



Parathyroid Crisis as Presentation of Atypical Parathyroid Adenoma: Two Diagnostically Challenging Cases

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Atypical parathyroid adenoma (APA) is a rare cause of primary hyperparathyroidism (PHPT) and represents a diagnostic challenge since it is an intermediate form of parathyroid neoplasm of uncertain malignant potential with atypical histological features that require differential diagnosis of parathyroid carcinoma (PC). We present 2 cases of parathyroid crisis as a presentation of APA. The first case was that of a 56-year-old man with parathyroid crisis, constitutional syndrome, and anemia, with evidence of APA after en bloc resection, evolving with hungry bone syndrome after surgery and curation criteria at 6 months after parathyroidectomy (PTX). The second case was a 64-year-old woman with acute chronic kidney disease and parathyroid crisis, with evidence of APA after selective PTX and >50% reduction in parathyroid hormone levels after surgery; however, persistent PHPT at 6 months post-surgery was observed. These cases represented a diagnostic challenge due to their rare clinical presentation (parathyroid crisis), with a heterogeneous spectrum of target organ damage and infrequent symptoms (constitutional syndrome and acute chronic renal disease), in turn caused by a rare pathology (APA). The presentation of these patients may be indicative of PC; however, histopathological diagnosis is a key to the diagnosis of APA. The differential diagnosis of APA vs. PC in clinical practice is indispensable.

Key Words: Adenoma · Hypercalcemia · Hyperparathyroidism · Primary · Parathyroid neoplasm

INTRODUCTION

Primary hyperparathyroidism (PHPT) is caused by the autonomous production of parathyroid hormone (PTH) by 1 or more of the 4 parathyroid glands and is characterized by hypercalcemia and inappropriately normal or elevated PTH.[1] PHPT predominates among women (female to male ratio, 3 to 4:1) and is usually postmenopausal.[2]

PHPT has a wide spectrum of clinical presentations; most patients are asymptomatic; however, there may be classic manifestations of PHPT in the kidney (hypercalciuria, nephrolithiasis, renal disease) and bone (osteoporosis, fractures, cystic fibrous osteitis), nonclassical manifestations at the cardiovascular, neurological

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Table 1. Biochemical characteristics of patients before surgery and at 72 hr, 1 month and 6 months after parathyroidectomy in case 1

	Before surgery	At 72 hr after parathyroidectomy	At 1 month after parathyroidectomy	At 6 months after parathyroidectomy
Parathyroid hormone (pg/mL)	996	105	18	16.2
Corrected calcium (mg/dL)	17.0	7.9	8.8	10.0
24 hr urinary calcium (mg/24 hr)	500	230	120	150
Phosphorus (mg/dL)	2.9	3.1	1.6	1.8
Mg (mg/dL)	2.4	2.2	2.2	1.6
Vitamin D (ng/mL)	13.9	18.7	16.5	41.1
Alkaline phosphatase (IU/L)	189	154	145	135
Urea (mg/dL)	10.7	21.4	27.8	21
Creatinine (mg/dL)	0.58	0.59	0.67	0.90

or gastrointestinal level, and even extreme states such as parathyroid crisis, which represents a severe emergency.[1] A constitutional syndrome is a rare and underreported manifestation.

Parathyroidectomy (PTX) is the only curative approach in PHPT.[1] Most patients with PHPT have single adenomas (80%) or hyperplasia (15%-20%); parathyroid carcinoma (PC) is reported in <1%.[2] Among patients with adenoma, atypical parathyroid adenoma (APA) may be found at a low frequency. The incidence of APA ranges from 0.5% to 4.4%.[3]

APA represents a diagnostic challenge for endocrinologists, surgeons, and pathologists because it is an intermediate form of parathyroid neoplasm of uncertain malignant potential, with atypical histological features that require differential diagnosis with PC.[3,4] This manuscript describes the clinical, biochemical, imaging, and histopathological features of 2 cases of PHPT with parathyroid crisis as a presentation of APA in a tertiary referral center in Mexico City.

