Parathyroidectomy for tertiary hyperparathyroidism related to tumor-induced osteomalacia (TIO)

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ABSTRACT

Rare mesenchymal tumors secreting fibroblast growth factor 23, a hormone with phosphaturic properties, can cause hypophosphatemia, hypercalcemia, and hyperparathyroidism (HPT), and be responsible for tumor-induced osteomalacia (TIO). When the tumor is not identified, or is not resectable, daily phosphate supplementation and calcitriol administration are recommended. Treatment is usually initiated with sodium phosphate 500 mg/twice daily and calcitriol 5 mg/day. Monitoring of serum and urinary biomarkers is essential for adjusting pharmacological doses.

We report the case of a patient with TIO but no identified primary tumor, who, despite taking phosphate and calcitriol continuously for over 17 years, developed TIO-related tertiary HPT. Parathyroidectomy was necessary. During surgery, two hyperplastic parathyroid glands were excised, with intraoperative monitoring of circulating parathyroid hormone (PTH) decline. Postoperatively, calcium levels returned to normal, and PTH levels slightly increased.

When TIO is diagnosed, laboratory monitoring every 3–6 months is recommended to adjust phosphate supplementation and prevent increased PTH secretion and the development of secondary HPT. If secondary HPT does develop, cinacalcet may be used to maintain normal serum calcium levels. In the presence of tertiary HPT, the extent of parathyroidectomy should be carefully evaluated to correct the HPT without causing hypoparathyroidism.

KEYWORDS

Hyperparathyroidism, tumor-induced osteomalacia, parathyroidectomy, fibroblast growth factor 23 (FGF23).

Introduction

Tumor-induced osteomalacia (TIO) is a rare syndrome characterized by bone pain, muscle weakness, fatigue, and fragility fractures caused by defective bone mineralization [1,2]. Hypophosphatemia and hyperphosphaturia underpin these symptoms. TIO results from mesenchymal tumors secreting fibroblast growth factor 23 (FGF23), a peptide hormone with phosphaturic properties, known as a phosphatonin. Primarily found in bones and soft tissues, these tumors typically develop very slowly and remain small, with a diameter of around 3 cm when initially discovered. Malignancy occurs in fewer than 2% of cases [3]. Detecting these tumors can be challenging, as most diagnostic imaging methods, such as CT scans or MRI, often fail to reveal them. More effective techniques include total body scintigraphy using fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET/CT), as well as OctreoScan and DOTA-Scan, both leveraging somatostatin receptor expression [4]. Systemic venous sampling of FGF23 is a method used to confirm or help to localize suspicious lesions identified in imaging studies [5]. Additionally, blood sampling and FGF23 measurement in the superior and inferior vena cava at various levels can aid in localizing these tumors [4].

Hyperparathyroidism (HPT) in TIO is driven by two main mechanisms, depending on the therapeutic management: it can be caused by low levels of calcitriol (which is inhibited by FGF23), leading to hypocalcemia in patients not supplemented with phosphate and calcitriol, or by hyperphosphatemia in patients supplemented with phosphate alone. However, it may also result from poorly balanced phosphate and calcitriol supplementation therapy. Secondary or tertiary HPT has, until recently, always been described as an exceptional event in TIO, with few cases reported. In 2024, a systematic review of the literature [3] documented the occurrence of 28 tertiary HPT cases, with a mean diagnostic delay of 12.8 ± 8.5 years. More recently, Hoong et al., performing a retrospective and aggregate analysis of a cohort of 68 patients with TIO, identified 30 (44.1%) who developed secondary or tertiary HPT; they showed that TIO patients with a longer time to diagnosis, a higher baseline FGF23 level, and a higher maximal dose of phosphorus replacement are the ones more prone to developing these two parathyroid complications [6]. Table I summarizes the main features of published single case reports of tertiary HPT in TIO [1,7–23].

We recently saw a patient affected by TIO but with no imaging evidence of primary FGF23-secreting tumor, in whom severe hypercalcemic tertiary HPT developed about 17 years after the diagnosis of TIO, despite treatment with calcitriol and

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phosphate supplementation. This observation prompted us to perform a parathyroidectomy.

Case presentation

In June 2006, a 44-year-old woman presented for rib pain following coughing episodes due to bronchitis. She had had two full-term pregnancies and two abortions. There was no family history of cancer or degenerative disease. In the same year, she began to experience pain in the left foot and hip, and to limbs. Some weeks later she was diagnosed, by scintigraphy examination, with osteonecrosis of the left hip, for which she underwent hip resection and prosthesis implantation in the second half of 2007, followed by prosthetic revision in 2021. Biopsy of the removed bone tissue revealed myelodysplasia.

