



## Case Report

## High bone turnover and hyperparathyroidism after surgery for tumor-induced osteomalacia: A case series

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## ABSTRACT

Tumor-induced osteomalacia (TIO) is an ultrarare disorder that is caused by renal phosphate wasting due to uncontrolled tumoral production of fibroblast growth factor 23 (FGF23) from phosphaturic mesenchymal tumors. Surgical removal of the tumor is curative. There is limited information on the biochemical changes in mineral metabolism and bone remodeling activity after surgery, but it is reported that surgery is followed by a hungry bone syndrome (HBS) with hypocalcemia and secondary hyperparathyroidism. We report the biochemical response to surgery in two patients, who presented with severe TIO, as manifested by proximal myopathy, multiple stress fractures, high FGF23, low serum phosphate, low maximum renal phosphate reabsorption threshold (TmP/GFR), and low 1,25-dihydroxy-vitamin D (1,25(OH)<sub>2</sub>D). Prior to surgery, both patients developed secondary hyperparathyroidism and one case had progressed to tertiary hyperparathyroidism. After surgery there was normalization of FGF23, TmP/GFR, and phosphate. High 1,25(OH)<sub>2</sub>D was recorded. One patient had hypocalcaemia and worsening secondary hyperparathyroidism consistent with HBS; the other patient did not have hypocalcemia but had worsening tertiary hyperparathyroidism that only resolved with cinacalcet. There was a marked increase in bone remodeling markers, both resorption and formation, consistent with a high bone turnover state. There was a different pattern of change in bone specific alkaline phosphatase, reflecting healing of osteomalacia. Biochemical monitoring in the post-surgical management of TIO is warranted for guiding adjustments in medical intervention, both short-term and long-term. Future use of burosumab prior to surgery for TIO may ameliorate the immediate post-surgery effects.

### 1. Introduction

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome, which is associated with phosphaturic mesenchymal tumors (PMT), resulting in an acquired form of severe chronic hypophosphatemia that leads to osteomalacia in adults (Ryan et al., 1984; Minisola et al., 2017). Most cases are caused by excess tumoral production of fibroblast growth factor 23 (FGF23), one of the factors that regulates phosphate excretion (McKenna et al., 2021; Ovejero et al., 2021). Increased circulating FGF23 in TIO inhibits sodium-dependent phosphate co-transporters (NaPi2a) on the luminal surface of the

proximal renal tubule, which results in reduced phosphate reabsorption. In addition, there is reduced synthesis of the active vitamin D metabolite, 1,25-dihydroxy-vitamin D (1,25(OH)<sub>2</sub>D); this diminution in active vitamin D leads to further decrease in phosphate by reducing intestinal absorption (Minisola et al., 2017; Florenzano et al., 2017). Clinically, TIO manifests with bone pain, muscle weakness and impaired mobility. As with other causes of osteomalacia, stress fractures of Looser type are common (McKenna et al., 2014). Biochemical assessment reveals a low maximum renal phosphate reabsorption threshold (TmP/GFR), elevated or inappropriately normal FGF23 in the setting of hypophosphatemia, low or low-normal 1,25(OH)<sub>2</sub>D, elevated total alkaline phosphatase, and

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elevated biomarkers of bone remodeling (Jan de Beur et al., 2021). There is marked osteoid accumulation with impaired mineralization on dynamic bone histomorphometry (Jan de Beur et al., 2021).

The diagnosis of TIO is often delayed due to failure to recognize the condition (Florenzano et al., 2017; Kumar and Diamond, 2020; Li et al., 2020). This delay in diagnosis is compounded by the subsequent difficulty in localizing the tumor. Highly developed imaging techniques are used to locate tumors: the most effective being <sup>68</sup>Gallium-DOTATATE positron emission tomography/computed tomography (<sup>68</sup>Ga-DOTATATE PET/CT) (Florenzano et al., 2017). If the tumor is located, then curative excision is an option. After successful surgery with normalization of FGF23, renal phosphate wasting ceases immediately and healing of osteomalacia happens steadily, reaching completion after many months (Minisola et al., 2017; Kumar and Diamond, 2020). There are sporadic reports of non-remission or recurrence after surgery (Li et al., 2020).

“Hungry bone syndrome” (HBS), as a term, was introduced to describe the phenomenon of hypocalcemia after surgery for hyperparathyroidism (either primary, secondary, or tertiary) (Witteveen et al., 2013). After surgery for hyperparathyroidism, hypocalcemia is consequent upon the onset of positive bone remodeling balance due to the sudden reduction of bone resorption following the abrupt decline in parathyroid hormone (PTH) coupled with ongoing high bone formation rate (Witteveen et al., 2013; Smith et al., 2005). An analogous response has been used to describe the response to surgery for TIO (Kumar and Diamond, 2020; Rendina et al., 2009; Raborn et al., 2020). The earliest report of HBS-like phenomenon in TIO, which included two cases, did not describe immediate changes but reported mild hypocalcemia at 1 month with high bone specific alkaline phosphatase (bone ALP), reduced bone resorption activity, and normal PTH (Rendina et al., 2009). The second report of a single case noted symptomatic hypocalcemia 3 weeks after surgery that persisted for 1 month; PTH was reported as being within the normal range but it is not clear if PTH was measured during the phase of acute hypocalcemia; and there were limited data on bone remodeling markers (Kumar and Diamond, 2020). The third report, in abstract form, closely monitored the immediate changes in two cases; they observed hypocalcemia and secondary hyperparathyroidism that resolved over 10 days; bone remodeling changes were not studied apart from showing decline in bone ALP (Raborn et al., 2020). Thus, the HBS after TIO is different compared to HBS after parathyroid surgery because there is increased degree of hyperparathyroidism in the former compared to reduced degree of hyperparathyroidism in the latter.