CASE REPORT

1. Case 1

A first case is a 56-year-old man with controlled arterial hypertension and benign prostatic hyperplasia under treatment. He started 6 months ago with involuntary weight loss of 35 kg in 11 months, accompanied by progressive anorexia, fatigue, and dyspepsia; 72 hr prior to his evaluation, he started with proximal muscle weakness, decreased ability to concentrate, and severe dyspepsia. Physical examination showed moderate dehydration and emaciation.

Blood pressure was 100/60 mmHg, heart rate 89 bpm, respiratory rate 22 rpm, weight 68 kg, height 170 cm, and body mass index (BMI) 23.52 kg/m².

Biochemical testing (Table 1) revealed PTH-dependent hypercalcemia (calcium, 17.0 mg/dL; normal, 8.4-10.2; PTH, 996 pg/mL; 6.5-36.8), hypophosphatemia (phosphorus, 2.9 mg/dL; normal, 2.3-4.7), hypercalciuria (24 hr urinary calcium 500 mg/24 hr; men <300 mg/24 hr), and alkaline phosphatase of 189 U/L (normal, 40-150). Other findings were normochromic normocytic anemia and hypoalbuminemia, integrating the diagnosis of PHPT and constitutional syndrome. The patient was urgently admitted for a parathyroid crisis. He was promptly treated with aggressive intravenous hydration with 0.9% saline solution, parenteral nutrition, and denosumab 60 mg administered in a single subcutaneous dose. Osteoporosis (absolute T-score in the lumbar spine, -2.8; femoral neck, -2.6; total hip, -2.9) and osteitis fibrosa cystica were evidenced.

The 99m methoxyisobutylisonitrile (^{99m}Tc-MIBI) single-photon emission computed tomography/CT (SPECT/CT) showed hyperfunctioning left paratracheal parathyroid tissue. Ultrasound of the neck identified a hypoechoic, cystic, hypervascular, and ovoid lesion of 40×30×22-mm, inferior to the left lobe of the thyroid compatible with a parathyroid adenoma (Fig. 1).

The patient evolved with clinical and biochemical improvement, with calcium reduction to 11.6 mg/dL 1 week later, so he underwent surgical treatment. Left lower PTX, ipsilateral hemithyroidectomy, and central lymph node dissection were performed. The histopathological report revealed a parathyroid chief cell neoplasm of 4.6 cm with well-demarcated borders, a thin fibrous capsule, cellular

