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Primary Hyperparathyroidism: A Rare Presentation and Etiology

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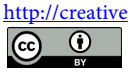

Abstract

Primary hyperparathyroidism is rare in children and adolescents. The typical biochemical features are hypercalcemia and hypophosphatemia, but the symptoms are vague and non-specific. This case illustrates a rare presentation of primary hyperparathyroidism, along with its clinical approach and follow-up. A 16-year-old male adolescent presented to the emergency department with abdominal pain and vomiting. Laboratory tests showed elevated amylase and hypercalcemia. The diagnosis of pancreatitis due to hypercalcemia was admitted. The subsequent study revealed an increase in parathormone, with normal 25-OH-vitamin D. Thyroid and parathyroid ultrasound showed a left parathyroid adenoma. The patient underwent surgical removal of the affected gland and its anatomopathological examination confirmed the parathyroid adenoma. A genetic analysis to diagnose its etiology was performed, allowing to exclude MEN and ended to reveal a CDC73 founder variant, a pathogenic mutation associated with hyperparathyroidism-jaw tumor syndrome. Further study was indicated and included renal ultrasound, orthopantomography, and limbs radiograph. Genetic counseling for the family was also advised. In conclusion, primary hyperparathyroidism is rare in children, with pancreatitis as an uncommon presentation, warranting genetic analysis to evaluate comorbidity risks and hereditary transmission.

Subject Areas

Pediatric Endocrinology, Genetic Disorders

Keywords

Primary Hyperparathyroidism, Pancreatitis, Hyperparathyroidism-Jaw

Tumor Syndrome

1. Introduction

Primary hyperparathyroidism (PHPT) is a disorder of calcium and phosphorus metabolism, mainly due to elevated parathyroid hormone (PTH) secretion. Most cases (90%) are caused by a single hormone-producing adenoma, with multiple adenomas (2% - 4%) and parathyroid carcinoma (<1%) being rarer causes [1] [2].

Although most adenomas are sporadic, 5% - 10% are hereditary, associated with multiple endocrine neoplasia (MEN) types 1 or 2A, hyperparathyroidism-jaw tumor syndrome (HPT-JT), familial hypocalciuric hypercalcemia (FHH), and familial isolated hyperparathyroidism (FIHPT) [3].

Pediatric PHPT is much less frequent than in adults, with an incidence of 2 - 5 per 100,000 children versus 1 per 1000 adults [4], and shows no clear sex predilection [5].

Elevated PTH causes hypercalcemia and relative hypophosphatemia. Symptoms vary with calcium levels and are often summarized as "stones, bones, abdominal groans, thrones, and psychiatric overtones." This includes nephrolithiasis, bone pain and fractures (from reduced cortical bone and bone mineral density) [6], gastrointestinal complaints (constipation, dyspepsia, nausea, vomiting—sometimes indicating pancreatitis [7] or peptic ulcer), polyuria, polydipsia, and neuropsychiatric disorders. Pediatric cases may show more vague, non-specific symptoms [4] [5].

Diagnosis is confirmed by laboratory tests of calcium and PTH, followed by parathyroid ultrasound [8].

Symptoms usually resolve with surgery. The standard treatment is partial or total removal of the affected gland [9].

2. Case Report

A previously healthy 16-year-old male from a Roma family presented to the emergency department with acute upper abdominal pain radiating to the back (≤24 hours), and two episodes of vomiting. He denied alcohol or medication use. Vital signs were normal. Examination revealed upper abdominal tenderness without rebound.

Laboratory tests (**Table 1**) showed leukocytosis with neutrophilia, normal C-reactive protein, and elevated amylase. Liver enzymes, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase, and albumin were normal. Ionogram revealed marked hypercalcemia; renal function was preserved.

Abdominal ultrasound showed slight pancreatic enlargement and heterogeneous echotexture, without duct dilatation or fluid collections. Hypercalcemia-related acute pancreatitis was suspected.

Venous blood gas confirmed elevated ionized calcium. PTH was high, with nor-

mal 25-OH-vitamin D. Urinary calcium was also elevated (Table 1).

Table 1. Summary of laboratory investigations. The markedly elevated amylase levels indicate acute pancreatitis, which was suspected as the primary clinical presentation. Further investigation revealed hypercalcemia and elevated PTH levels, consistent with primary hyperparathyroidism, a recognized but rare cause of pancreatitis.