We report the impact of surgical resection on biochemical indices of phosphate metabolism, calcium metabolism, vitamin D metabolism, and bone remodeling activity in two cases of TIO after surgery that showed a marked increase in bone remodeling markers (both resorption and formation), coupled with exacerbation of secondary hyperparathyroidism in the one case and of tertiary hyperparathyroidism in the other case. The role of calcimimetic medication in managing hyperparathyroidism, both before and after surgery, was also monitored.

## 2. Methods

The following analytes were measured in accordance with methods previously described (McKenna et al., 2021; McKenna et al., 2019), based on fasting samples of blood and of second morning-void timed urine: TmP/GFR; C-terminal FGF23 (cFGF23), intact FGF23 (iFGF23); parathyroid hormone (PTH); creatinine; estimated glomerular filtration rate (eGFR); ionized calcium; phosphate; 25-hydroxyvitamin D (25OHD); 1,25 dihydroxyvitamin D (1,25(OH)<sub>2</sub>D), bone ALP; N-mid fragment osteocalcin (OC[1–43]); total procollagen type I N-terminal propeptide (PINP); C-terminal telopeptide of type I collagen (CTX); urine N-terminal telopeptides of type I collagen (uNTX) and urine calcium (uCa/Cr). Bone mineral density (BMD) at lumbar spine and proximal femur (femur neck and total hip sites) was monitored by dual-

energy X-ray absorptiometry (DXA) using Hologic Discovery Model A until 2018 before switching to Hologic Horizon Model A. All graphs were created using GraphPad Prism version 9.1.2. Both patients gave written informed consent about submission of this manuscript for publication.

## 3. Patients and results

### 3.1. Case one

A 52-year-old postmenopausal woman was referred to our specialist bone clinic in June 2011 with a five-year history of bone pain and muscle aches. She had a waddling gait and proximal myopathy. There was radiographic evidence of Looser zones in the superior and inferior pubic rami on the right side; magnetic resonance imaging identified stress fractures in both sacral ala, right femoral neck, left proximal tibia metaphysis, and left distal tibial metaphysis. At presentation, TmP/GFR was low, cFGF23 was high, 25OHD was sufficient, 1,25(OH)<sub>2</sub>D was low-normal, PTH was low-normal, adjusted calcium and eGFR were normal (Table 1). Serum and urine biomarkers of bone resorption (CTX and uNTX) and serum biomarkers of bone formation (bone ALP and PINP) were elevated; OC[1–43] was not elevated (Table 1). BMD T-scores were + 1.6 at lumbar spine and – 0.1 at left total hip site. Bone biopsy was not performed.

As regards medical management, she was treated initially with elemental phosphate (starting at 2000 mg daily, reducing to 1000 mg daily after 2 years), alfacalcidol (starting at 2 µg daily). After 1 year, she was started on cinacalcet in view of its known efficacy in treating TIO (Geller et al., 2007), but it was stopped shortly afterwards because she was poorly tolerant due to nausea. Then, she had a spell of hypercalcemia (ionized calcium = 1.43 mmol/L) and low-normal PTH (1.6 pmol/L) that resolved when alfacalcidol dose was reduced to 1 µg daily (Fig. 1). She gradually developed secondary hyperparathyroidism that progressed to borderline tertiary hyperparathyroidism just 3 months prior to surgery (Table 1). Medical treatment prior to surgery was

**Table 1**  
Biochemical results at key time points in case 1.

Variables	At diagnosis	Before surgery	Shortly after surgery	33 months after surgery	Reference Intervals
TmP/GFR, mmol/L	0.29	0.19	0.81	0.46	0.81, 1.35
Phosphate, mmol/L	0.48	0.39	1.19	0.74	0.80–1.50
cFGF23, RU/mL	1025	2520	107	200	< 100
iFGF23, ng/L	n/a	n/a	54.1	85.8	33, 110
1,25(OH) <sub>2</sub> D, pmol/L	n/a	44	281	130	55, 139
25OHD, nmol/L	65	60	48	55	30, 125
Total calcium, mmol/L	2.42	2.57	2.81	2.40	2.20, 2.60
Ionized calcium, mmol/L	1.32	1.37	1.56	1.16	1.15, 1.33
PTH, pmol/L	2.7	9.6	11.9	11.6	1.6, 6.9
PINP, µg/L	175	95	341	30	22, 96
OC[1–43], µg/L	18	27	64.7	13	11, 43
Bone ALP, µg/L	221.3	75.2	178.6	13.8	2.9, 20.9
CTX, µg/L	0.768	0.752	3.300	0.281	0.016, 0.584
uNTX/Cr, nM BCE/mM Cr	143	51	235	20	13, 78
uCa/Cr	0.24	0.24	1.19	0.39	0.07, 0.41