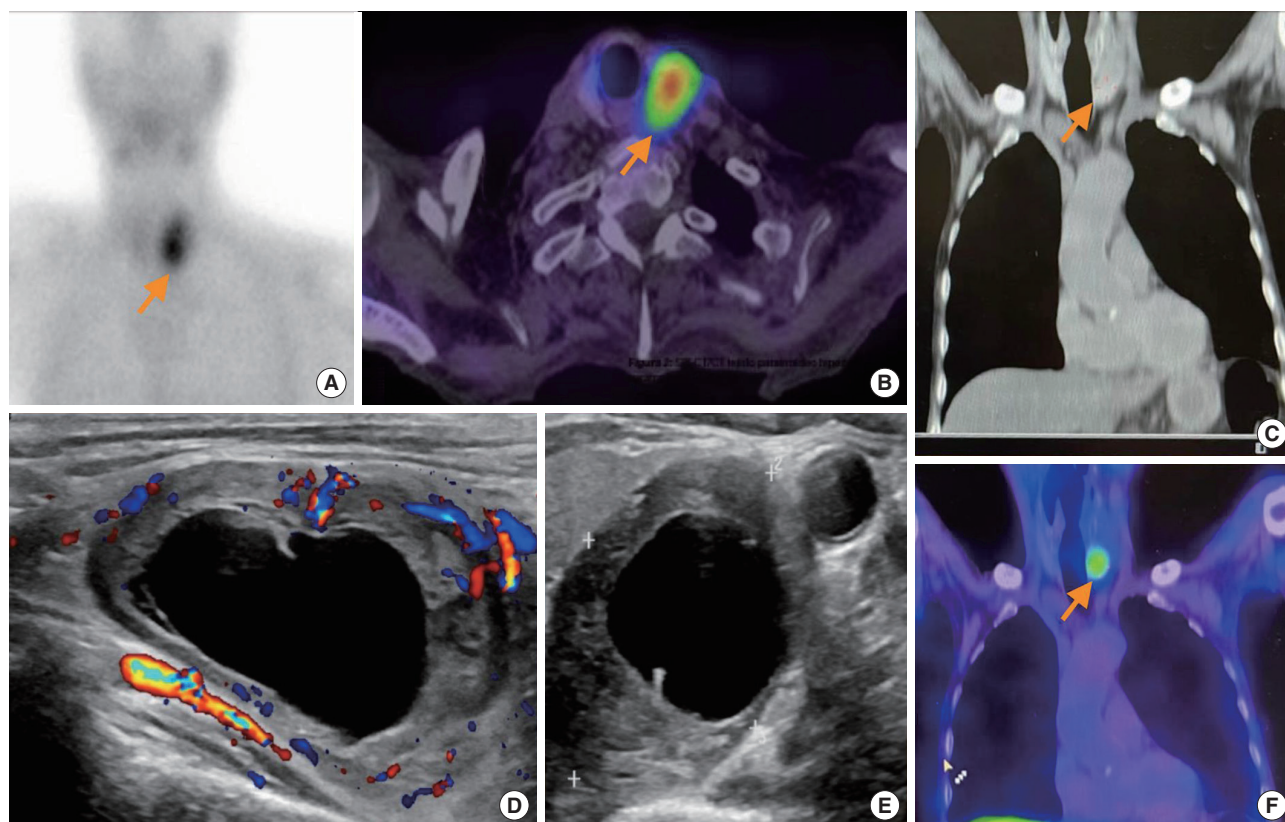


Fig. 1. (A) The ^{99m}Tc -methoxyisobutylisonitrile (^{99m}Tc -MIBI) planar scintigraphy with hyperfunctioning left paratracheal parathyroid tissue (arrow). Axial (B) and coronal (C, F) ^{99m}Tc -MIBI singlephoton emission computed tomography (SPECT)/CT with hyperfunctioning left paratracheal parathyroid tissue (arrow). (D, E) Ultrasound of the neck identified a hypoechoic, cystic, and ovoid lesion of $40 \times 30 \times 22$ mm, inferior to the left lobe of the thyroid, with hypervascularization from the periphery to the center.

pleomorphism, nuclear atypia, dense fibrous bands, focal vascular invasion, and Ki67 of 1%, compatible with APA (Fig. 2).

After surgery, there was a $>50\%$ reduction in PTH and normalization of calcium; however, he presented hypocalcemia and hypophosphatemia at 72 hr, with criteria of hungry bone syndrome (HBS), requiring the administration of intravenous calcium gluconate and transition to the administration of calcium carbonate 1 g orally every 8 hr (Table 1). During follow-up, remission of symptoms, progressive weight gain, remission of anemia, normalization of PTH, and maintenance of adequate calcium concentrations with the administration of calcium carbonate 1 g every 12 hr were observed (Table 1).

2. Case 2

The second case is a 64-year-old woman with a history of newly diagnosed chronic kidney disease stage 2 attributed to long-standing recurrent nephrolithiasis. The pa-

tient had no other chronic degenerative diseases. She started 6 months ago with fatigue, headache, and dyspnea; 48 hr prior to her assessment, she reported proximal muscle weakness, decreased ability to concentrate and dyspepsia. Physical examination showed moderate dehydration. Blood pressure was 120/76 mmHg, heart rate 66 bpm, respiratory rate 20 bpm, weight 68 kg, height 149 cm, and BMI 30.62 kg/m^2 .

