection and tends to affect males and females equally (Jiang et al. 2012; Ryan and Reiss 1984; Florenzano et al. 2017), hence, the female dominance of our series could merely reflect referral bias. However occasional case series depicting a female preponderance has been reported in the past (Folpe et al. 2004; Qari et al. 2016). Most of our patients complained of bone pain and
proximal muscle weakness. However, only 40% of our patients had radiologically proven pathological fractures. This appears fairly low when compared to world literature that has reported fractures rates as high as 84-100% (Yu et al. 2017; Jiang et al. 2012). The mean delay in presentation was 3.8 years, which is very similar to earlier reports (Yu et al. 2017; Zuo et al. 2017). Thirteen percent of the tumors were clinically identifiable as palpable or visible lumps, highlighting the importance of a thorough head-to-toe examination.

Biochemical investigations revealed hypophosphatemia and normocalcemia in all patients. Hypophosphatemia was severe in 60% of the patients having serum phosphate levels below 0.50 nmol/L. Only 43.3% of the cases were vitamin D deficient or insufficient, as opposed to 70-100% of the general population in the Indian subcontinent (Ritu and Ajay 2014). This is because most of our patients had been supplemented with vitamin D as an empirical treatment at primary care hospitals. The calculated TmP/GFR was low (compared to age and sex-specific reference range) in all the patients, implying renal phosphate wasting. Serum FGF23 levels were elevated above the upper limit of the assay range in all but 2 patients (patients 5 and 20). These two patients had serum FGF 23 levels of 102 RU/ml and 147 RU/ml with a corresponding serum phosphate of 0.42 nmol/L and 0.65 nmol/L, respectively, implying “inappropriately normal” FGF23 for the degree of hypophosphatemia (Zuo et al. 2017; Amblee et al. 2014). Moreover, estimation of FGF23 in our patients was done with C-terminal assay, the sensitivity of which does not reach 100% (Smith et al. 2014; Imel et al. 2006). Other phosphatonin could also be implicated in causing phosphaturia in these 2 patients (Rowe et al. 2004; Schiavi and Moe 2002; Shaikh et al. 2008; Berndt et al. 2003; Jonsson et al. 2003). We could not find any statistically significant correlation between serum phosphate and FGF23
levels ($r_s = -0.22, p=0.24$), probably because serum phosphate correlates with FGF23 measured by the intact assay rather than by the C-terminal assay (Burnett et al. 2006). Functional imaging (SSTR-based scintigraphy or FDG-PET) could localize a tracer-avid lesion in 28 out of 29 patients. However, subsequent attempt at anatomical localization could pin-point a culprit lesion in only 25 patients. The concordance rate between SSTR-based scintigraphy and anatomical imaging (defined as the ability of both the imaging modalities to localize a common lesion) was 100%, while concordance between FDG-PET and anatomical imaging was only 50%. The superiority of SSTR-based scintigraphy over FDG-PET in localizing culprit lesions in TIO is well documented in world literature (Agrawal et al. 2015; Jadhav et al. 2014; El-Maouche et al. 2016). Most of the localized lesions were of soft tissue origin (60%). Forty percent of the tumors were seen to arise from bones, similar to what has been reported in most case series (Jiang et al. 2012; Folpe et al. 2004). Although recent literature supports no clear anatomical predilection for the tumors (Minisola et al. 2017), we found a striking lower limb predominance (72%); thighs being the most common site. Two of our patients had multifocal benign tumors (patients 19 and 21), something that has rarely been reported (Sahoo et al. 2014; Annamalai et al. 2016; Arai et al. 2017; Higley et al. 2015). One of them (patient 21), a 42-year-old male (Sahoo et al. 2014), had an FDG-avid nodule in the right leg (measuring 0.9x0.6x1.0 cm) and a synchronous non-FDG avid nodule in the left thigh that was picked up on MRI (measuring 0.8x0.7 cm). Excision of the FDG-avid nodule did not lead to the resolution of hypophosphatemia. However, when the non-FDG avid lesion was removed, hypophosphatemia settled, and serum FGF23 came down to 22 RU/ml.