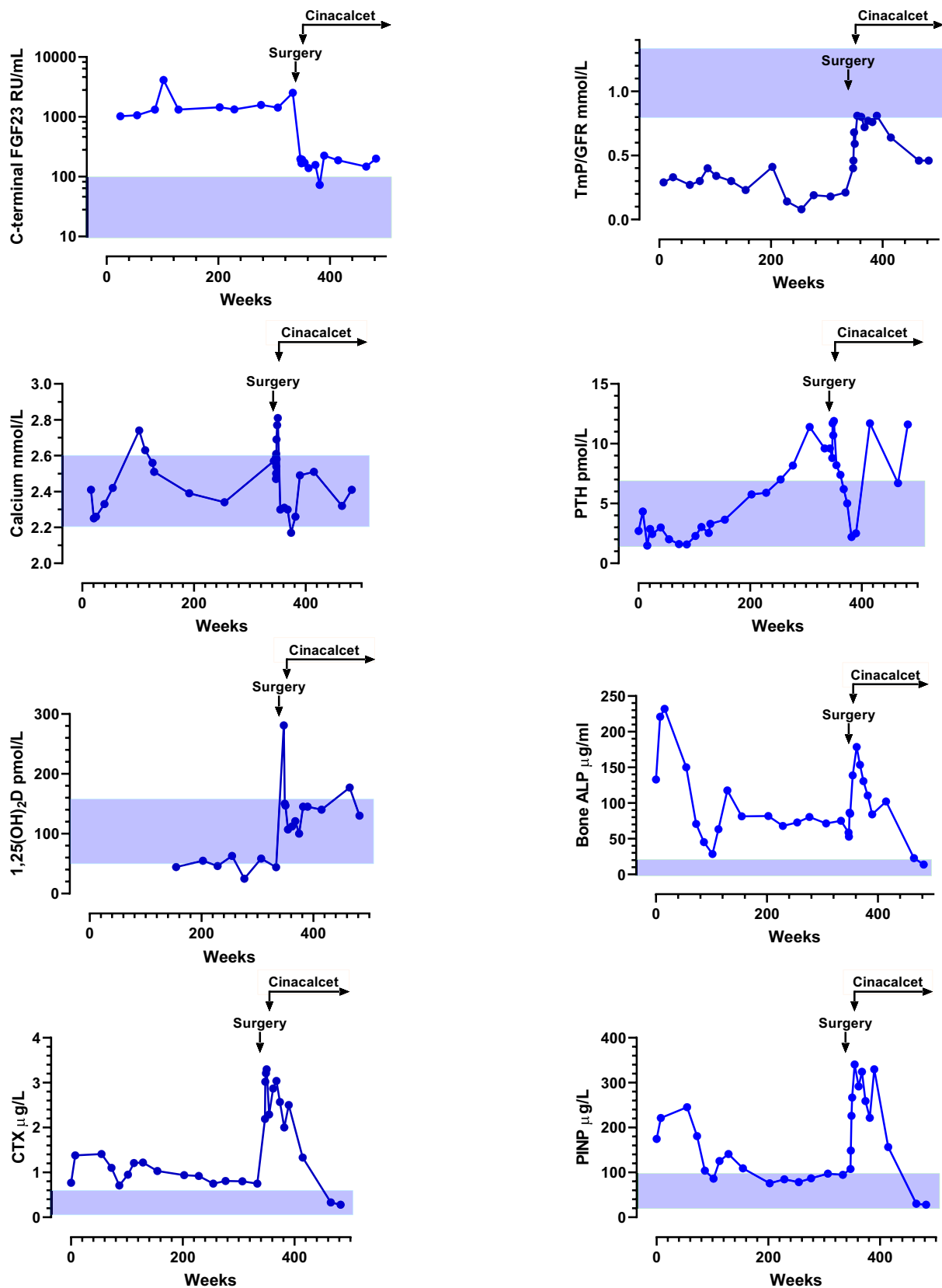


Fig. 1. Biochemical response to surgical resection of the PMT in case 1. Shaded areas represent reference intervals.

effective as judged by resolution of waddling gait, healing of the Looser zones, substantial improvement of bone remodeling markers (Fig. 1) and improvement in BMD, but she still had generalized aches and fatigue.

Imaging studies using computed tomography (CT) of chest and abdomen, magnetic resonance imaging (MRI) of total body, octreotide scintigraphy, and fluorodeoxyglucose PET all failed to identify a lesion that could be a source of excess FGF23. In August 2017, six years after diagnosis, she was referred to Uppsala University Hospital, Sweden, for  $^{68}\text{Ga}$ -DOTATATE-PET/CT. This identified a lesion deep in the left groin (Fig. 2). Subsequent MRI localized the lesion to left pectineus muscle (Fig. 2). Ultrasound-guided fine needle aspiration biopsy was performed, and histological findings were consistent with a PMT. At surgery, since the tumor was embedded in the pectineus muscle, both tumor and the surrounding muscle were excised. Surgical resection confirmed a PMT, and the margins were intact. The tumor was composed of uniform small ovoid to stellate cells embedded in a hyalinised eosinophilic matrix with a delicate background vascular network and characteristic grungy extracellular calcification (Fig. 3). An alteration involving the fibronectin 1 gene, typically described in PMTs was detected via fluorescent in situ hybridisation (FISH) studies that demonstrated break apart signals (Fig. 3) (Lee et al., 2016).

Immediately after surgery, she continued maintenance therapy with phosphate and alfacalcidol. TmP/GFR increased substantially but remained low ranging from 0.46 to 0.68 mmol/L. There was a marked decline in cFGF23, but it remained elevated (Fig. 1); iFGF23 was normal on 2 occasions (Table 1).  $1,25(\text{OH})_2\text{D}$  was high (Table 1, Fig. 1). Serum calcium adjusted for albumin (2.58 mmol/L) remained unchanged, but unexpectedly on day 4 after surgery she developed tertiary hyperparathyroidism with adjusted total calcium reaching a peak of 2.84 mmol/L at which time PTH was high 11.9 pmol/L (Table 1). She remained hypercalcemic for 15 days despite stopping treatment with phosphate and alfacalcidol. On starting cinacalcet 30 mg once daily, this led promptly to reversal of tertiary hyperparathyroidism with normalization of both calcium and PTH, and near-normalization of TmP/GFR (ranging from 0.72 to 0.81 mmol/L). By day 5 after surgery, there was a marked surge in the bone resorption markers (CTX and uNTX) and bone formation markers (PINP, OC[1–43], bone ALP) consistent with a high bone turnover state (Table 1, Fig. 1). The pattern of change in bone ALP was different compared to that of CTX and PINP, as evidenced by a smaller rise in bone ALP (Fig. 1).

