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Case Report

Hyperparathyroidism Jaw Tumor Syndrome, an Unforeseen Diagnosis

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Abstract

Asymptomatic primary hyperparathyroidism (PHPT) is often missed in developing nations due to limited formal healthcare exposure and biochemical screening programs. Many patients are thus only diagnosed once symptomatic. We present a 32-year-old female who developed bony protrusions in her jaw during pregnancy, resulting in a stillbirth. Three months later, during a dental consultation for worsening toothache, jaw abnormalities were detected. Radiological studies revealed bilateral mandibular radiolucent lesions, and bone biopsy confirmed histological features consistent with a brown tumor. These findings raised concerns about underlying PHPT, which was confirmed with a markedly elevated parathyroid hormone level in the presence of significant hypercalcemia. Further examination revealed impaired renal function, normal urine calcium excretion, and bilateral nephrocalcinosis. Low bone mineral density was measured with dual-energy X-ray absorptiometry, and conventional radiology identified additional low-density bony lesions in keeping with brown tumors. A parathyroid MIBI confirmed the presence of a singular parathyroid adenoma. A vague but possible family history, the patient's young age, and the severe renal and skeletal involvement prompted genetic testing. A cell division cycle 73 (*CDC73*) pathogenic variant, in keeping with primary hyperparathyroidism jaw tumor syndrome, was identified.

Key Words: hyperparathyroidism jaw tumor syndrome, brown tumor, familial hyperparathyroidism, parathyroid cancer, hypercalcaemia

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by excessive secretion of parathyroid hormone (PTH) and typically results in frank hypercalcemia (1). Most hyperparathyroidism (HPT) cases are sporadic and are caused by single parathyroid adenomas. Familial forms of hyperparathyroidism represent the minority of cases (2-5%). These include syndromic familial HPT such as multiple endocrine neoplasia (MEN) types 1, 2A, and 4; hyperparathyroidism jaw tumor syndrome (HPT-JT syndrome); and familial isolated hyperparathyroidism (FIHP). The familial syndromes are characterized by identifiable germline pathogenic variants, whereas most FIHP families (~80%) have no defined genetic basis and may, in some, merely reflect the clustering of sporadic cases among close relatives (1, 2).

We present a case of overt PHPT and an associated *CDC73* pathogenic variant in keeping with HPT-JT syndrome. This syndrome is very rare, and we discuss the clinical relevance of identifying syndromic forms of PHPT regarding their diagnostic approach, management, and surveillance.

Case Presentation

A 32-year-old female patient noted bilateral, painless growths on her lower jaw during her first pregnancy. The pregnancy was complicated by polyhydramnios, resulting in a stillbirth at 28 weeks' gestation. She did not seek immediate medical attention for the jaw lesions as she had no pain. Three months postpartum, she developed severe toothache. Her attending dentist noted the jaw tumors and confirmed the presence of bilateral radiolucent lesions on a mandibular x-ray. A computed tomography scan (Fig. 1) of the mandible illustrated keratocystic odontogenic tumors. A biopsy of 1 of the lesions was performed, and, on histology, fibrous tissue and an abundance of multinucleated giant cells were noted, in keeping with a diagnosis of a brown tumor.

This prompted an endocrine referral for assessment of suspected underlying PHPT. She had no specific complaints but, on questioning, reported constipation and generalized muscle aches and pains. Apart from endometriosis, she had no other medical history of note. She had not sustained any prior skeletal injury. She was unaware of specific diseases in her family but mentioned that her mother had neck surgery for an indication and at an age unknown to her. On clinical examination, bilateral bony lesions of the mandible (1-2 cm in width) were clearly visible, along with a nontender, bony prominence (2 × 3 cm) on the upper border of the second rib just lateral to the left sternal border. There were no other bony lesions or deformities. The thyroid examined normally, but a fullness was palpated left inferior to the thyroid with spotty lymph nodes concerning for a palpable parathyroid adenoma. She was normotensive, and her systemic examination was otherwise essentially normal.

Diagnostic Assessment

Diagnostic studies included an assessment of calcium homeostasis and parathyroid status, a radiological skeletal survey,

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ultrasonography of the neck and abdomen, a technetium-99 sestamibi parathyroid scan, a dual-energy X-ray absorptiometry (DXA) scan for assessment of bone mass, and genetic testing.

