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Atypical parathyroid tumor: A rare cause of primary hyperparathyroidism in an adolescent

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ABSTRACT

Hyperparathyroidism is a rare entity in pediatrics. It is defined as the increased production of parathyroid hormone. It may be due to a primary defect of the parathyroid glands (primary hyperparathyroidism) or to a compensatory parathyroid hormone production to correct hypocalcemia states of various origins (secondary hyperparathyroidism).

We describe the case of a 15-year-old adolescent girl with a history of several months of deteriorating school performance, anxiety crises, weight loss, and tachycardia. Laboratory results showed hypercalcemia, hypophosphatemia, increased parathyroid hormones, and hypovitaminosis D; imaging studies showed generalized bone involvement and parathyroid nodular formation. A parathyroidectomy and right hemithyroidectomy were performed, after which she presented persistent hungry bone syndrome. The anatomopathological diagnosis was an atypical parathyroid tumor.

We describe the form of presentation, the results of the different complementary tests performed, and the short- and long-term evolution.

Keywords: *primary hyperparathyroidism; hypercalcemia; parathyroid neoplasms; adenoma; pediatrics.*

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INTRODUCTION

Hyperparathyroidism is defined as an increased production of parathyroid hormone (PTH), which may be due to a primary defect of the parathyroid glands, primary hyperparathyroidism (PHPT), or to a compensatory production of PTH, usually to correct hypocalcemic states of various origin, secondary hyperparathyroidism.[1]

There are many publications on the epidemiology, clinical course, and treatment outcomes of PHPT in adult patients.[2,3]

On the contrary, in pediatrics, this entity is infrequent and presents with non-specific symptoms, so a high index of suspicion is needed to reach a diagnosis.[1,4,5] Atypical parathyroid tumor defines a subgroup of rare parathyroid neoplasms with certain histologic features shared with parathyroid carcinoma but lacking unequivocal signs of malignancy and with uncertain malignant potential.[6,7] They are very infrequent in the pediatric population, with only a few cases reported in the literature.[8,9]

For this reason, we present a patient of 15 years old with a diagnosis of PHPT with severe target organ damage caused by an atypical parathyroid tumor.

CLINICAL CASE

We present a 15-year-old female adolescent with a history of anxiety crises, impaired school performance, decreased muscle strength, weight loss, and tachycardia of approximately one year's duration. In the months before diagnosis, she added polyuria and polydipsia; she consumed approximately 7 liters of water per day.

Initially, the picture was interpreted as anxiety disorder, potomania, and apparent repeated urinary tract infections. However, due to the persistence of these signs and symptoms, her pediatrician requested a laboratory test that showed anemia and severe hypercalcemia. To rule out neoplastic disease, a whole-body CT scan was performed, which revealed a heterogeneous mass of 42 mm in length in the posteroinferior region of the right thyroid lobe, in addition to renal lithiasis and multiple focal bony lesions, blastic and lytic, with greater involvement in the pelvis. With these findings, she was treated with hyperhydration, furosemide, and pamidronate, and it was decided to refer her to our institution.

On initial evaluation, she was thin, with severe muscle waste and pallor, and her weight was 36.5 kg (Z -2.5) and a body mass index of 15.3 kg/m^2 (Z -2.5). Difficulty in ambulation due to weakness, tachycardia at rest (116 beats per minute), and arterial hypertension (137/90 mmHg) were noted. A tumor was palpable in the anterior cervical region, and the rest of the physical examination did not present findings of note. The patient had not received any previous medications and had no other relevant personal or family history.

Laboratory showed hypercalcemia (total calcium 13.1 mg/dL, ionic calcium 1.74 mmol/L) with normal serum albumin (3.55 g/dL), increased alkaline phosphatase (972 IU/L), hypomagnesemia (0.8 mg/dL), hypophosphatemia (2 mg/dL), hypovitaminosis D (7.9 ng/mL) and PTH of 6432.6 pg/mL (normal value 8.7-77.1 pg/mL). The clinical findings added to hypercalcemia, hypophosphatemia, and a significantly increased PTH, which highly suggest PHPT. She had normal growth hormone, prolactin, insulin, and thyroid profile.