Over the following 33 months, she had persistent mild lowering in

TmP/GFR in the presence of elevated cFGF23 (ranging from 147 to 200 RU/mL) but normal iFGF23 at 85.8 ng/L;  $1,25(\text{OH})_2\text{D}$  was high-normal and PTH was mildly elevated (Table 1). At 33 months after surgery, serum and urine biomarkers of bone resorption and bone formation markers had normalized (Table 1, Fig. 1). She has remained on cinacalcet. She had a short spell of non-adherence to cinacalcet at 33 months after surgery that resulted in temporary worsening of secondary hyperparathyroidism as evident by rise in PTH to 11.2 pmol/L and lowering of TmP/GFR to 0.46 mmol/L (Fig. 1). Since she was postmenopausal and had persistent high remodeling activity with secondary hyperparathyroidism, for the final year of follow-up she had been treated with alendronate 70 mg once weekly that would have contributed to further lowering of bone biomarkers. Clinically, her symptoms of hypophosphatemia, related to bone and muscle, completely resolved but she had a mild left-sided limp related to the removal of the pectineus muscle. BMD was monitored 6 times over 8 years. After 4 years of medical therapy prior to TIO surgery, BMD increased by 6.5% at lumbar spine and by 16.5% at left hip but then declined back to baseline over the next 3 years coincident with secondary hyperparathyroidism. BMD 15 months after surgery increased by 5.0% at spine and by 7.6% at left total hip.

### 3.2. Case two

A 37-year-old man presented in February 2018 with a recent history of severe proximal myopathy, bone pain, and spinal hyperkyphosis with estimated 12 cm loss of height. Spinal radiographs demonstrated biconcavity of all vertebrae in the dorso-lumbar spine, typical of the “codfish” spine seen in osteomalacia. A radionuclide bone scan identified stress fractures of the first and second metatarsal bones. Tests performed at presentation showed low TmP/GFR, high cFGF23, low  $1,25(\text{OH})_2\text{D}$ , minimally elevated PTH, normocalcemia, and normal renal function (Table 2, Fig. 4). Serum and urine biomarkers of bone resorption (CTX and uNTX) and serum biomarkers of bone formation (bone ALP and PINP) were elevated; OC[1–43] was not elevated (Table 2, Fig. 4). BMD, which was reported as Z-scores because he was under 40 years old, showed BMD to be below expected for age with Z-scores as follows:  $-3.3$  at lumbar spine,  $-2.5$  at left femur neck, and  $-0.2$  at left total hip site.

Medical therapy from the outset included elemental phosphate 1 g daily as replacement therapy, alfacalcidol 2  $\mu\text{g}$  daily, and cinacalcet 60