Biochemical tests (Table 2) revealed PTH-dependent hypercalcemia (calcium, 16 mg/dL ; $8.4\text{--}10.2$; PTH, 759 pg/mL ; $6.5\text{--}36.8$), hypophosphatemia (phosphorus, 2.4 mg/dL ; $2.3\text{--}4.7$), hypercalciuria (24 hr urinary calcium, 300 mg/24 hr ; women $<250 \text{ mg/24 hr}$), and alkaline phosphatase of 240 U/L ($40\text{--}150$), establishing the diagnosis of PHPT. There was evidence of elevated creatinine levels with respect to baseline (baseline, 1.3 mg/dL vs. 3.5 mg/dL at assessment; normal, $0.57\text{--}1.1$), with criteria for acute on chronic renal injury. The patient was urgently admitted for a parathyroid crisis. She was promptly treated with aggressive intravenous

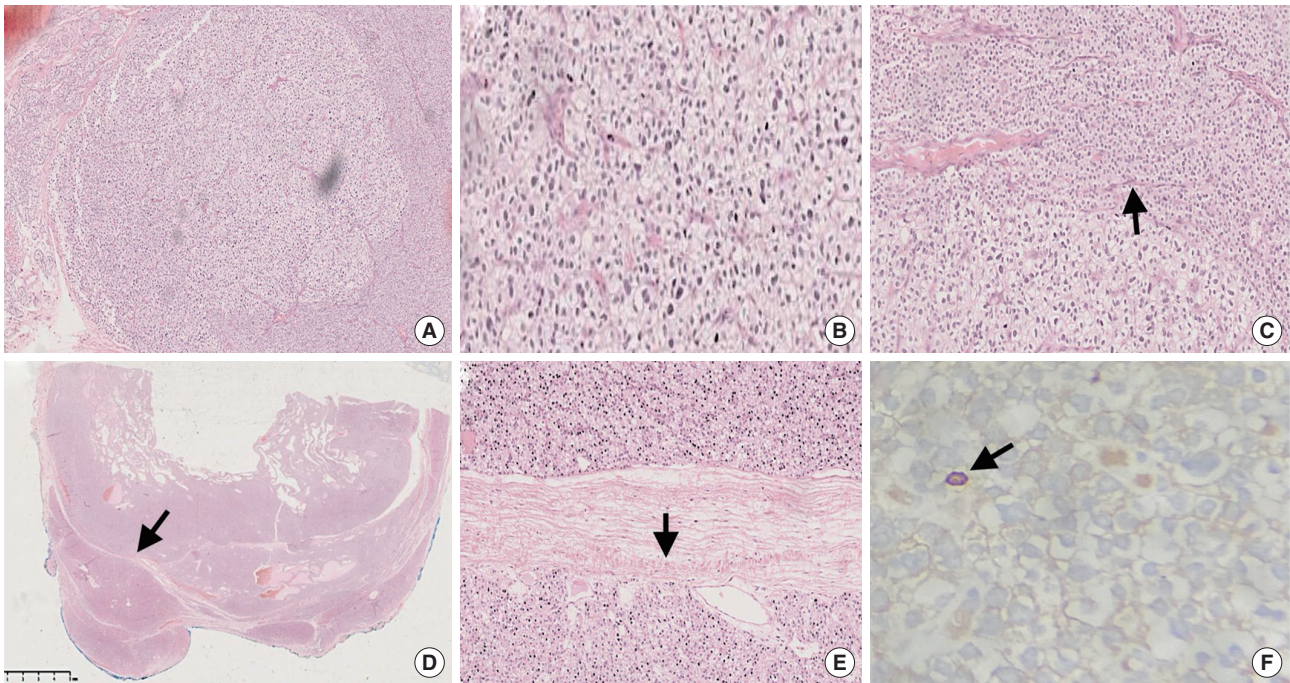


Fig. 2. (A) Hematoxylin and eosin (H&E) $\times 100$ magnification. Parathyroid chief cell neoplasm, with a well-demarcated 'pushing' tumor border and no stromal adipocytes. (B) H&E $\times 40$ magnification. Neoplasm with thin fibrous capsule and focal capsular invasion. (C) H&E $\times 40$ magnification. Emergence of thick and dense fibrous bands (arrow). (D) H&E $\times 40$ magnification. Transition between conventional chief cell focus and chief cells with atypia (arrow). (E) H&E $\times 40$ magnification. Neoplasm characterized by the presence of cells with well-demarcated, clear and abundant cytoplasm, with central, hyperchromatic, pleomorphic nuclei (arrow). (F) H&E $\times 40$ magnification. Ki67. Nuclear positivity in 1% of atypical cells (arrow).