Laboratory Parameter	Result	Reference Range
White Blood Cell Count (WBC)	14,700 cells/μL	4000 - 11,000 cells/μL
Neutrophils (Percentage)	87%	40% - 75%
C-Reactive Protein (CRP)	0.7 mg/L	<5 mg/L
Amylase	502 U/L	25 - 125 U/L
ALT	7 U/L	7 - 56 U/L
AST	13 U/L	10 - 40 U/L
Alkaline Phosphatase	105 U/L	44 - 121 U/L
Gamma-Glutamyl Transferase (GGT)	13 U/L	9 - 48 U/L
Lactate Dehydrogenase (LDH)	122 U/L	140 - 280 U/L
Ionized Calcium	2.14 mmol/L	1.13 - 1.32 mmol/L
Parathyroid Hormone (PTH)	265 pg/mL	14 - 72 pg/mL
25-OH Vitamin D	32 ng/mL	20 - 50 ng/mL
Urinary Calcium	374 mg/24h	100 - 300 mg/24h

Ultrasound of the thyroid/parathyroid revealed a solid, hypoechogenic, highly vascularized lesion (15 × 13 × 33 mm) located superior and posterior to the left thyroid lobe, suggestive of a parathyroid adenoma (Figure 1).

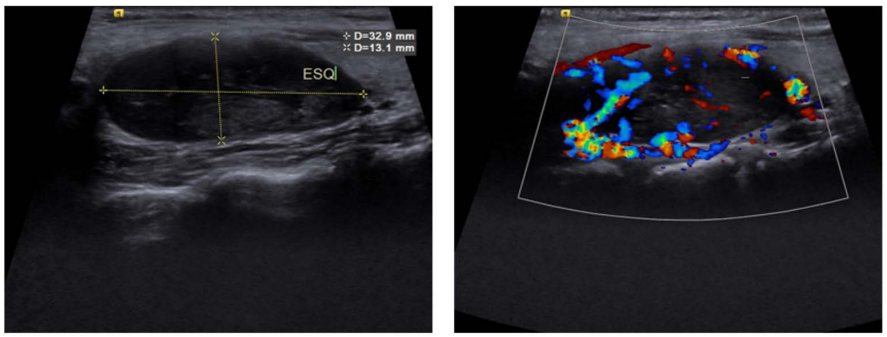

Figure 1. Parathyroid ultrasound. Ultrasound of the thyroid and parathyroid showing a solid and hypoechogenic lesion in a superior and posterior topography to the left lobe of the thyroid, measuring 15 × 13 × 33 mm and highly vascularized on Doppler evaluation, suggestive of a parathyroid adenoma.

A diagnosis of primary hyperparathyroidism due to a parathyroid adenoma was established. Serum calcitonin was normal. Early IV fluid therapy was started without antibiotics, leading to clinical and biochemical improvement of pancreatitis.

Calcium normalized after a single 4 mg dose of IV zoledronic acid.

The patient was referred for genetic testing; blood was collected for DNA extraction.

A left parathyroidectomy was subsequently performed (**Figure 2**). Pathology showed a primary parathyroid neoplasm with features of an atypical parathyroid tumor.

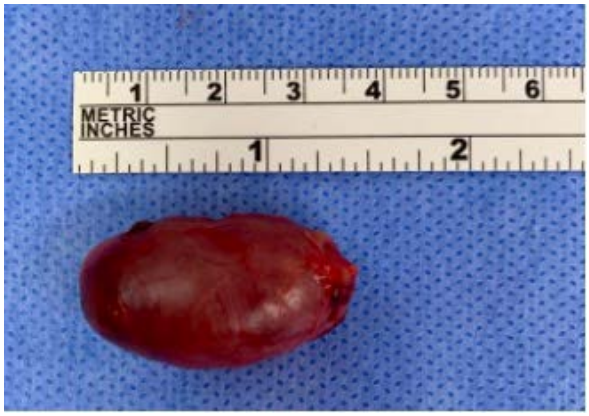

Figure 2. Appearance of the removed parathyroid. Macroscopic specimen resulting from a left parathyroidectomy, corresponding to the excised parathyroid adenoma.

On the first postoperative day, PTH was low and serum calcium at the upper normal limit. The patient was discharged without complications.

Genetic analysis identified a founder CDC73 gene variant (c.766_767delGT, p.(Val256Lysfs*10)), a pathogenic mutation linked to hyperparathyroidism-jaw tumor syndrome.

3. Discussion

Primary hyperparathyroidism (PHPT) is rare in children and adolescents, often presenting with vague symptoms [1]. Pancreatitis secondary to PHPT has a low prevalence of 3.6% [2]. Hypercalcemia is a key factor in its pathogenesis through several mechanisms: activation of trypsinogen to trypsin, activation of pancreatic enzymes through the lysosomal system, and the formation of pancreatic calculi leading to acute pancreatitis [2].