At the beginning of 2008, following hematological and bone metabolism consultations, osteomalacia due to hyperphosphaturia was diagnosed. A decrease in circulating calcitriol was also observed. TIO was suspected. CT and PET were negative, and bone scintigraphy was positive at the level of ribs VII, X, and XI, where fractures were detected on radiological examination. Total body somatostatin receptor scintigraphy revealed a low-density lesion in the left hip with SST2 receptor expression, consistent with post-surgical inflammatory repair processes following prosthesis implantation 6 months earlier. Evaluation of bone mineral density (BMD) showed hip osteopenia with a T score of -2.3 and a Z score of -2.0, and lumbar vertebral osteoporosis with a T score of -2.6 and a Z score of -2.1.

Starting in April 2008, the patient was treated with bisphosphonates (taken discontinuously), calcium supplementation (1000 mg/day, until 2013), phosphate supplementation (sodium phosphate 500 mg effervescent capsules, initially twice a day, increased to 3 capsules/day in 2020), and calcitriol (0.5 mcg once a day). The patient remained well, without undergoing further clinical evaluation, until the summer of 2023, continuing phosphate supplementation and calcitriol. She discontinued the bisphosphonates in 2020.

Table II summarizes the pharmacological therapies taken by the patient between April 2008 and December 2025.

Biochemical screening indicated persistently increased parathyroid hormone (PTH) levels, first documented in April 2008, suggestive of HPT, eventually leading to hypercalcemia detected in October 2024, over 17 years after the diagnosis of TIO (Table III).

PET with ^{18}F-choline revealed two areas of tracer accumulation. One was located in the posteroinferior portion of the left thyroid lobe, the other (larger and with higher uptake) was located posterior and inferior to the lower pole of the right thyroid. Neck ultrasound revealed two images on the right, one immediately above the subclavian artery measuring 12x10x7 mm, and two other smaller ones (9x7x3) near the lower thyroid poles bilaterally. The diagnosis of tertiary hyperparathyroidism was made. Whole-body PET/CT with ^{68}Ga-DOTATOC tracer was positive at cervical level in the area detected by the choline PET, but negative for other pathological locations with high SST2 receptor expression.

On May 30, 2025, the patient underwent parathyroid surgery to treat the tertiary HPT. Bilateral cervical exploration was performed: on the right, the superior parathyroid gland was located in its usual position, with normal volume, appearance, and consistency; the right inferior parathyroid gland was not in its usual position. The inferior right ectopic gland and superior left parathyroid were removed. The right thymic remnant was removed, but it did not contain any ectopic and/or supernumerary parathyroid glands. The subclavian artery was prepared near its emergence, and between it and the right carotid artery, a parathyroid gland measuring 20x16x11 mm was found embedded in the arterial adventitia. The left cervical side was then explored, where a parathyroid gland of normal size and appearance was found at the lower pole of the thyroid gland. Exploration of the anterior mediastinum was negative. The thymic remnant was removed, but no parathyroid glands were found. Instead, a clearly pathological mass measuring 14x8x6mm was found behind the thyroid lobe near the carotid artery. Upon section, the parenchyma showed cystic areas. Intraoperatively, the PTH level decreased from a baseline of 442 ng/L to 368 ng/L (n.v. 18–88) at the time of clamping the pathological right parathyroid gland, further decreasing to 198 ng/L 20 minutes after removal of this gland, and finally reaching 62 ng/L five minutes after removal of the pathological left parathyroid gland. Pathology showed nodular hyperplasia in both the excised parathyroid glands.

The postoperative course was uneventful. No symptoms of hypocalcemia were observed. After parathyroid surgery the patient continued treatment with two 250 mg effervescent capsules of sodium phosphate daily and calcitriol 0.25 mcg twice daily. Results of postoperative biochemical screening, available up to December 2025, are summarized in Table IV. Postoperative biochemical values of PTH and calcium indicated persistence of HPT in normocalcemia, to be reevaluated over time.

Discussion

Most patients with TIO are adults with a mean age at diagnosis of around 46 years [3,21]. Male sex is prevalent. The time to diagnosis is estimated to be between 3 and 4 years [24]. Rheumatic, musculoskeletal, or neuropsychiatric misdiagnoses are common [17]. Osteoporosis is frequently detected at diagnosis, especially in female patients [17]. Prolonged exposure to phosphaturia prior to diagnosis may lead to severe osteomalacia due to impaired osteoid mineralization and decreased bone apposition.

At diagnosis, most patients (more than 95%) have hypophosphatemia, elevated serum phosphatase alkaline levels, and high levels of circulating FGF23. Osteocytes physiologically produce FGF23 and are the principal regulators of serum phosphorus homeostasis, acting through a combination of effects on renal phosphate transport and vitamin D metabolism. Phosphate reabsorption in the proximal convoluted tubule is dramatically reduced if FGF23 is increased. Synthesis of 1,25(OH)$_2$ vitamin D is also reduced since FGF23 inhibits 25(OH) vitamin D 1α-hydroxylase activity. The consequences include subnormal circulating 1,25(OH)$_2$ vitamin D levels, decreased bowel phosphorus absorption, and a decrease in renal tubular phosphate reabsorption [25].