Table 2. Biochemical characteristics of patients before surgery and at 72 hr, 1 month and 6 months after parathyroidectomy in case 2

	Before surgery	At 72 hr after parathyroidectomy	At 1 month after parathyroidectomy	At 6 months after parathyroidectomy
Parathyroid hormone (pg/mL)	759.0	50.30	178.0	160.0
Corrected calcium (mg/dL)	16.0	9.4	10.3	10.9
24 hr urinary calcium (mg/24 hr)	300	260	280	300
Phosphorus (mg/dL)	2.4	2.0	3.2	2.8
Mg (mg/dL)	2.1	2.1	2.2	2.1
Vitamin D (ng/mL)	11.6	12	31	45.3
Alkaline phosphatase (IU/L)	240	172	250	308
Urea (mg/dL)	83.5	32.3	35.2	35.7
Creatinine (mg/dL)	3.54	1.25	1.37	1.42

hydration with 0.9% saline solution. Osteitis fibrosa cystica was evident, but bone density remained normal (absolute T-score in the lumbar spine, -0.3; femoral neck, -0.4; total hip, -0.1). During her evolution, she presented remission of the acute renal injury but no decrease in calcium levels.

SPECT/CT with ^{99m}Tc -MIBI showed hyperfunction of the right lower parathyroid tissue. Neck ultrasound identified a $16 \times 20 \times 25$ -mm, ovoid, heterogeneous and hyper-

vascular lesion near the lower pole of the thyroid, compatible with a parathyroid adenoma (Fig. 3). The patient underwent right lower PTX according to the findings of the expert surgeon, with a $>50\%$ reduction in PTH and normalization of calcium following surgery, without presenting HBS. The histopathological report revealed a 4.5 cm parathyroid chief cell neoplasm with a trabecular pattern, pleomorphic and hyperchromatic nuclei, thin fibrous capsule