Her biochemical profile at presentation is noted in Table 1 and is in keeping with severe PHPT complicated by impaired renal function. Of note is the markedly more than 10-fold elevation in circulating PTH levels and an overt hypercalcemia of 3.4 mmol/L (2.15-2.50 mmol/L; 13.6 mg/dL).

X-ray findings of the chest and forearm were in keeping with multicentric brown tumors (Fig. 2A and 2B). A neck ultrasound revealed a suspected mixed cystic and solid nodule in or below the pole of the left thyroid lobe (Fig. 3). A parathyroid sestamibi scan confirmed the ultrasound finding to be due to a left inferior parathyroid adenoma (Fig. 4). A baseline DXA scan noted skeletal demineralization and low bone mass with a bone mineral density (BMD) Z-score lower than −3SD at all measured sites (axial spine and all proximal hip regions).

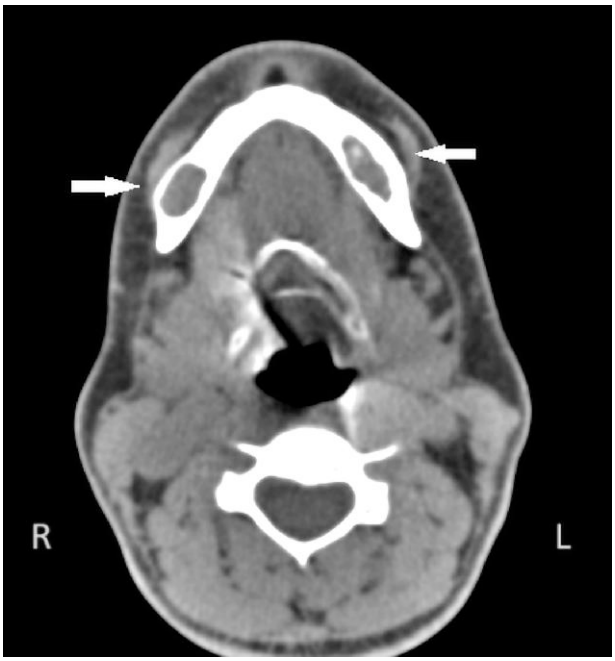

Figure 1. Computed tomography scan (axial view) of the mandible showing keratocystic odontogenic tumors.

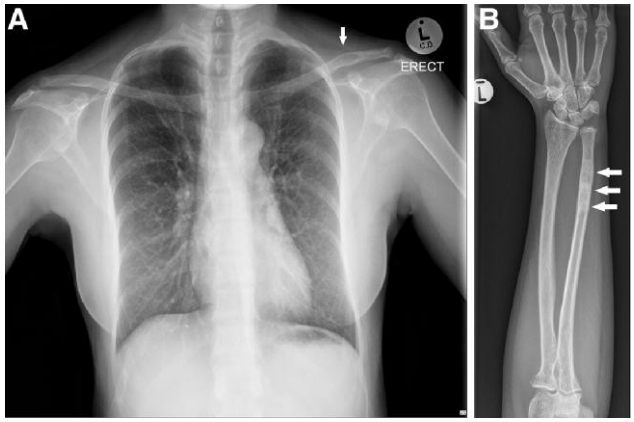

Figure 2. (A) Chest radiograph demonstrating a single lytic lesion in the distal one-third of the left clavicle; (B) X-ray of the left forearm showing multiple lytic lesions of the distal radius.

Table 1. Laboratory values

Biochemical parameter	Reference interval	Baseline	One-year post-surgery
Serum/plasma			
Parathyroid hormone	1.6-6.9 pmol/L 15.1-65.1 pg/mL	89.3 pmol/L (H) 842.1 pg/mL (H)	14.2 pmol/L (H) 133.9 pg/mL (H)
Total calcium	2.15-2.50 mmol/L 8.62-10.02 mg/dL	3.41 mmol/L (H) 13.67 mg/dL (H)	2.32 mmol/L 9.3 mg/dL
Inorganic phosphate	0.78-1.42 mmol/L 2.42-4.4 mg/dL	0.27mmol/L (L) 0.84 mg/dL (L)	0.68 mmol/L (L) 2.11 mg/dL (L)
Magnesium	0.63-1.05 mmol/L 1.53-2.55 mg/dL	0.77 mmol/L 1.87 mg/dL	
Albumin	35-52 g/L	50 g/L	
Alkaline phosphatase	42-98 U/L	317 U/L (H)	129 U/L (H)
25(OH)vitamin D	50-150 nmol/L 20-60 ng/mL	50.1 nmol/L 20.1 ng/mL	74.1 nmol/L 26.7 ng/mL
Creatinine	49-90 umol/L 0.55-1.02 mg/dL	107 umol/L 1.21 mg/dL	101 umol/L (H) 1.14 mg/dL (H)
eGFR[a]	>60 mL/min/1.73 m2	59	63
24-hour urine			
Daily urine calcium	2.50-7.50 mmol/24 hours 100-300 mg/24 hours	6.11 mmol/24 hours (H) 244.9 mg/24 hours (H)	
CCCR[b]	CCCR of <0.01 is suggestive of FHH;>0.02 excludes FHH	0.0282	