Data on tumor size (as noted on CT/MRI) was available in 17 patients. Tumor size and serum phosphate were negatively correlated, though not statistically significant
(r_s = -0.13, p=0.61); on the contrary, there was a statistically significant positive correlation between tumor size and serum FGF23 levels (r_s = 0.57, p=0.016), highlighting the fact that tumor size probably dictates the FGF23 levels. Data on maximum standardized uptake volume (SUVmax) from 68Ga-labeled peptide scintigraphy was available in 15 patients. No statistically significant correlation between SUVmax and serum FGF23 levels (r_s=-0.17, p=0.51) was found. Since SUVmax is a surrogate marker of SSTR expression (Campana et al. 2010), it may be inferred that signal transduction via somatostatin receptors is possibly not involved in regulation of FGF23 secretion by the tumor tissue. As firm evidence to our hypothesis is the fact that octreotide, a somatostatin receptor ligand, is largely ineffective in correcting the biochemical abnormalities in TIO (Paglia et al. 2002; Ovejero et al. 2017; Mékinian et al. 2011).

All the resected tumors (n=22) were benign in nature. Sixteen of them (72.7%) were found to have phosphaturic mesenchymal tumors (PMT) with the mixed connective tissue variant (PMTMCT) being most common seen in 15 patients, while one had an osteoblastoma-like variant. Three patients (13.6%) had hemangiopericytomas while two had giant cell tumors (GCTs) and the other harbored an arteriovenous hemangioma. The present data is consistent with world literature showing a predominance of PMTMCT cases (Yu et al. 2017; Jiang et al. 2012).

Although surgery remains the mainstay of therapy, other treatment modalities have been tried with varying degrees of success. Image-guided ablation using different techniques (including percutaneousethanol ablation, radiofrequency ablation and cryoablation) offers a minimally invasive and safe treatment option for patients with inoperable TIO. However efficacy varies, and long-term effects are not known (Jadhav et al. 2014; Hesse et al. 2007; Tutton et al. 2012). Radiotherapy, either as an
adjuvant or primary treatment modality, remains a viable option for unresectable or incompletely resected tumors (Caudell et al. 2003; Hautmann et al. 2015). Deliberate total parathyroidectomy as a novel treatment approach has also been advocated in refractory cases (Bhadada et al. 2013). Cinacalcet and octreotide have been tried with variable success (Geller et al. 2007; Seufert et al. 2001). In addition, anti-FGF23 antibody, also known as KRN23 (Burosumab) is being evaluated for the treatment of TIO (Kinoshita and Fukumoto 2014).

Post-operatively serum phosphorous normalized in 18 out of 22 patients over a period of 3 days to 2 months. Two patients (9.1%) had a local recurrence within 6 months and had to be re-operated. A local recurrence rate of less than 5% has been reported in world literature (Yavropoulou et al. 2015), mostly in patients harboring a malignant tumor or in whom the operating surgeon was not able to resect the tumor en-bloc; the later being the most likely reason in our two patients. In 4 patients (18.2%), serum phosphorous never got normalized, and they were believed to have persistent disease. Disease persistence following surgical excision is well documented in literature (Chong et al. 2013). Repeat SSTR-based scintigraphy in these 4 patients revealed a new tracer-avid lesion in the right femur in one patient and the right foot of another patient. However, CEMRI was inconclusive. The other two patients had local residues but were unwilling for repeat surgery.

Post-operative FGF23 levels showed a statistically significant decline compared to pre-operative values (figure 4). However, contrary to our expectations, FGF23 levels did not fall below the upper limit of the reference range of the assay (0-150 RU/ml) in 4 patients with unequivocal evidence of clinical and biochemical cure. This highlights the fact that the percentage decline in FGF23 after surgery, rather than the absolute
value, correlates with disease cure. The mean percentage decline in FGF23 that was associated with clinical and biochemical cure was 81.1% (range 27.5% - 99.2%).