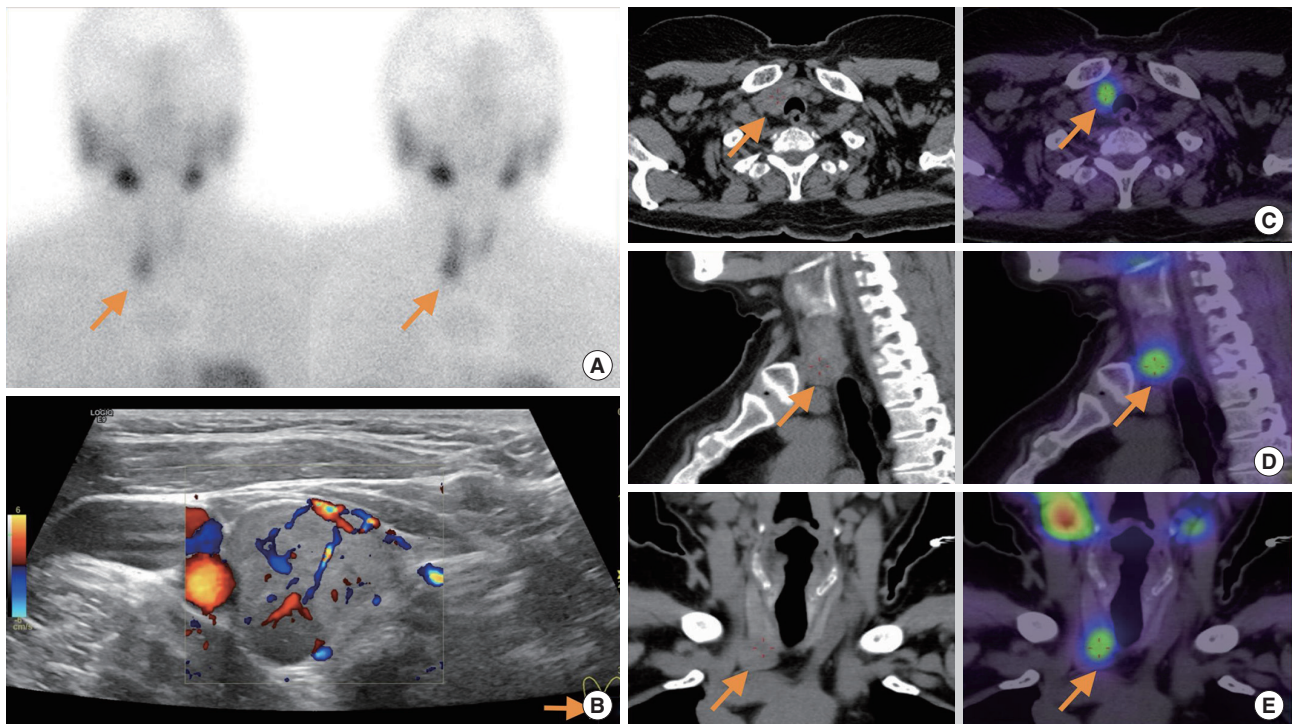


Fig. 3. (A) The 99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) planar scintigraphy with hyperfunctioning right parathyroid tissue (arrow). (B) Neck ultrasound identified a 16 × 20 × 25 mm, ovoid, heterogeneous and hypervascular lesion near the lower pole of the thyroid. Axial (C), sagittal (D) and coronal (E) ^{99m}Tc-MIBI single photon emission computed tomography (SPECT)/CT with hyperfunctioning right lower parathyroid tissue (arrow).