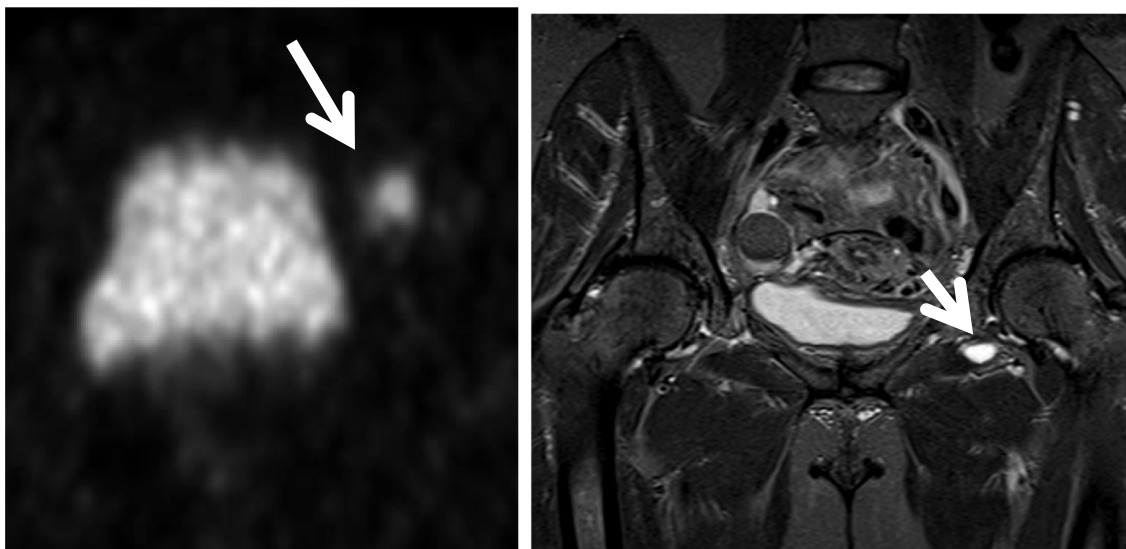
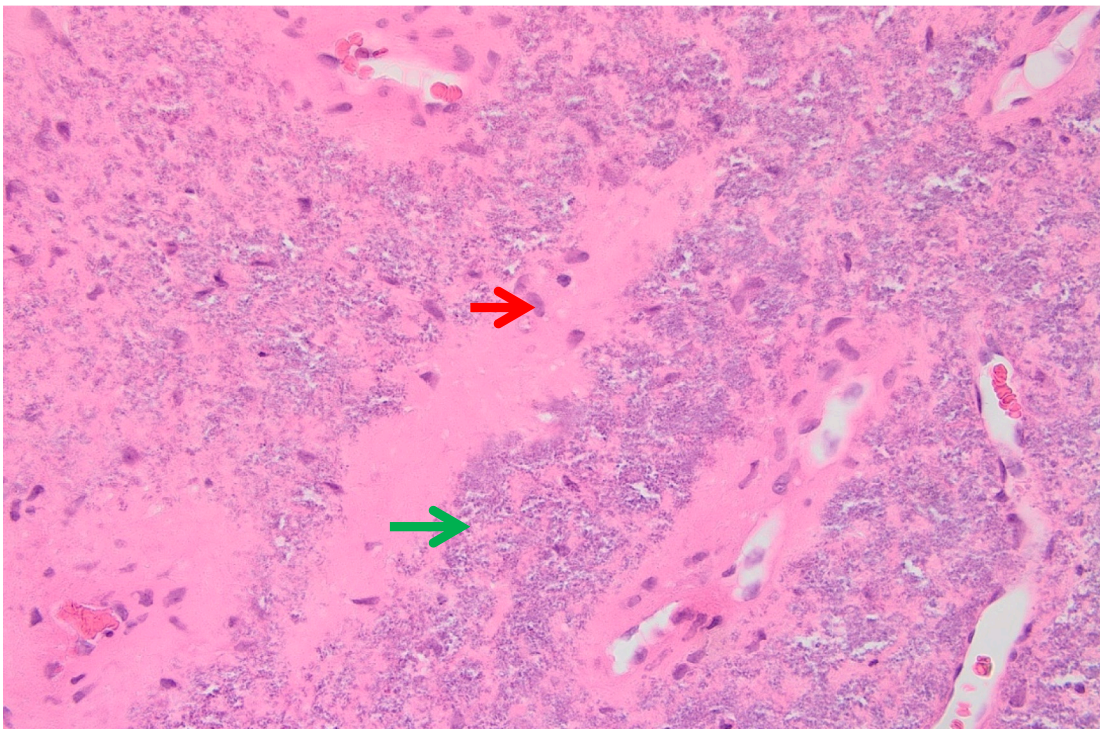
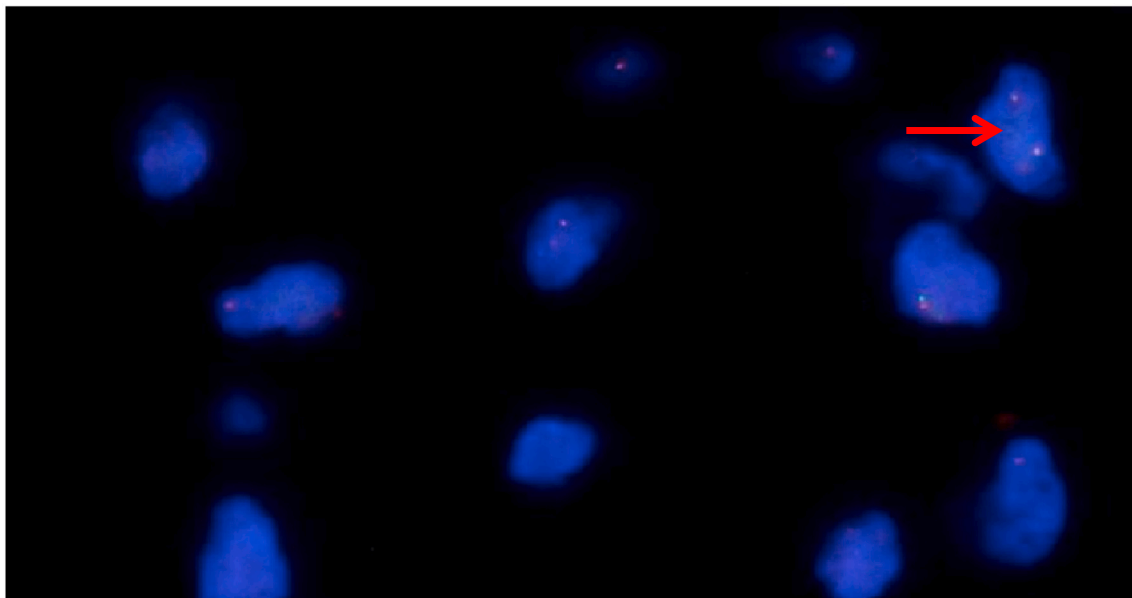


Fig. 2. Imaging in case 1: Left panel is an axial image from the  $^{68}\text{Ga}$ -Dotatate PET/CT scan demonstrating a lesion in the left inguinal region, with physiological activity in the adjacent urinary bladder; Right panel is a coronal section fat-suppressed (STIR) MR image demonstrating a corresponding high signal lesion in left pectineus.



a



b

**Fig. 3.** a: Histopathology of case 1 showing small uniform stellate cells (red arrow) embedded in a hyalinised eosinophilic matrix with characteristic grungy basophilic extracellular calcification (green arrow).

b: Fluorescent in-situ hybridization in case 1 demonstrating FN1 gene alteration in tumor specimen characterised by break apart signals (red arrow).

mg daily because he had secondary hyperparathyroidism at the time of initial presentation to our care; PTH returned to normal, but he had a transient episode of hypocalcemia (Fig. 4). A few months after presentation, he was referred in August 2018 to Uppsala University Hospital for  $^{68}\text{Ga}$ -DOTATATE-PET/CT that identified a lesion in his right foot (Fig. 5). Subsequent MRI localized the lesion adjacent to the first metatarsal, which coincidentally was the site of a Looser zone (Fig. 5).

Ultrasound-guided biopsy identified histological features of PMT. It was excised, and it was shown to be infiltrating bone and muscle. Surgical resection confirmed a PMT. This tumor showed the typical characteristic features, including small uniform stellate cells embedded in a hyalinised matrix with scattered giant cells and grungy extracellular calcification. FISH studies did not detect an alteration of the fibronectin 1 gene in this tumor.