Abbreviations: 25(OH)vitamin D, 25-hydroxyvitamin D; CCCR, calcium to creatinine clearance ratio; eGFR, estimated glomerular filtration rate; FHH, familial hypocalciuric hypercalcemia; H, high; L, low.

[a]CKD-EPI (2021) eGFR = 142×min(SCr/κ,1)α×max(SCr/κ, 1) − 1.200 × 0.9938Age × 1.012 (if female). κ = 0.7 if female or 0.9 if male, α = −.241 if female or −0.302 if male. SCr is the serum creatinine in mg/dL, min is the minimum, and max is the maximum.

[b]$CCCR = \frac{urine\ calcium\ 2.34 mmol/L \times (serum\ creatinine\ 107 umol/L \div 1000)}{serum\ calcium\ 3.41\ mmol/L \times urine\ creatinine\ 2.6\ mmol/L}$.

No morphometric vertebral fractures were present. Abdominal ultrasonography illustrated the presence of bilateral nephrolithiasis with no adrenal mass lesions noted.

Given her young age, overt disease, and possible family history, a syndromic familial HPT was considered. Her clinical assessment and a detailed assessment of pituitary function excluded any MEN1 associations. MEN2A was unlikely as the patient was confirmed to be normotensive on numerous occasions; the neck imaging excluded any thyroid pathology, with no demonstrable adrenal lesion on abdominal ultrasonography. Genetic testing was performed to identify any potential pathogenic variants using the Invitae© hyperparathyroid panel consisting of the following 7 genes: *AP2S1, CASR, CDC73, CDKN1B, GNA11, MEN1,* and *RET*. The patient's genomic DNA was enriched with target regions using the hybridization protocol and gene sequencing with Illumina technology, which revealed a heterozygous *CDC73* pathogenic variant c.376C > T (p.Arg126) in keeping with a diagnosis of HPT-JT syndrome.

Treatment

The patient underwent a focused left inferior parathyroidectomy. Intraoperative PTH monitoring noted a more than 50% decline in levels in keeping with the successful removal of the hyperfunctioning parathyroid tissue. The intraoperative PTH levels decreased from a baseline value of 67 pmol/L (1.6-6.9 pmol/L; 631.8 pg/mL) to 11.6 pmol/L (109.4 pg/mL) at 10 minutes and to 9.7 pmol/L (91.5 pg/mL) at 20 minutes. Given the positive intraoperative PTH response, the attending surgeon did not proceed to further exploration of the neck. The postoperative course was uneventful; despite being at high risk for hungry bone syndrome, the patient maintained normal calcium levels on modest oral calcium and vitamin D support. Histology revealed a well-circumscribed, thinly encapsulated, solitary, oncocytic parathyroid adenoma. No increased mitosis, necrosis, capsular, or vascular invasion was found. The KI67 proliferation index was <1%, and multiple stains were negative for vascular invasion. A parafibromin stain for parathyroid carcinoma was not performed.

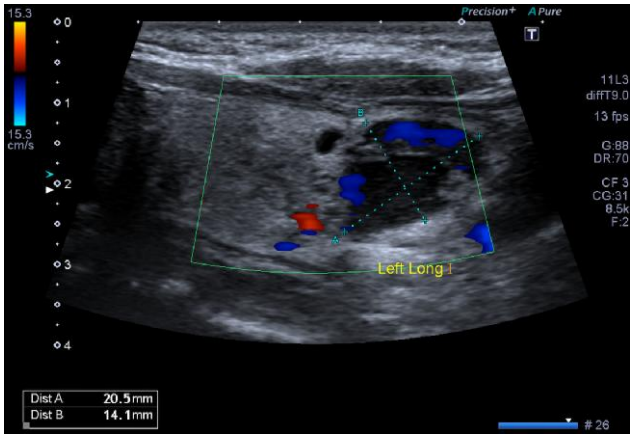

Figure 3. Ultrasound of the neck suggestive of a mixed cystic solid nodule of the inferior left thyroid lobe.