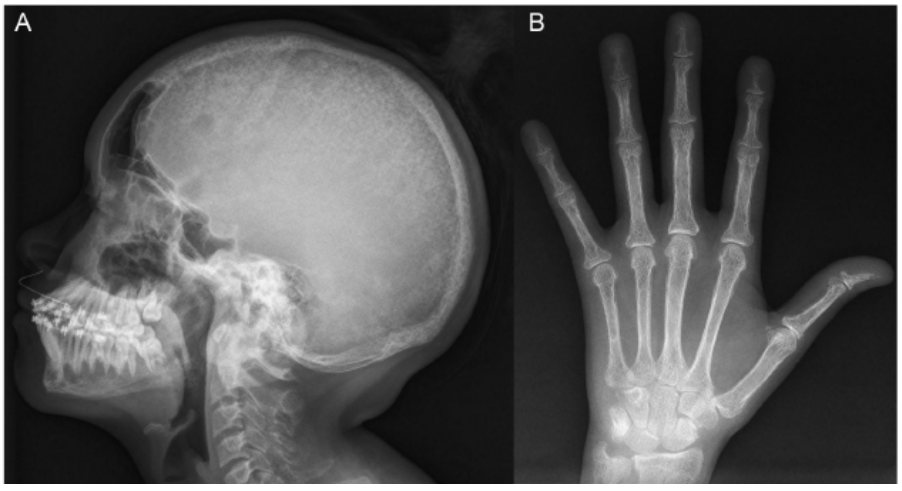
X-rays of the skull, hands, abdomen, pelvis, spine, and lower limbs showed marked bone involvement (*Figures 1 and 2*) and body densitometry with low bone mass (lumbar spine *Z* -4.3). The scintigraphic study with sestamibi and whole-body single photon emission computed tomography (SPECT-CT) showed a voluminous nodular formation located behind the right thyroid lobe compatible with hyperfunctioning parathyroid tissue (*Figure 3*) and multiple bone lesions, with brown tumors at the level of the sternal body, left lower jaw, pelvis, and femurs.

To reduce calcemia, she received hyperhydration, furosemide, and, during her hospitalization, three infusions of pamidronate disodium (40 mg) as a bone resorption inhibitor.

Regarding the surgical approach, because the patient had risk factors for malignancy (palpable mass larger than 3 cm, severe hypercalcemia, and marked increase in PTH),[6] subtotal parathyroidectomy with right thyroid lobectomy was performed; no involvement of the capsule, invasion of vessels or adjacent tissues was observed. During the intervention, serial PTH determinations were performed with a decrease of 93% of the values. The pathological anatomy revealed findings compatible with atypical parathyroid tumors according to the World Health Organization 2022 criteria (*Figure 4*).[6]

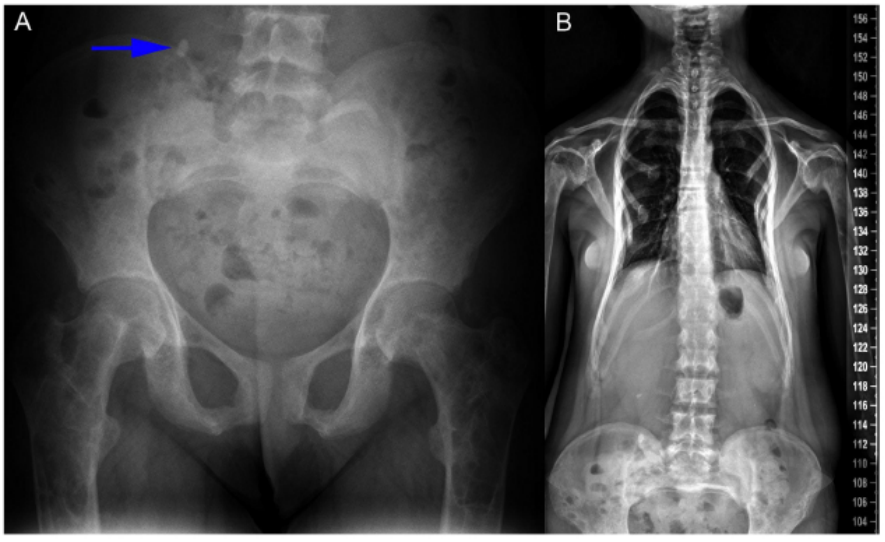
As postoperative complications, the patient evolved with bone syndrome severe starvation with symptomatic hypocalcemia (nadir of 7 mg/dl), hypophosphatemia (nadir of 2.3 mg/dl), and persistently increased alkaline phosphatase, for

Figure 1. A: Skull radiograph. B: X-ray of the right hand



A. Bone resorption lesions in salt-and-pepper skull appearance.
B. Subperiosteal resorption with cortical thinning of phalanges and metacarpus.