**Table 2**  
Biochemical results at key time points in case 2.

Variables	At diagnosis	Before surgery	Shortly after surgery	37 months after surgery	Reference intervals
TmP/GFR, mmol/L	0.35	0.23	1.83	1.30	0.81, 1.35
Phosphate, mmol/L	0.57	0.42	1.56	1.08	0.80, 1.50
cFGF23, RU/mL	309	362	79	65	< 100
iFGF23, ng/L	n/a	n/a	46.8	27.9	33, 110
1,25(OH) <sub>2</sub> D, pmol/L	15	49	326	111	55, 139
25OHD, nmol/L	43	31	23	27	30, 125
Total calcium, mmol/L	2.35	2.22	1.98	2.49	2.20, 2.60
Ionized calcium, mmol/L	1.24	1.15	1.05	1.25	1.15, 1.33
PTH, pmol/L	7.0	3.2	8.3	5.5	1.6, 6.9
PINP, µg/L	131	109	595	55.8	22, 96
OC[1–43], µg/L	20	20	142	27.1	11, 43
Bone ALP, µg/L	131.8	160.2	125.8	18.6	2.9, 20.9
CTX, µg/L	0.792	0.892	5.320	0.362	0.016, 0.584
uNTX/Cr, nM BCE/mM Cr	85	79	350	25	13, 78
uCa/Cr	0.11	0.03	0.09	0.33	0.07, 0.41

After surgery, he continued maintenance therapy with phosphate, alfacalcidol and cinacalcet. TmP/GFR increased steadily to a high level, being 1.83 mmol/L on day 23 (Table 2, Fig. 4). All post-operative cFGF23 measurements were within the reference interval, ranging from 61 to 86 RU/mL (Table 2, Fig. 4). After surgery, 1,25(OH)<sub>2</sub>D was high and it remained high for 3 months (Fig. 4). He became hypocalcemic immediately after surgery; serum adjusted total calcium remained low for 4 days with the nadir being 2.03 mmol/L. Oral calcium 1000 mg in split doses was added. Despite continuing cinacalcet, PTH increased after surgery being high on day 3. Cinacalcet was reduced to 30 mg daily before being stopped 8 weeks after surgery. TmP/GFR, which had remained high, settled to within the reference interval after stopping cinacalcet (Fig. 4). Regarding bone remodeling indices, immediately after surgery there was a marked surge in the bone resorption markers (CTX and uNTX) and bone formation markers (PINP, OC[1–43], bone ALP) consistent with a high bone turnover state (Table 2, Fig. 4). The pattern of change in bone ALP was different compared to that of CTX and PINP, as evidenced by a smaller rise in bone ALP (Fig. 4). At 37 months post op, all biochemical indices had returned to normal (Table 2, Fig. 4). He had complete resolution of all symptoms related to hypophosphatemia but had residual shortened stature and dorsal hyperkyphosis. BMD, 2 years after surgery, showed a marked increase (by 70.0% at spine and by 28.3% at total hip) with Z-scores of +1.3 at spine, +1.6 at left femur neck, and – 0.2 at left total hip.

#### 4. Discussion

We have shown the immediate impact of PMT resection on the biochemical indices of phosphate metabolism, calcium metabolism, vitamin D metabolism, and bone remodeling activity. At presentation, both patients had clinical, biochemical, and imaging findings consistent with severe proximal myopathy and osteomalacia (McKenna et al., 2014; McKenna et al., 1983). Both patients had secondary hyperparathyroidism. Medical therapy prior to TIO surgery partly improved remodeling markers in both cases. The impact of surgical resection was

dramatic in both cases as manifested by: normalization of TmP/GFR; high 1,25(OH)<sub>2</sub>D; transient worsening of hyperparathyroidism that was responsive to cinacalcet; and a marked increase in markers of bone resorption and bone formation that was consistent with high bone turnover.

The reasons for the dramatic changes in calcium, PTH, 1,25(OH)<sub>2</sub>D, and bone remodeling markers are best explained by considering four factors: clinical severity of osteomalacia at presentation; the success of the surgery in eliminating ectopic FGF23 production; the degree of hyperparathyroidism at the time of surgery; and healing of osteomalacia. Both patients had severe TIO at presentation and both had successful surgery. In addition, both patients had hyperparathyroidism prior to surgery that was exacerbated after surgery. Case 2 had hypocalcemia with secondary hyperparathyroidism that has been shown in other TIO cases immediately after surgery (Kumar and Diamond, 2020; Rendina et al., 2009; Raborn et al., 2020). Case 1 had worsening of tertiary hyperparathyroidism, without hypocalcemia, that did not settle until cinacalcet was administered; this phenomenon has not been described previously. Healing of osteomalacia proceeded steadily, as evident by the decline in bone ALP, which is the best biochemical marker of mineralization (Szulc and Delmas, 2008).

We speculate that the marked increase in bone turnover after surgery is explained, in part, by exacerbation of hyperparathyroidism in both cases. Unlike the HBS that is reported after parathyroid surgery where there is a negative remodeling balance due to sudden curtailment of bone resorption, the bone response after surgery for TIO is a high bone turnover state. We also speculate that the tendency to hypocalcaemia as a consequence of osteoid mineralization with healing of osteomalacia may be mitigated by the high bone turnover state.

There are two possible explanations for hyperparathyroidism in TIO based on observations in adults with X-linked hypophosphatemia (XLH), a congenital disorder that is analogous to TIO. Firstly, the commonest cause of secondary hyperparathyroidism in XLH is phosphate supplementation. A prospective cohort study of adults with XLH showed that those treated with phosphate and activated vitamin D compared to untreated had higher PTH and higher CTX that was deemed to be consistent with hyperparathyroidism driving the increase in bone resorption (Shanbhogue et al., 2018). Secondly, there is a tendency for hyperparathyroidism in untreated patients with XLH (Carpenter et al., 1994). By lowering 1,25(OH)<sub>2</sub>D, FGF23 impairs intestinal calcium absorption, thereby predisposing to hyperparathyroidism. After TIO surgery, the tendency towards hyperparathyroidism is compounded by HBS; healing of osteomalacia predisposes to hypocalcemia that exacerbates hyperparathyroidism. This negative calcium balance is offset, in part, by increased Cyp27b1 activity with increased 1,25(OH)<sub>2</sub>D synthesis, because FGF23 declines and PTH increases; both patients had increased 1,25(OH)<sub>2</sub>D immediately after surgery and this high reading persisted for 3 months in case 2 that also may have mitigated the hypocalcemic effect of surgery.