Table I Published cases of tertiary HPT caused by TIO.

REFERENCE	YEAR OF PUBLICATION	N. CASE(S)	CLINICAL CASE(S)	PHARMACOLOGICAL TREATMENT FOR TIO	TUMOR RESECTION*	FEATURES OF TERTIARY HPT	TREATMENT FOR TERTIARY HPT	PARATHYROIDECTOMY OUTCOME
Olefsky *et al.*[7]	1972	Single case report	A 40-year-old man with TIO caused by an ossifying mesenchymal tumor of right lateral pharyngeal wall.	Initial therapy: Oral vitamin D (500,000 IU) and 1.9 g phosphorus (administered as a 1:1 mixture of sodium phosphate and sodium biphosphate). Discontinuation of vitamin D after about 2 years, due to onset of hypercalcemia. Vitamin D (200,000 IU/day) was resumed about 3 years after interrupting the treatment.	Yes	Rapid increase of serum calcium values to hypercalcemic levels immediately after tumor resection, not controlled by cessation of vitamin D intake.	LSTPT	Data were retrospectively collected over a 6-year period.
Firth *et al.*[8]	1985	Single case report	A 44-year-old man with adult-onset hypophosphatemic osteomalacia due to a chondroblastoma in the lateral condyle of right femur.	Initial therapy: 50,000 IU vitamin D daily, increased to 200,000 IU/day nine months later. After 3 years vitamin D was decreased back to 50,000 IU/day. The same year, calcium supplement (6 g daily) was added. Three year later, calcium was discontinued replaced by an oral neutral sodium phosphate supplement (1.5 g/day) associated with 100,000 IU vitamin D a day.	Yes A first localized resection of the primary tumor, followed three years later by an above-the-knee amputation because a local recurrence of malignant metastatic chondrosarcoma.	Persistently elevated PTH in normocalcemia, identified by the time of surgery for recurrent chondrosarcoma. Calcium rose progressively over the following 9 years.	STPT The right inferior, left superior, and left inferior parathyroids and one third of the right superior gland were removed, and all found to be hyperplastic.	Serum calcium decreased to normal range, while phosphate remained lower than normal range.
Reid *et al.*[9]	1987	Single case report	A 57-year-old woman with a 16-year history of unexplained hypophosphatemia at the time of parathyroid surgery, initially diagnosed as "phosphate diabetes". A firm, mobile, soft tissue mass on the anteromedial aspect of the right ankle, was identified, showing intense uptake of technetium-99m on bone scintigraphy.	Initial therapy: Vitamin D2 and inorganic phosphate supplements (dosages not indicated).	No	Elevated PTH levels and marked hypercalcemia were found 13 years after the occurrence of hypophosphatemic osteomalacia.	LSTPT A single hyperplastic gland was removed.	Persistence of elevated PTH after surgery in normocalcemia.

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Narváez *et al.* [10]	1996	Single case report	A 44-year-old man with a sporadic form of adult-onset hypophosphatemic osteomalacia. The presence of a causative tumor was not investigated	Initial therapy: Oral phosphate 2g daily, calcium supplements (1–3 g/day) and vitamin D 200,000 IU daily. Vitamin D was increased to 400,000 IU/day 18 months later. Six months later, due to an episode of vitamin D toxicity, this was decreased to 200,000 IU daily and calcium was discontinued. About 20 months later, vitamin D was substituted by calcitriol 0.25 mcg/day in association with inorganic phosphorus (2–2.5 g daily).	No	Eleven years after the diagnosis of hypophosphatemic osteomalacia, serum calcium rose progressively and was found to be associated with elevated PTH and serum creatinine.	STPT The right superior, right inferior and left inferior parathyroids, and one half of the left superior gland were removed, and all found to be hyperplastic.	PTH and serum calcium decreased to normal values a month after surgery; impairment of renal function remained unchanged.
Huang *et al.* [11]	2000	Single case report	A 39-year-old woman with TIO caused by grade III osteosarcoma of the right scapula.	Initial therapy: High-dose phosphate (3.5 g daily) and alphacalcidol (2 µg daily). Discontinued after osteosarcoma resection.	Yes	First symptoms (elevated PTH, elevated serum calcium, reduced serum phosphate) appeared 9 months after primary osteosarcoma resection due to the presence of metastases in the lung.	STPT The left (adenoma) and right superior parathyroids were removed.	Serum calcium decreased to normal range, while phosphate remained lower than normal range.
Moreira *et al.* [12]	2006	Single case report	A 49-year-old woman with hypophosphatemic osteomalacia of unknown cause (no tumor was identified).	Initial therapy (before parathyroid surgery): phosphate solution (2 g/day) + vitamin D3 in increasing doses (initially 28,000 IU/day), in addition to calcium carbonate. After 5 years: vitamin D supplement was replaced by calcitriol (1 µg /day), while maintaining the phosphate solution (2 g/day) After parathyroid surgery: calcitriol 0.25 µg /day and calcium carbonate were restarted.	No	Frank hypercalcemia and elevated levels of intact PTH were detected for the first time at the age of 59 years.	STPT Three visibly enlarged parathyroid glands were removed (all adenomas); the fourth gland was not located.	Four days after surgery, calcium and PTH levels remained at the upper limit of normal, suggesting persistent autonomous HPT (probably due to a fourth adenoma, not yet located). Eight months after surgery, laboratory tests remained unchanged (still with low phosphorus), without, however, overt hypercalcemia.
Tartaglia *et al.* [13]	2006	Single case report	A 65-year-old woman with TIO caused by a left groin hemangiopericytoma.	Initial therapy: clodronate, oral administration of calcium salts and vitamin D (dosages not indicated). After tumor surgery: calcitriol and phosphate supplement (dosages not indicated).	Yes	Persistence of low levels of serum phosphate after hemangiopericytoma resection, in association with increased values of serum calcium and PTH. Not resolved by phosphate supplement discontinuation.	STPT Both the left parathyroid glands and the inferior right parathyroid gland were removed (all enlarged and found to be hyperplastic). The left superior parathyroid gland appeared normal in size and was left *in situ*.	Serum calcium, PTH and phosphate returned to normal values.