Figure 2. A: X-ray of the pelvis in front. B: Spinogram

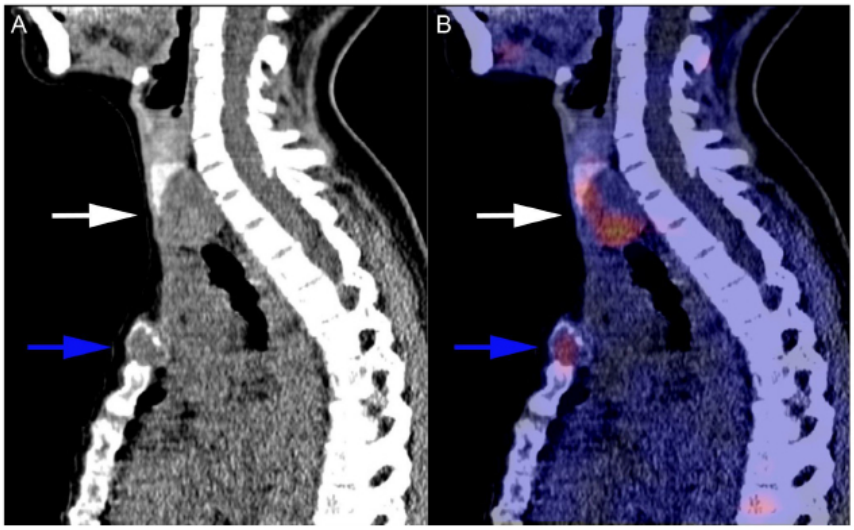


A. Cystic fibrous osteitis of the ilium and femurs. Subchondral resorption of the sacroiliac joint. Blue arrow: image attributable to renal lithiasis.
B. Bilateral costal subchondral resorption that alters the configuration of the thorax. Height of the vertebral bodies decreased, with sclerotic bands in the vertebral plates and increased vertebral subperiosteal bone resorption.

which she required intravenous corrections with calcium gluconate during 12 days, and then high doses of calcium and phosphorus orally. She remained hospitalized for 33 days.

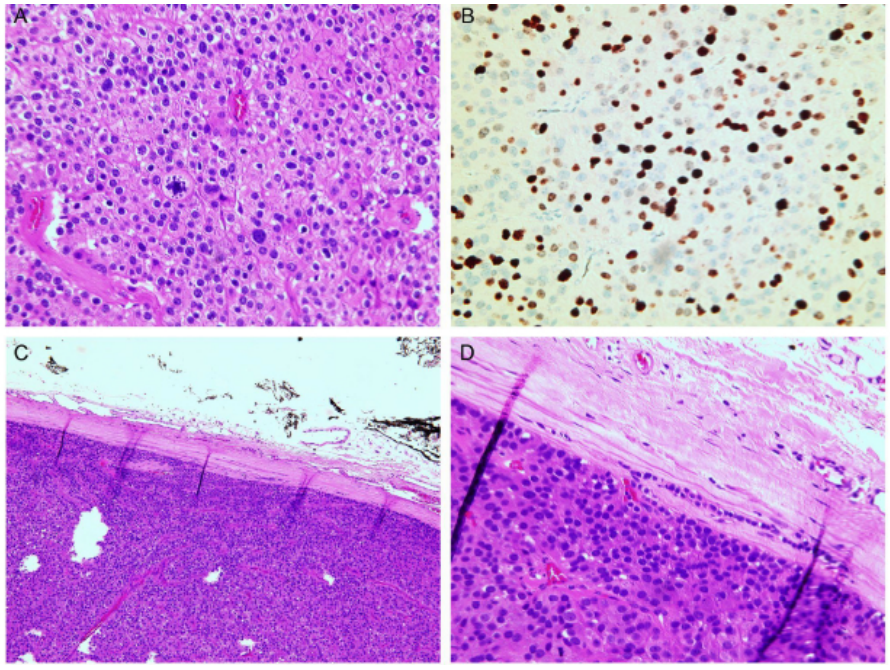
At two years of ambulatory follow-up, she presented calcemia and phosphatemia values; magnesemia and PTH were stable under treatment with 6000 units/day of cholecalciferol. In addition, a genetic study (massively parallel sequencing) was performed using a hyperparathyroidism panel with 14 genes, including multiple endocrine neoplasia type 1 (*MEN1*) and those involved in hyperparathyroidism and jaw tumor (*HPT-JT*), with negative results.