When hypercalcemia is detected, differential diagnosis involves distinguishing between high PTH conditions, like primary hyperparathyroidism (low phosphate, normal/high urinary calcium) and familial hypocalciuric hypercalcemia (low urinary calcium), and low PTH causes such as malignancy, granulomatous diseases, or vitamin D intoxication [3]-[5]. In this case, hypercalcemia with elevated PTH and urinary calcium supported the diagnosis of primary hyperparathyroidism.

Calcium levels normalized after a single 4 mg dose of IV zoledronic acid. As a bisphosphonate, it inhibits osteoclast-mediated bone resorption, reducing calcium release from the skeleton and rapidly lowering serum calcium levels in acute

hypercalcemia [6]. Bisphosphonates are the first-line pharmacologic treatment for this condition, and zoledronic acid was used in this patient based on clinical practice and evidence demonstrating its efficacy [6]-[8].

Regarding etiological investigation, first-line imaging, including parathyroid ultrasound and scintigraphy, is essential to localize hyperfunctioning glands [9]. Most PHPT cases (90%) are caused by a single benign adenoma [10]. In our patient, ultrasound suggested a parathyroid adenoma, confirmed by pathological examination.

Surgical intervention (parathyroidectomy) is the treatment of choice and is curative in most cases, as it was in our patient [11]. While genetic syndromes account for only 5% - 15% of PHPT cases, they are more common in younger patients [12].

Because the patient belonged to the Roma population, blood was collected for DNA extraction, and genetic testing was initially performed to screen for the CDC73 founder mutation previously described in this population. This testing revealed a founder mutation in the CDC73 gene: c.766_767delGT, p.(Val256Lysfs*10), associated with hyperparathyroidism-jaw tumor (HPT-JT) syndrome [13].

Conditions linked to CDC73 follow an autosomal dominant inheritance pattern. The CDC73 mutation can be inherited from an affected parent or arise de novo [14]. If the mutation is identifiable, prenatal screening can be offered for pregnancies at risk. In our case, no relevant family history or previously identified genetic mutations were reported.

In addition to the typical single parathyroid adenoma [12], HPT-JT syndrome also presents with ossifying fibromas of the maxilla and mandible in 30% - 40% of cases [14]. These benign tumors can be locally aggressive, causing facial disfigurement if not treated. Other manifestations of HPT-JT include renal tumors, cysts, and uterine tumors [14].

Although firm surveillance guidelines are lacking, suggested screening strategies for individuals with HPT-JT include biannual measurement of serum calcium and PTH levels for early detection of hyperparathyroidism, starting as early as age five, along with periodic parathyroid ultrasound examinations [15] [16]. Orthopantomogram is recommended at least every five years, while renal lesions should be monitored with renal ultrasound at similar five-year intervals, beginning at the time of diagnosis [15] [16]. From reproductive age onward, women with HPT-JT should undergo regular gynecologic evaluation, including pelvic ultrasound, with additional imaging as clinically indicated [15] [16].

Further evaluation and follow-up were recommended for our patient. An initial orthopantomogram was normal. Renal ultrasound revealed a small kidney stone. Renal involvement in HPT-JT most often consists of cysts, hamartomas, or, more rarely, Wilms tumor, while nephrolithiasis is not typically regarded as a characteristic manifestation of the syndrome. The kidney stone identified in our patient is therefore more plausibly interpreted as a secondary complication of hypercalcemia and hypercalciuria related to primary hyperparathyroidism, rather than a direct expression of HPT-JT [15] [16].

Additionally, limb radiographs revealed a radioulnar synostosis. As this anomaly is not recognized among the characteristic manifestations of HPT-JT, current evidence suggests it is best considered an incidental finding rather than a direct feature of the syndrome [15].

Subsequent laboratory tests showed a mild increase in PTH, a vitamin D deficiency, and calcium at the lower limit of normal. Despite the patient's non-compliance with calcium and vitamin D supplementation, normalization of these levels and a reduction in PTH were later achieved.

Genetic counseling was provided to the family, and the patient's younger sister was found to be a carrier of the same mutation.

4. Conclusion

In conclusion, PHPT is a rare condition in the pediatric population, with pancreatitis being an uncommon initial presentation. In cases of acute pancreatitis, elevated serum calcium levels may suggest PHPT, with parathyroid ultrasound being the preferred first-line imaging test for diagnosis. Genetic analysis is crucial for detecting hereditary forms of PHPT, identifying mutations, and assessing potential comorbidities. Early mutation identification allows for appropriate follow-up, genetic counseling, and proper management of affected patients and their families. Regular monitoring of calcium, PTH, and imaging is essential for patients with hyperparathyroidism-jaw tumor syndrome.

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Conflicts of Interest

The authors declare that there are no conflicts of interest and no sources of funding.

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