Outcome and Follow-up

Follow-up was delayed by 12 months due to an unrelated interim illness and work commitments. She remained well with no new skeletal concerns. She was counseled by her attending endocrinologist regarding her genetic profile and referred to a clinical geneticist for a more in-depth consultation, especially as she expressed the desire to conceive again. Follow-up biochemistry at 12 months confirmed a normal serum calcium level (Table 1). Although a significant decline in the PTH level was noted, it remained more than twice elevated in the presence of normal 25-hydroxyvitamin D levels (3). Of note is the persistence of impaired renal function (stage 2 chronic kidney disease) to partially account for the PTH elevation. A marked improvement in bone mineralization was confirmed with near normalization of alkaline phosphatase levels and a significant increase in DXA-BMD at all the measured skeletal sites 1 year after surgery (BMD increase 6.3-32.7%) (Fig. 5).

Discussion

This case describes a young female with overt PHPT, jaw lesions, and a *CDC73* pathogenic variant, findings that are in keeping with the rarely encountered familial HPT-JT syndrome. Jaw tumors complicated by dental involvement brought the index case to medical attention with a subsequent finding of severe PHPT.

PHPT is a common metabolic disease and, in countries with well-resourced screening programs, is mostly diagnosed while asymptomatic (4). In lesser-resourced countries, PHPT is still often only diagnosed when it manifests with systemic complications of hypercalcemia (4). Continuous skeletal exposure to high levels of PTH overshadows its anabolic effects, leading to excessive bone resorption, bone loss, and the formation of fibrous cysts (5). PTH binds to PTH1 receptors on the surface of osteoblasts, stimulating the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) (2). RANKL binds to RANK

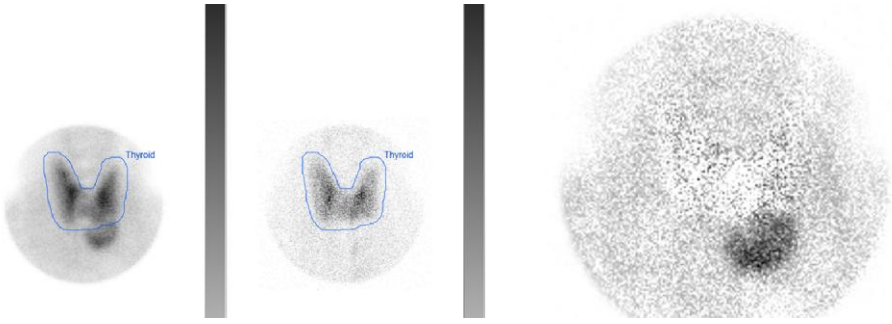

Figure 4. Technetium-99 sestamibi parathyroid scan demonstrating a single large area of discordance below the inferior pole of the left thyroid lobe in keeping with a hyperfunctioning left inferior parathyroid adenoma.

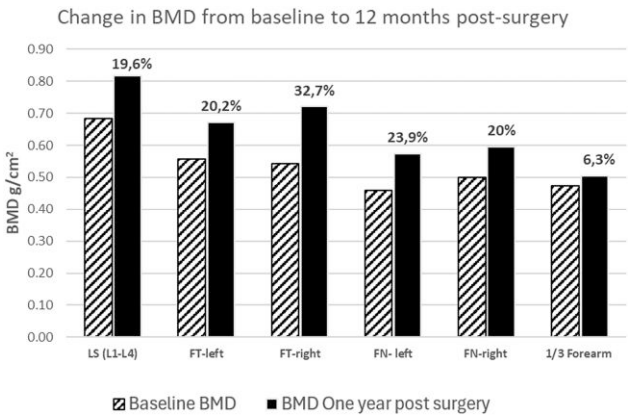

Figure 5. Dual-energy X-ray absorptiometry-bone mineral density-BMD response to successful removal of parathyroid adenoma at 12 months. BMD response indicated as change in areal BMD in g/cm^2 and as percentage change from baseline at different skeletal sites. Abbreviations: BMD, bone mineral density; FN, femoral neck region; FT, total femoral region; LS, lumbar spine.

precursors on osteoclasts, thereby enhancing the formation of activated osteoclasts and increased bone resorption (2).