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Nguyen [14]	2006	Single case report	A 65-year-old man with oncogenic osteomalacia caused by a PMT located within the medial aspect of the proximal right thigh.	Initial therapy: Synthetic vitamin D analog (dosage not indicated).	Yes	Hypercalcemic tertiary HPT.	STPT The right superior and the left inferior parathyroid glands were removed, both being hyperplastic.	Not reported.
Hu *et al.* [15]	2015	Single case report	A 26-year-old woman initially diagnosed with vitamin D-resistant hypophosphatemic osteomalacia. Twenty years later, a PMT located in the right forearm was discovered, leading to the diagnosis of TIO.	Initial therapy: Phosphate (1 g four times daily) and calcitriol (0.5 µg twice daily).	Yes	Elevated intact PTH and increased serum calcium at the time of TIO diagnosis, not resolved after PMT resection and discontinuation of calcitriol and phosphate supplement. Two right extrathyroidal nodules (~ 1 cm) were detected by neck ultrasound and focus was seen at the right upper pole of the thyroid on a sestamibi scan.	Cinacalcet 30 mg twice daily for 8 months, then decreased to 30 mg once a day.	Normalization of calcium values and reduction of intact PTH levels.
Yavropoulou *et al.* [16]	2015	Single case report	A 39-year-old man diagnosed with oncogenic osteomalacia caused by a recurrent left leg PMT.	Initial therapy: Oral phosphate and calcitriol supplementation (dosages not indicated).	Yes	First symptoms (elevated PTH, elevated serum calcium, reduced serum phosphate) appeared 9 months after primary osteosarcoma resection due to the presence of metastases in the lung.	STPT The left (adenoma) and right superior parathyroids were removed.	Serum calcium decreased to normal range, while phosphate remained lower than normal range.
Huang *et al.* [11]	2000	Single case report	A 39-year-old woman with TIO caused by grade III osteosarcoma of the right scapula.	Initial therapy: High-dose phosphate (3.5 g daily) and alphacalcidol (2 µg daily). Discontinued after osteosarcoma resection.	Yes First surgery: Resection of a large PMT located in the upper part of the left gastrocnemius measuring and infiltrating the upper third of the fibula. Second surgery (one year later): resection of the remnant PMT due to recurrence. Third surgery (9 years after first intervention): Amputation of left limb up to the height of the distal femur due to a recurrent PMT in the head and the upper third of the left fibular diaphysis.	Three months after amputation, increase of serum calcium and PTH and hypercalciuria.	LSTPT The hyperplastic left inferior parathyroid gland was removed.	PTH and serum calcium levels decreased, but did not normalize. Cinacalcet was added.