Serum phosphate in the surgically treated group was significantly higher at their last follow-up compared to the medically managed group ($p=0.006$) (figure 5). However, even within the medically managed group, serum phosphate level at the last follow-up was significantly higher compared to baseline values ($p=0.001$). Thus, phosphate and calcitriol supplementation in TIO patients, in whom the tumor cannot be localized, does improve biochemical milieu; whether this translates into improved quality of life is however debatable.

The principal strength of the study is the relatively large sample size. Prior case series from India were mostly single center experiences and had included no more than 9 patients (Jagtap et al. 2011). On the contrary, this was a multicenter study involving 30 patients with cases being recruited from three tertiary care hospitals catering to the northern, western and southern parts of the nation. In addition, somatostatin-receptor based scintigraphy was used in most of the patients which is the best imaging modality as per published literature. Moreover, an attempt was made to correlate tumor characteristics with serum FGF23 levels (which might bear therapeutic implications) which, to the best of our knowledge, have never been reported earlier. The primary limitation of our study is the fact that not all of our patients underwent surgery; 8 patients in whom either the tumor could not be anatomically localized or was unwilling for surgery were put on medical management. Hence, data on tumor histology was not available in these 8 patients. Lastly, we measured serum FGF23 levels by C-terminal ELISA technique that measures both intact FGF23 and C-terminal fragments of FGF23. Traditionally it was believed that intact FGF23 was the only biologically active molecule mediating phosphaturia (Shimada et al. 2010).
Hence estimation of both intact and C-terminal fragments of FGF23 would theoretically overestimate the actual bioactivity of the circulating molecule. However, animal studies have shown that carboxyl-terminal fragments of FGF23 are phosphaturic (Berndt et al. 2007); the same might hold true for humans as well, and in fact, estimation of FGF23 by C-terminal ELISA might correlate better with bioactivity.

In conclusion, TIO should always be kept as a differential diagnosis while evaluating a patient of osteomalacia. Persistent hypophosphatemia despite normalization of vitamin D status in the absence of a similar family history strengthens the possibility of TIO. A thorough physical examination is always rewarding and might obviate the need for imaging. Serum FGF23 levels may be “inappropriately normal” for the degree of hypophosphatemia. Somatostatin-receptor based scintigraphy should be used as the preferred imaging modality to localize the tumor. Surgical resection offers a definitive cure, however, recurrences do occur and long-term follow-up is necessary.

**Declaration of Interest**

All the authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement (optional)

Study design: RP and SKB. Study conduct: RP, SKB and AB. Data collection: VD, AS, SK, MC, PC, DCS and VA. Providing scintigraphy data: ASD. Providing histopathology data: UNS and DC. Data analysis: RP and VD. Data interpretation: SKB, RP and AB. Drafting manuscript: RP, SKB, SK, ASD and MC. Revising manuscript content: SKB, SK, ASD and AS. Approving final version of manuscript: RP, SKB, AB, AS, MC, PC and SK. SKB takes responsibility for the integrity of the data analysis.

Acknowledgements

None

References


**Figure legends**

**Figure 1.** Clinical photographs of patient 8 showing a small lump just below the medial aspect of the right knee (figure 1A, marked in black arrow) and patient 17 showing a large lobulated lump over the lateral aspect of the upper left leg (figure 1B).

**Figure 2.** Fused $^{68}$Ga-DOTATATE PET/CT images showing focal tracer-avid lesions over the right back (figure 2A, patient 11), left nasal cavity (figure 2B, patient 10), right gluteal region (figure 2C, patient 9) and medial aspect of the leg just below the right knee (figure 2D, patient 8).

**Figure 3.** Photomicrograph of a phosphaturic mesenchymal tumor-mixed connective tissue type. Figure 3a: Photomicrograph showing a relatively well-circumscribed and focally tissue permeating mass (Hematoxylin and Eosin; 20x). Figures 3b and 3c: Myoid spindle cell component along with hemangiopericytomatous blood vessels and scattered osteoclastic giant cells and siderophages (Hematoxylin and Eosin) (100x;
4b) (200x; 4c). Figure 3d: Other areas showing areas of grungy calcification along with the spindle cell component (Hematoxylin and Eosin; 40x).