Tertiary hyperparathyroidism, by definition, implies that it is preceded by secondary hyperparathyroidism usually of long duration. This transition to autonomous parathyroid function indicates 4-gland hyperplasia that is less responsive to usual feedback control (van der Plas et al., 2020). It is most common after successful renal transplantation for end-stage kidney disease with a prevalence ranging from 17% to 50% (Dulfer et al., 2017). Case 1 had long-standing untreated secondary hyperparathyroidism for over 5 years that had transitioned to tertiary hyperparathyroidism just prior to surgery. The worsening of tertiary hyperparathyroidism after surgery persisted for 2 weeks not resolving until introduction of cinacalcet. She remains on cinacalcet with ongoing evidence of mild secondary hyperparathyroidism.

Case 1 had a persistently low TmP/GFR after initial normalization. Although, cFGF23 has remained mildly elevated, iFGF23 was normal. As recently described, both PTH and FGF23 independently lower TmP/GFR but both are required for normalcy of renal phosphate handling (McKenna et al., 2021; Ovejero et al., 2021). It is possible that residual

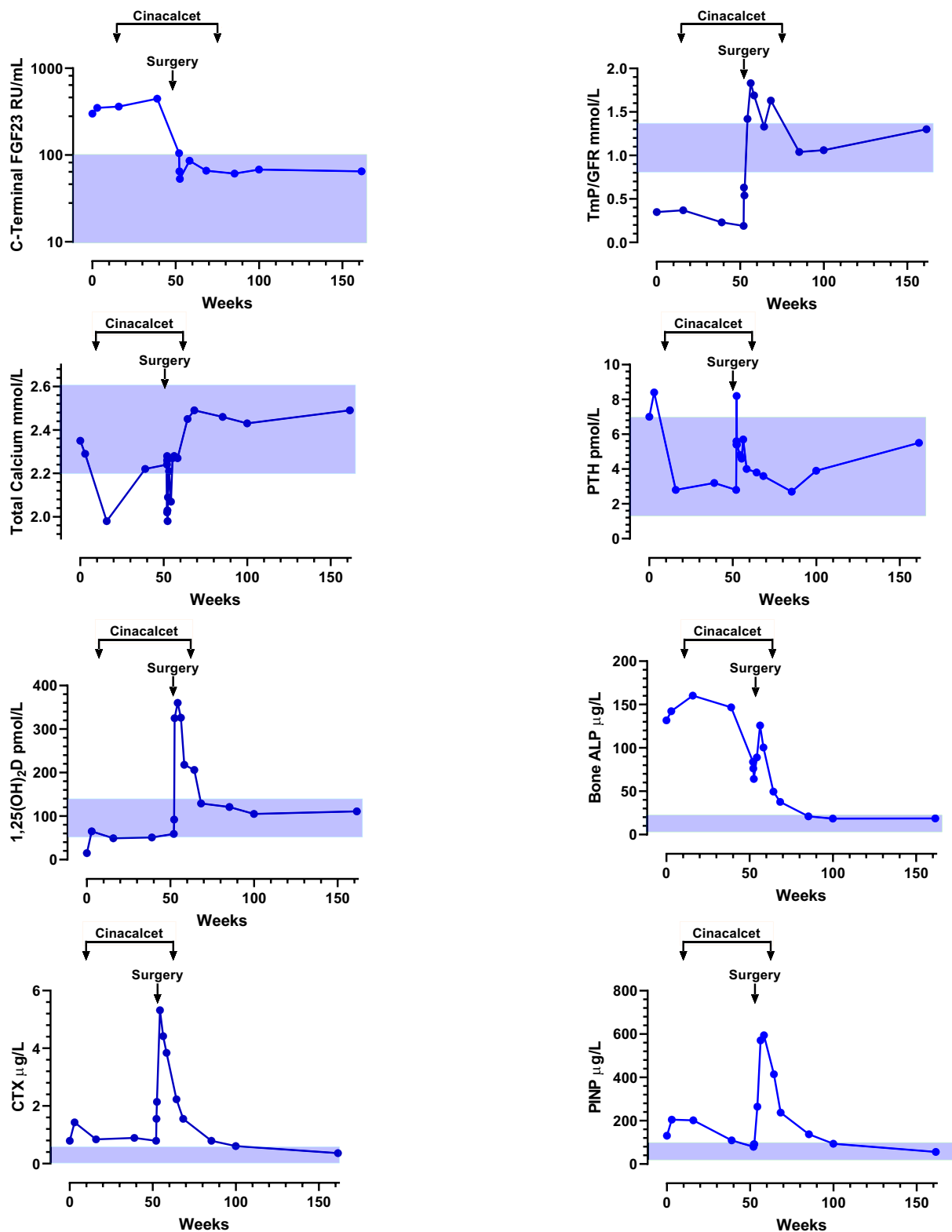
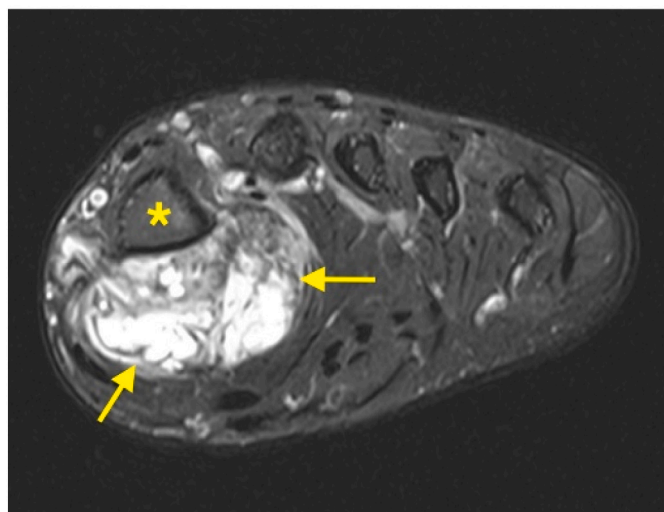
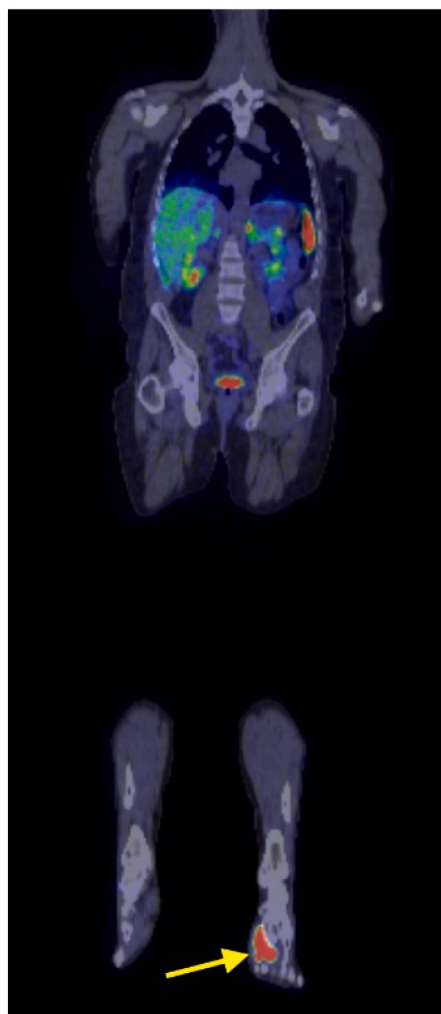