Osteitis fibrosa cystica is a late and rare manifestation of prolonged and severe PHPT (5). It is characterized clinically by bone pain and radiographically by severe skeletal demineralization with subperiosteal bone resorption on the radial aspect of the middle phalanges, tapering of the distal clavicles, a "salt and pepper" appearance of the skull, bone cysts, and the presence of so-called "brown" tumors (6). These brown tumors result from excess osteoclast activity and consist of collections of osteoclasts intermixed with fibrous tissue and poorly mineralized woven bone (6). Their development is closely linked to severe HPT and high circulating PTH levels and are named "brown tumors" due to their color, resulting from vascularity, hemorrhage, and deposits of pigment hemosiderin (7). They occur widely throughout the skeleton and may involve the jaw, skull, clavicle, ribs, pelvis, femur, and spine (7). Histopathological observations consist of abundant multinucleated giant osteoclast-like cells, spindle-shaped cells, and a mixture of fibrous tissue and inadequately mineralized bone (6).

HPT-JT syndrome is a rare, autosomal dominant combination of primary hyperparathyroidism, cemento-ossifying fibromas of the mandible and maxilla, renal manifestations, and uterine tumors (2). PHPT is the most common feature (80%), followed by bony fibromas (30%) (2). The bone lesions are generally benign and, although mostly small and asymptomatic, may present as large, destructive lesions. Unlike brown tumors, their appearance and/or enlargement appear to be unrelated to the underlying hyperparathyroidism in some family members, and the fibromas have been noted to occur following surgical cure of the associated metabolic abnormality in index cases. They are exclusively found in the mandible or maxilla (2). Histologically, they are fibro-osseous lesions without the osteoclast-like giant cells typically observed in brown tumors. The syndrome is also associated with renal lesions, including Wilms tumor, and variable penetrance of uterine tumors (2). Importantly, parathyroid cancer is markedly overrepresented in HPT-JT syndrome, whereas, in contrast, parathyroid cancer almost never occurs in MEN1, MEN2A, MEN4, or FIHP (2). HPT-JT syndrome results from a germline pathogenic variant in the *CDC73* tumor suppressor gene located on chromosome 1q31.2 (8). This pathogenic variant can lead to a functional loss of the parafibromin protein, promoting unregulated cell growth and neoplasia. In affected individuals, the pathogenic variant is detectable in 70% of cases (9).

Our patient presented with bilateral jaw tumors following a pregnancy complicated by polyhydramnios and fetal loss. In the presence of confirmed PHPT, the jaw lesions raised the possibility of either brown tumors or the rarely encountered mandibular fibromas of HPT-JT syndrome. Although genetic testing did identify the *CDC73* pathogenic variant in keeping with HPT-JT syndrome, the jaw lesions were not ossifying fibromas but were histologically confirmed to be brown tumors. The presence of a *CDC73* pathogenic variant, however, requires ongoing surveillance post-parathyroidectomy as carriers are significantly more likely to develop parathyroid cancer. Screening of family members should be offered, and the patient was counseled that there is a 50% chance with each pregnancy of inheritance of the *CDC73* pathogenic variant. Elevated maternal hypercalcemia is suggested to trigger fetal polyuria, leading to polyhydramnios. This condition poses a 3.5-fold higher risk of miscarriage (10).

PHPT is a common endocrinopathy and is mostly due to underlying solitary benign parathyroid adenomas. Genetic testing should be offered to select patients with PHPT who manifest with features of syndromic PHT, in young patients (< 30 years), in patients with a positive family history, in those with multiglandular involvement, and in patients with atypical parathyroid adenoma and parathyroid carcinoma (11). Identification of pathogenic variants in this minority group ensures optimal patient management and dictates required long-term surveillance and the need to evaluate family members. While there are no established carrier surveillance guidelines, it is recommended to undergo biannual biochemistry assessments and to review dental X-rays and renal scans every 5 years. Additionally, regular gynecological examinations are advised during reproductive years (8).

Learning Points

- PHP-JT syndrome is a rare autosomal dominant disorder.
- Features include jaw fibromas and renal and uterine tumors.
- There is an associated increased risk of parathyroid carcinoma.
- Young age, family history, and a significantly elevated calcium and PTH level should prompt genetic testing.

Contributors

All authors made individual contributions to authorship. M.C. was involved in the diagnosis and management of this patient. A.Z. prepared the initial manuscript; M.C. reconceptualized, reviewed, and edited the manuscript; A.Z., E.C.K., and A.E.Z. reviewed and edited the manuscript. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

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