REFERENCE	YEAR OF PUBLICATION	N. CASE(S)	CLINICAL CASE(S)	PHARMACOLOGICAL TREATMENT FOR TIO	TUMOR RESECTION*	FEATURES OF TERTIARY HPT	TREATMENT FOR TERTIARY HPT	PARATHYROIDECTOMY OUTCOME
Florenzano *et al.* [17]	2017	Single case report	A 55-year-old woman with TIO caused by a PMT in the posterior right lateral aspect of the T8 vertebral body.	Initial therapy: Calcitriol (2.25 µg twice a day), phosphorus (750 mg three times a day), and calcium (500 mg three times a day).	Yes (after STPT)	At the age of 53 years: high serum PTH with normal calcium, low phosphorus and very low 24-hour urine calcium.	STPT Right hemi-thyroidectomy with resection of three parathyroid glands, all hyperplastic.	Significant transient hypocalcemia, requiring intravenous calcium, and persistent hypophosphatemia.
Kumar *et al.* [18]	2020	Single case report	An 8-year-old child with TIO caused by a PMT located on the left X rib.	Initial therapy: Oral phosphorus, activated vitamin D and calcium supplements (dosages not indicated) for 5 years. After TPT: oral phosphate supplementation and activated vitamin D (dosages not indicated).	Yes (after TPT, at the age of 21 years)	Marked hypercalcemia and elevated levels of PTH at the age of 13 years. Recurrent hypercalcemic tertiary HPT at the age of 19 years after 2 years discontinuation of cinacalcet.	LSTPT (first surgery at 13 years) The left inferior parathyroid was removed (adenoma). TPT (second surgery at 19 years) All the three removed glands were hyperplastic.	Calcium levels failed to normalize after first LSTPT, hence cinacalcet was added and continued for one year. After TPT, both calcium and PTH were reduced, while serum phosphate remained low.
Kilbane *et al.* [19]	2021	Single case report (within a case series of two patients)	A 52-year-old postmenopausal woman with TIO caused by a PMT located deep in the left groin.	Initial therapy: Elemental phosphate (starting at 2000 mg daily, reducing to 1000 mg daily after 2 years), alfacalcidol (2 µg daily). Post surgery: phosphate and alfacalcidol.	Yes	Gradually-developed secondary HPT that progressed to borderline tertiary HPT just 3 months prior to PMT surgery. Four days after PMT surgery, development of hypercalcemic tertiary HPT, which persisted even 15 days after discontinuation of phosphate and alfacalcidol.	Cinacalcet 30 mg once daily.	Reversal of tertiary HPT with normalization of both calcium and PTH.
Padera *et al.* [20]	2022	Single case report	A 27-year-old man with hypophosphatemic hyperphosphaturia initially diagnosed with "phosphate diabetes." TIO was caused by a small FGF23-expressing PMT, identified during investigations of a non-healing tibial fracture.	Initial therapy: Phosphate, calcium and vitamin D supplementation (dosages not indicated).	Yes	Immediately after PMT surgery, phosphatemia normalized but calcemia and PTH levels slowly increased (diagnosis of primary HPT). Nine years later diagnosis of hypercalcemic tertiary HPT with hypophosphatemia and nephrolithiasis.	STPT All the removed glands were hyperplastic.	PTH fell to undetectable levels while phosphatemia normalized.
Ni *et al.* [21]	2023	Seven single cases (within a series of 202 patients with TIO)	Case 1 TIO caused by a PMT	Initial therapy: Phosphate and calcitriol (dosages not indicated).	Yes	Hypercalcemic tertiary HPT	LSTPT Two parathyroid glands were removed (hyperplasia).	Normalization of total calcium, persistence of elevated PTH. Recurrence of tertiary HPT after one month, treated with cinacalcet.