**Figure 4.** Box and whisker plot showing pre-operative and post-operative serum FGF23 levels in 17 surgically treated TIO patients ($p=0.002$).

**Figure 5.** Bar diagram showing serum phosphate levels in surgically (n=22) and medically (n=8) treated TIO patients as measured at presentation (p=0.217) and at their last follow-up ($p=0.006$).
The graph shows the mean serum phosphate levels in patients treated surgically versus medically. At presentation, the levels are similar, but at the last follow-up, there is a significant difference in favor of the medically treated group (p=0.006).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>Mean age (range)</td>
<td>39.6 ± 11.9 (19-67) years</td>
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<tr>
<td>Female:Male</td>
<td>3:2</td>
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<tr>
<td>Mean delay in diagnosis (range)</td>
<td>3.8 (0.5-15) years</td>
</tr>
<tr>
<td>Mean serum phosphate (range)</td>
<td>0.50 ± 0.13 (0.23-0.78) mmol/L</td>
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<tr>
<td>Mean TmP GFR (range)</td>
<td>0.36 ± 0.16 (0.07-0.74) mmol/L</td>
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<td>Mean corrected serum calcium</td>
<td>2.24 ± 0.18 mmol/L</td>
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<td>Median serum ALP (IQR)</td>
<td>230 (177-404) IU/L</td>
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<td>Median serum iPTH (IQR)</td>
<td>6.76 (5.37-10.27) pmol/L</td>
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<tr>
<td>Median serum 25(OH)D (IQR)</td>
<td>75.4 (52.1-129) nmol/L</td>
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<td>Median serum FGF23 (IQR)</td>
<td>518 (102-6235) RU/ml</td>
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**Table 1.** Table summarizing the demographic data and biochemical investigations of all the thirty TIO patients.
Table 2. Table showing demographic data and biochemical investigations of individual TIO patients (n=30).
<table>
<thead>
<tr>
<th>Patient</th>
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<th>Site localized on functional imaging</th>
<th>Anatomical imaging used</th>
<th>Site localized on anatomical imaging</th>
<th>Tissue of origin</th>
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<td>68Ga-DOTATATE</td>
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<td>CEMRI</td>
<td>Concordant</td>
<td>Soft tissue</td>
<td>PMTMCT</td>
</tr>
<tr>
<td>2</td>
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<td>Bone</td>
<td>HPT</td>
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<td>Head of left fibula</td>
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<td>Concordant</td>
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<td>GCT</td>
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<td>Right nasal cavity</td>
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<td>Concordant</td>
<td>Soft tissue</td>
<td>AV hemangioma</td>
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<td>Right thigh</td>
<td>CEMRI</td>
<td>Concordant</td>
<td>Soft tissue</td>
<td>PMTMCT</td>
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<tr>
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<td>Shaft of right femur</td>
<td>CECT</td>
<td>Concordant</td>
<td>Bone</td>
<td>PMTMCT</td>
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<td>Concordant</td>