Fig. 4. Biochemical response to surgical resection of the PMT in case 2. Shaded areas represent reference intervals.

secondary hyperparathyroidism in case 1 accounts for lowering of TmP/GFR rather than residual tumor. The question about residual disease will only be resolved by long-term follow-up. Should long term follow-up favor residual tumor, then use of burosumab could be considered as an intervention if there was biochemical or radiographic evidence of osteomalacia (Jan de Beur et al., 2021; Imanishi et al., 2021).

Our case series and other reports of TIO (Kumar and Diamond, 2020; Rendina et al., 2009; Raborn et al., 2020) highlight the importance of comprehensive biochemical monitoring in the immediate post-operative period. There is a risk of profound hypophosphatemia; one case report showed respiratory failure necessitating mechanical ventilation (Ryhänen et al., 2021). We suggest that activated vitamin D and



**Fig. 5.** Imaging in case 2: top panel is a coronal fused  $^{68}\text{Ga}$ -DOTATATE PET/CT image showing focal avid increased uptake in the medial aspect of the left foot (arrow); there is physiological uptake in the liver, spleen, and urinary tract. Bottom panel is a short-axis short-tau inversion recovery (STIR) image from subsequent MRI left foot showing a corresponding lobulated hyperintense soft tissue mass (arrows) which is plantar to the first metatarsal (asterisk).

phosphate treatment be continued after surgery. If HBS occurs after surgery, then additional supplemental calcium and phosphate may be indicated but minimizing use of intravenous phosphate would be advisable to avoid undue stimulation of parathyroid glands (Florenzano et al., 2017). Cinacalcet has a proven role in ameliorating the PTH effect on renal phosphate wasting in TIO (Geller et al., 2007). Based on our cases, we suggest that cinacalcet be considered for continuation through surgery or that it be started after surgery in the event of tertiary hyperparathyroidism. Administration of burosumab in advance of surgery for many months may be a future approach in preparing patients to avoid the catastrophic effects in the immediate post-operative time (Jan de Beur et al., 2021; Imanishi et al., 2021).

There are limitations to our observations and conclusions. A major limitation is the absence of bone histomorphometry that would discern the degree of osteomalacia and the degree of hyperparathyroid bone disease (Insogna et al., 2019). Since metabolic changes are rapid after surgery, even bone biopsy would be unlikely to detect and explain the rapid phenomena that we observed in our two cases. Thus, bone remodeling markers play a key role in patient follow-up and monitoring for disease recurrence. Another limitation is that case 1 with tertiary hyperparathyroidism did not have parathyroid gland imaging in order to assess for coincidental parathyroid adenoma.

## 5. Conclusion

In conclusion, we describe the bone and mineral changes, both immediate and long term, in two cases of TIO after surgical resection. Prior to surgery, both cases had severe TIO and hyperparathyroidism. Immediately after surgery there was evidence of a HBS in conjunction with secondary hyperparathyroidism in one case and tertiary hyperparathyroidism in the other case that was responsive to cinacalcet. After surgery, there is a marked increase in bone remodeling activity, both resorption and formation, consistent to a high bone turnover. Burosumab prior to surgery should ameliorate both osteomalacia and hyperparathyroidism, thereby minimizing perturbations in mineral metabolism after surgery for TIO.

## CRedit authorship contribution statement

Mark Kilbane: Conceptualization; data curation; formal analysis; investigation; co-writing original draft; writing-review and editing. Rachel Crowley: Conceptualization; writing-review and editing. Eric Heffernan: review of imaging studies; curation of imaging figures; writing review and editing. Clare D'Arcy: review of pathology; curation of pathology figures; writing review and editing review. Gary O'Toole: performing surgery on both cases; writing-review and editing. Patrick Twomey: methodology; writing-review and editing. Malachi Mc Kenna: conceptualization; data curation; methodology; validation; preparing graphs; co-writing original draft; writing-review and editing.

## Declaration of competing interest

MMcK received fees for lectures or advice from: Amgen, Clonmel Healthcare, Mylan, Pharmacosmos, and UCB. None of the other authors have any conflicts of interest.

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