REFERENCE	YEAR OF PUBLICATION	N. CASE(S)	CLINICAL CASE(S)	PHARMACOLOGICAL TREATMENT FOR TIO	TUMOR RESECTION*	FEATURES OF TERTIARY HPT	TREATMENT FOR TERTIARY HPT	PARATHYROIDECTOMY OUTCOME
			Case 2 TIO caused by a PMT	Initial therapy: Phosphate and calcitriol (dosages not indicated).	Yes	Hypercalcemic tertiary HPT	STPT Three parathyroid glands were removed (adenoma in one gland, hyperplasia of two glands)	Normalization of PTH and total calcium. No recurrence.
			Case 3 TIO caused by a PMT	Initial therapy: Phosphate and calcitriol (dosages not indicated).	Yes	Borderline calcium tertiary HPT	STPT Three parathyroid glands were removed (hyperplasia).	Normalization of PTH and total calcium. No recurrence.
			Case 4 TIO caused by a PMT	Initial therapy: Phosphate and calcitriol (dosages not indicated).	Yes	Borderline calcium tertiary HPT	LSTPT Two parathyroid glands were removed (adenoma).	Normalization of total calcium, persistence of elevated PTH. No recurrence.
			Case 5 TIO caused by a PMT and a spindle cell tumor	Initial therapy: Phosphate and calcitriol (dosages not indicated).	Yes	Borderline calcium tertiary HPT	STPT Three parathyroid glands were removed (hyperplasia).	Normalization of total calcium, persistence of elevated PTH. No recurrence.
			Case 6 TIO caused by a PMT	Initial therapy: Phosphate and calcitriol (dosages not indicated).	Yes	Hypercalcemic tertiary HPT	LSTPT Two parathyroid glands were removed (adenoma).	Normalization of PTH and total calcium. No recurrence.
			Case 7 TIO caused by a PMT	Initial therapy: Phosphate and calcitriol (dosages not indicated).	Yes	Hypercalcemic tertiary HPT	STPT Three parathyroid glands were removed (hyperplasia).	Normalization of PTH and total calcium. No recurrence.
Yang *et al.* [22]	2023	Single case report	A 57-year-old woman with hypophosphatemic osteomalacia caused by a PMT in the body of the hyoid bone.	Initial therapy: Phosphate and calcium supplements and vitamin D (dosages not indicated)	Yes	Hypercalcemic tertiary HPT	LSTPT (first surgery) A left hyperplastic parathyroid gland was removed. LSTPT (second surgery, performed 8 years after first LSTPT). The remaining left hyperplastic parathyroid gland was removed. Both the removed left parathyroids were classified as adenomatous nodular hyperplasia.	After first LSTPT, PTH levels remained high, and the patient presented with hypophosphatemia and hypercalcemia. After second LSTPT, serum phosphorus returned to normal. Two months later, a follow-up CT scan and parathyroid ultrasound showed no abnormalities.
Lai *et al.* [23]	2024	Single case report (within a series of 6 patients with PMTs)	A 38-year-old man with hypophosphatemic osteomalacia due to a PMT located at the left fibular head.	Initial therapy: irregular sodium phosphate treatment for 12 years (dosage not indicated).	Yes	Twelve years after phosphate treatment, highly elevated PTH levels were found, associated with persistent reduced eGFR and elevated serum creatinine, suggesting renal impairment. After PMT resection, PTH remained elevated despite normalization of serum phosphate levels. Neck ultrasound revealed multiple hypoechoic lesions on the posterior aspect of the parathyroid glands bilaterally.	TPT	Phosphate remained within the normal range, while elevated serum creatinine levels persisted, indicating ongoing renal impairment.

Abbreviations: **HPT** = hyperparathyroidism; **TIO** = tumor-induced osteomalacia; **PMT** = phosphaturic mesenchymal tumor; **TPT** = total parathyroidectomy; **STPT** = subtotal parathyroidectomy; **LSTPT** = less than subtotal parathyroidectomy; **eGFR** Estimated glomerular filtration rate. * = unless otherwise indicated, surgery for the phosphaturic tumor was performed before parathyroidectomy.

Table II Dosages and durations of pharmacological therapies between April 2008 and December 2025.

DRUG	DOSAGE	START OF THERAPY	END OF THERAPY	NOTE
Bisphosphonates	Neridronate sodium salt, 25 mg injected intramuscularly once a month	April 2008	2020	Taken discontinuously
	Oral ibandronate sodium salt, 150 mg once a month	April 2008	2020	Taken discontinuously
Calcium supplement	1,000 mg once a day	April 2008	2013	Taken discontinuously
Phosphate salt	Sodium phosphate, 500 mg/twice a day	April 2008	2020	
	Sodium phosphate, 500 mg/three times a day	2020	November 2024	
	Sodium phosphate, 500 mg/twice a day	November 2024	July 2025	
	Sodium phosphate, 250 mg/three times a day	July 2025 (post-parathyroidectomy)	Ongoing	
Calcitriol	0.5 mcg once a day	April 2008	July 2025	
	0.25 mcg twice a day	July 2025 (post-parathyroidectomy)	Ongoing	

Table III Results of biochemical screenings performed before parathyroidectomy for tertiary HPT.

DATE OF ANALYSES	PTH	TOTAL SERUM CALCIUM (uncorrected)	IONIZED CALCIUM	SERUM PHOSPHATE	25(OH) VITAMIN D	1,25(OH)^2 VITAMIN D	BONE ALKALINE PHOSPHATASE	SERUM FGF23	SERUM CREATININE	URINARY CREATININE 24H	URINARY CALCIUM 24H	URINARY PHOSPHATE 24H	eGFR
April 2008	**10.1 pmol/L** (n.v. 1.3–7.6)	9.7 mg/dl (n.v. 8.2–10.7)	Not assessed	**1.6 mg/dl** (n.v. 2.5–5.0)	53.2 ng/ml (n.v. 30–100)	**78.8 pg/ml** (n.v. 19.9–67.0)	42.1 µg/L (n.v. 4.0–14.3)	Not assessed	**0.42 mg/dl** (n.v. 0.50-0.90)	846 mg/24h (n.v. 800–1800)	**59 mg/24h** (n.v. 100–300)	763 mg/dl (n.v. 400–1000)	Not assessed
16 September 2024	**331 ng/dl** (n.v. < 72)	2.79 mmol/L (n.v. 2.15–2.55)	Not assessed	**0.92 mg/dL** (n.v. 0.81–1.45)	31 ng/ml (n.v. 30–100)	Not assessed	69.7% of total ALP activity Total ALP activity: 64 IU/L (n.v. 35–105)	Not assessed	**1.02 mg/dl** (n.v. < 0.9)	Not assessed	Not assessed	Not assessed	Not assessed
31 October 2024	**151 ng/dl** (n.v. < 72)	**12.0 mg/dl** (n.v. 8.2–10.7)	Not assessed	**1.6 mg/dl** (n.v. 2.5–5.0)	35 ng/ml (n.v. 30–100)	Not assessed	Not assessed	Not assessed	**1.06 mg/dl** (n.v. < 0.9)	Not assessed	186 mg/24h (n.v. 100–300)	836 mg/24h (n.v. 400–1000)	Not assessed
16 December 2024	Not assessed	Not assessed	Not assessed	Not assessed	51.2 ng/ml (n.v. 30–100)	49.9 pg/ml (n.v. 19.9–79.3)	Not assessed	**1652 pg/ml** (n.v. 23.2–95.4)	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed

Abbreviations: **PTH** = parathyroid hormone; **FGF23** = fibroblast growth factor 23; **eGFR** = estimated glomerular filtration rate; **n.v.** = normal values; **ALP** = alkaline phosphatase. Red color indicates values upper the limit of normal, while blue color indicates values lower the limit of normal.

Table IV Results of biochemical screenings performed after parathyroidectomy for the tertiary HPT.

DATE OF ANALYSES	PTH	TOTAL SERUM CALCIUM (uncorrected)	IONIZED CALCIUM	SERUM PHOSPHATE	25(OH) VITAMIN D	SERUM FGF23	SERUM CREATININE	URINARY CALCIUM 24H	URINARY PHOSPHATE 24H	eGFR
31 May, 2025 (first postoperative day)	7.5 ng/L (n.v. 18–88)	10.1 mg/dl (n.v. 8.3–10.6)	Not assessed	2.1 mg/dl (n.v. 2.3–5.1)	Not assessed	Not assessed	1.21 mg/dl (n.v. 0.55–1.02)	Not assessed	Not assessed	48 ml/min/1.73m² (n.v. ≥ 90; 45-59 = moderate decrease)
03 June, 2025 (4 days after surgery)	93.5 ng/L (n.v. 18–88)	8.6 mg/dl (n.v. 8.3–10.6)	Not assessed	2.0 mg/dl (n.v. 2.3–5.1)	Not assessed	231.6 pg/ml (n.v. 23.2–95.4)	1.09 mg/dl (n.v. 0.55–1.02)	Not assessed	Not assessed	54 ml/min/1.73m² (n.v. ≥ 90; 45–59 = moderate decrease)
12 June, 2025 (13 days after surgery)	103.0 pg/ml (14.0–72.0)	2.24 mmol/L (n.v. 2.15-2.55)	Not assessed	0.57 mmol/L (n.v. 0.81–1.45)	40 ng/ml (n.v. 31–100)	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
27 June, 2025 (4 weeks after surgery)	108.0 pg/ml (14.0–72.0)	2.30 mmol/L (n.v. 2.15–2.55)	4.0 mg/dl (n.v. 4.6–5.2)	0.62 mmol/L (n.v. 0.81–1.45)	51 ng/ml (n.v. 31–100)	Not assessed	Not assessed	0.3 mmol/24h (n.v. 2.5–7.5)	Not assessed	Not assessed
02 July, 2025 (about 5 weeks after surgery)	102.0 pg/ml (14.0–72.0)	2.34 mmol/L (n.v. 2.15–2.55)	4.1 mg/dl (n.v. 4.6–5.2)	0.48 mmol/L (n.v. 0.81–1.45)	52 ng/ml (n.v. 31-100)	Not assessed	0.94 mg/dl (n.v. 0.50–0.90)	0.8 mmol/24h (n.v. 2.5–7.5)	16 mmol/24h (n.v. 13–42)	Not assessed
02 December, 2025 (6 months after surgery)	Not assessed	9.85 mg/dl (n.v. 8.8–10.2)	Not assessed	2.1 mg/dl (n.v. 2.5–4.5)	62.7 ng/ml (n.v. 31–100)	Not assessed	1.04 mg/dl (n.v. 0.51–0.95)	33 mg/24h (n.v. 100–300)	1.3 g/24h (n.v. 0.4–1.3)	57 ml/min/1.73m² (n.v. > 60; 30-59 = moderate decrease)

Abbreviations: **PTH** = parathyroid hormone; **FGF23** = fibroblast growth factor 23; **eGFR** = estimated glomerular filtration rate; **n.v.** = normal values. Red color indicates values upper the limit of normal, while blue color indicates values lower the limit of normal

Chronic administration of phosphate and the increase in serum phosphate caused by calcitriol can contribute to increasing PTH secretion. Moreover, FGF23-induced inhibition of 1α-hydroxylase, leading to low calcitriol levels and potential hypocalcemia, further contributes to chronic PTH stimulation, if calcitriol is not adequately supplemented.