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<td>9</td>
<td>68Ga-DOTATATE</td>
<td>Right gluteal region</td>
<td>CEMRI</td>
<td>Concordant</td>
<td>Soft tissue</td>
<td>PMTMCT</td>
</tr>
<tr>
<td>10</td>
<td>68Ga-DOTATATE</td>
<td>Left nasal cavity</td>
<td>CECT</td>
<td>Concordant</td>
<td>Soft tissue</td>
<td>HPT-sinonasal type</td>
</tr>
<tr>
<td>11</td>
<td>68Ga-DOTATATE</td>
<td>Right back</td>
<td>CECT</td>
<td>Concordant</td>
<td>Soft tissue</td>
<td>PMTMCT</td>
</tr>
<tr>
<td>12</td>
<td>68Ga-DOTATATE</td>
<td>Right pelvic blade</td>
<td>CEMRI</td>
<td>Concordant</td>
<td>Bone</td>
<td>PMTMCT</td>
</tr>
<tr>
<td>13</td>
<td>68Ga-DOTANOC</td>
<td>Right thigh</td>
<td>CECT</td>
<td>Concordant</td>
<td>Soft tissue</td>
<td>PMTMCT</td>
</tr>
<tr>
<td>14</td>
<td>FDG-PET</td>
<td>Left thigh</td>
<td>CECT</td>
<td>Concordant</td>
<td>Soft tissue</td>
<td>GCT</td>
</tr>
<tr>
<td>15</td>
<td>68Ga-DOTANOC</td>
<td>Right acetabulum</td>
<td>CEMRI</td>
<td>Concordant</td>
<td>Bone</td>
<td>PMTMCT</td>
</tr>
<tr>
<td>16</td>
<td>FDG-PET</td>
<td>Left nasal cavity</td>
<td>CECT</td>
<td>Concordant</td>
<td>Soft tissue</td>
<td>HPT-lipomatous type</td>
</tr>
<tr>
<td>17</td>
<td>NOT DONE</td>
<td>NA</td>
<td>CECT</td>
<td>Left proximal fibula</td>
<td>Bone</td>
<td>PMTMCT</td>
</tr>
<tr>
<td>18</td>
<td>68Ga-DOTANOC</td>
<td>Right heel</td>
<td>CEMRI</td>
<td>Concordant</td>
<td>Soft tissue</td>
<td>PMTMCT</td>
</tr>
<tr>
<td>19</td>
<td>99mTc-HYNIC-TOC</td>
<td>Right medial femoral condyle and S2 vertebral body</td>
<td>CECT</td>
<td>Concordant</td>
<td>Bone</td>
<td>PMT-osteoblastoma like variant</td>
</tr>
<tr>
<td>20</td>
<td>99mTc-HYNIC-TOC</td>
<td>Left thigh</td>
<td>CEMRI</td>
<td>Concordant</td>
<td>Soft tissue</td>
<td>PMTMCT</td>
</tr>
<tr>
<td>21</td>
<td>FDG-PET</td>
<td>Right thigh</td>
<td>CECT and CEMRI</td>
<td>Left thigh</td>
<td>Soft tissue</td>
<td>PMTMCT</td>
</tr>
<tr>
<td>22</td>
<td>FDG-PET</td>
<td>Right proximal fibular shaft</td>
<td>CECT</td>
<td>Concordant</td>
<td>Bone</td>
<td>PMTMCT</td>
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<td>23</td>
<td>FDG-PET</td>
<td>Left ala of sacrum</td>
<td>CEMRI</td>
<td>Not localized</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>24</td>
<td>68Ga-DOTATATE</td>
<td>Head of left femur</td>
<td>CEMRI</td>
<td>Concordant</td>
<td>Bone</td>
<td>NA</td>
</tr>
<tr>
<td>25</td>
<td>68Ga-DOTATATE</td>
<td>Right patella</td>
<td>CECT</td>
<td>Not localized</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>26</td>
<td>68Ga-DOTATATE and FDG-PET</td>
<td>Not localized</td>
<td>NOT DONE</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>27</td>
<td>68Ga-DOTATATE</td>
<td>Right obturator muscle</td>
<td>CEMRI</td>
<td>Concordant</td>
<td>Soft tissue</td>
<td>NA</td>
</tr>
<tr>
<td>28</td>
<td>68Ga-DOTATATE</td>
<td>Mandible</td>
<td>CECT</td>
<td>Not localized</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>29</td>
<td>FDG-PET</td>
<td>C4 vertebra</td>
<td>CECT</td>
<td>Not localized</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>30</td>
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<td>Mid left fibula</td>
<td>CECT</td>
<td>Concordant</td>
<td>Bone</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Table 3.** Table showing the various functional and anatomical imaging modalities used for tumor localization and histopathology of the tumors that were excised [NA → not applicable].