Figure 3. Single photon emission computed tomography (SPECT-CT)



A and B. White arrows: increased radiotracer uptake in nodular neck formation. Blue arrows: brown tumor in the sternum.

Figure 4. Pathological anatomy of parathyroid tumor



A. Epithelial proliferation with atypical nuclei and mitotic figures (hematoxylin-eosin 40×).
B. Ki67 proliferation index showing positivity in 30-35% of the cells (40×).
C and D. Expansive growth with the presence of fibrous capsule, without invasion to adjacent tissues (hematoxylin-eosin 20× and 40×).

DISCUSSION

Most of the published literature on PHPT describes adult patients, especially postmenopausal women. In contrast, there is scant information on etiology and the disease's short- and long-term consequences in pediatric patients.[1,3,10]

Pediatric PHPT differs from the adult variant in several respects. The most frequent form of presentation in adults is the asymptomatic

detection of hypercalcemia in routine tests.[1,2] In contrast, in children and adolescents, the disease is usually symptomatic at the time of diagnosis and with a high associated morbidity (80% with severe symptoms), with the possibility of severe renal and bone involvement.[4,5] Presentations are described with vague and unspecific symptoms such as lack of appetite, weight loss, abdominal pain, polyuria, nausea, weakness, and neuropsychiatric symptoms such as anxiety and depression.[11,12] They present a higher frequency of hypercalcemic crises and renal lithiasis. In the immediate postoperative period, an increased risk of starving bone syndrome is described due to a higher prevalence of skeletal involvement.[1,10]

Our patient presented with many of these features: a prolonged history of initially vague and non-specific symptoms, renal and bone target organ damage at diagnosis, and severe hungry bone syndrome in the immediate postoperative period.

Regarding etiology, it has a bimodal age distribution, with different causes in infants and children or adolescents.[5,13]

In children and adolescents, PHPT is usually caused by a single adenoma (90%) or multiple adenomas, previously called parathyroid hyperplasia.[4,6] It may be sporadic (65% to 70%) or familial (27% to 31 %) and be a form of presentation of several syndromic disorders, such as *MEN1*.[5,10-12]

Our patient had no personal or family medical history of related tumors and no other relevant hormonal alterations, and the genetic study by the hyperparathyroidism panel was negative, so her disease was assumed to be isolated and sporadic.

Atypical parathyroid tumors and parathyroid carcinoma are sporadic in pediatric patients, with only a few cases reported in the literature. Formerly called atypical parathyroid adenoma, the term atypical parathyroid tumor has been used to define a subgroup of rare parathyroid neoplasms with certain histologic features shared with parathyroid carcinoma but lacking unequivocal signs of malignancy.[6] They present more severe clinical manifestations and laboratory findings than typical adenomas, and considering that their malignant potential and future are uncertain, careful and strict follow-up is suggested.[7,14] It has been recommended to perform an atypical tumors genetic study of variants of the *CDC73* gene in the germline associated with HPT-JT syndrome, an entity with a carcinoma risk of up to 15% and a higher risk of recurrence, which was negative in our patient.[7,15]

In pediatrics, so far, we have only found a few case reports of patients with atypical parathyroid tumors, describing adolescent females with severe manifestations due to delays in diagnosis, like our patient.[8,9]

PHPT is infrequent in pediatrics and even more so in atypical parathyroid tumors. A high index of suspicion is needed to reach the diagnosis. It should be considered in patients with a history of weight loss, polyuria, fatigue, weakness, and neuropsychiatric symptoms such as anxiety and depression. ■

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