Recent years have seen growing attention to the occurrence of secondary and tertiary HPT in TIO. In 2022, Ni *et al*. [21] investigated the prevalence of HPT in a large cohort of 91 Chinese patients affected by TIO, finding secondary HPT in 41.6% and tertiary HPT in 3.5%. The 2024 systematic review of TIO cases by Alvarez-Rivas *et al*. documented the presence of tertiary HPT in 28 out of 1,979 TIO cases (1.4%) [3]. Secondary and tertiary HPT appeared several years after the onset of TIO. Elevated circulating FGF23 has been directly associated with PTH levels in TIO. However, the significant risk factor for the development of secondary and tertiary HPT is prolonged high-dose oral phosphate supplementation [26], as clearly observed in a longitudinal study of patients with X-linked hypophosphatemia (XLH) [8,26]. XLH is a congenital form of osteomalacia due to loss of function of the phosphate-regulating gene with homology to endopeptidases (*PHEX*) gene, located on the X chromosome. The consequence of this mutation is reduced expression of sodium-phosphate cotransporters on the apical surface of proximal renal tubule cells and a dramatic reduction of phosphate tubular reabsorption [27].

Laboratory monitoring, at 3- to 6-month intervals, of blood levels of calcium, phosphate, creatinine, PTH, and 25(OH) vitamin D, and of 24h urinary calcium excretion is recommended to modulate the phosphate supplementation and adjust the calcitriol dosage, in order to avoid increased secretion of PTH and the development of secondary HPT [28]. Our patient did not adhere to monitoring recommendations, continuing phosphate supplementation for several years without serum and urinary biomarker assessment.

A prolonged period of secondary HPT, characterized by hyperplasia of all parathyroid glands, can over time lead to the development of tertiary HPT. Although cinacalcet can be used

to maintain normal serum calcium levels, it generally has limited or no efficacy in tertiary HPT [29].

Surgery is the treatment of choice in tertiary HPT. However, its management in patients with TIO is challenging. The surgical option most commonly used in this setting is total parathyroidectomy with or without autotransplantation or subtotal parathyroidectomy, leaving a fragment of the less enlarged parathyroid gland. These surgical approaches have been widely adopted for resolving tertiary HPT related to chronic renal failure, where the risk of persistent or recurrent HPT is very high, and it is preferable to remove all the hyperplastic or adenomatous parathyroid tissue [30].

HPT in TIO may differ from that observed in chronic renal failure, potentially allowing better control of hypercalcemia with cinacalcet and/or adjustment of phosphate intake. Therefore, the extent of parathyroidectomy should be carefully evaluated in order to achieve correction of HPT without inducing hypoparathyroidism. Seven Chinese patients with tertiary HPT observed at Peking Union Medical College underwent surgical removal of only two or three parathyroid glands. Their circulating PTH level decreased from 427.0 pg/ml before surgery to 73.7 pg/ml after parathyroidectomy. HPT recurred in only one of these seven patients. The authors considered the HPT in the TIO patients to be less aggressive than that occurring in XLH patients, in whom a high rate of persistent and recurrent HPT was observed after total or subtotal parathyroidectomy [11]. One possible explanation is the lifetime use of phosphate supplementation in XLH patients.

Surgery for parathyroid disease has undergone significant changes in the past decade. While exploration of the parathyroid glands by experienced surgeons remains essential for successful HPT surgery, preoperative localization is also necessary in order to visualize ectopic parathyroid glands, which are frequently found in secondary and tertiary HPT [31]. Furthermore, neural monitoring is effective in preserving the integrity of the recurrent laryngeal nerves. Finally, intraoperative circulating PTH evaluation is helpful to check the surgical correction of HPT. Within minutes of the removal of hyperfunctioning parathyroid tissue, the circulating PTH level decreases or normalizes, as the half-life of intact PTH is very short (1–3 min).

This method has been widely applied in surgery for renal tertiary HPT and appears to be beneficial in optimizing surgical outcomes, as indicated by a recent systematic review [16]. In patients with chronic kidney failure, successful surgery of HPT is defined by a PTH decline of ≥80% within 20 minutes of parathyroidectomy [32,33].

In conclusion, HPT is a consequence of long-term phosphate treatment. Therefore, in TIO patients without localization of the phosphatonin-producing tumor, calcium metabolism and PTH secretion should be closely monitored. This approach allows clinicians to adjust phosphate supplementation therapy and introduce cinacalcet before tertiary HPT develops.

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