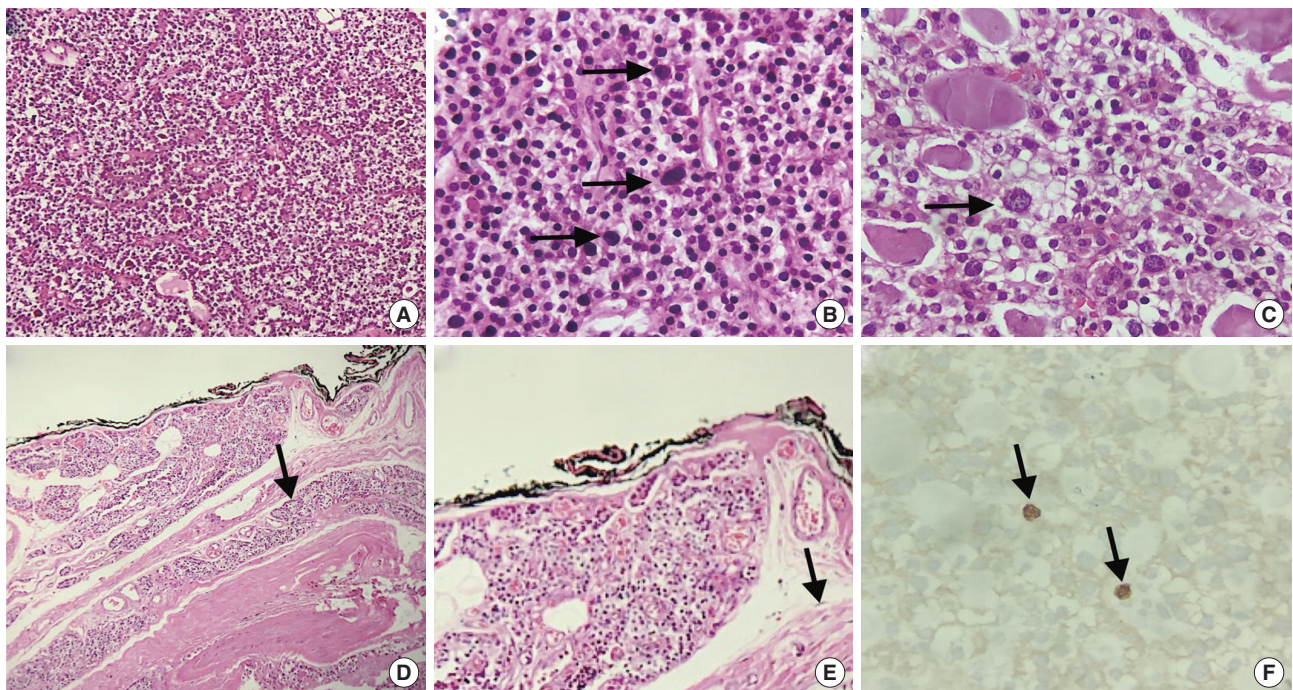


Fig. 4. (A) Hematoxylin and eosin (H&E) ×100 magnification. Parathyroid neoplasm with trabecular pattern, formed by chief cells without stromal adipocytes. (B, C) H&E ×40 magnification. Neoplasm of cells with well-demarcated, clear and abundant cytoplasm, with central, pleomorphic and hyperchromatic nuclei (arrow). (D, E) H&E ×40 magnification. Neoplasm with thin fibrous capsule and focal capsular invasion (arrow). (F) H&E ×40 magnification. Ki67. Nuclear positivity in 1% of the lesions (arrow).

and focal capsular invasion and Ki67 of 1%, compatible with APA (Fig. 4). An intraoperative biopsy of the right upper parathyroid gland showed normocellularity, without hyperplasia. During follow-up, remission of symptoms and normocalcemia were observed, however, with persistent hyperparathyroidism at 6 months (Table 2).

DISCUSSION

We report 2 diagnostically challenging cases of PHPT by APA presenting as a parathyroid crisis. A parathyroid crisis is a rare manifestation of PHPT (1%-2%) and is characterized by severe hypercalcemia (>14 mg/dL) with multiorgan involvement, including renal failure, gastrointestinal symptoms, metabolic encephalopathy, and cardiac dysrhythmia, as well as other manifestations, such as proximal muscle weakness, neuropsychiatric syndrome with decreased ability to concentrate, depression and normochromic anemia.[5]

In our cases, the first patient had muscular, gastrointestinal and neuropsychiatric manifestations, with normochromic anemia and an interesting finding of constitutional syndrome. The constitutional syndrome includes the presence of fatigue, anorexia, and unintentional weight loss [6] and is a rare and underreported manifestation in PHPT.

On the other hand, our second patient had renal ('acute on chronic kidney disease'), muscular, gastrointestinal and neuropsychiatric manifestations.

Classically, parathyroid crisis has been associated with the presence of PC; however, cases of typical parathyroid adenoma,[7] hyperplasia,[5] and, less frequently, APA has been reported.[3,4]

The presence of parathyroid crisis, serum calcium levels >14 mg/dL, and very high serum PTH concentrations (>500 ng/dL) in our patients suggested the possibility of parathyroid neoplasia initially making the diagnosis of PC vs. APA a challenge.

PC is the rarest cause of PHPT (<1%).[8] The pathophysiological mechanisms of APA are unclear, but it has been proposed that it may share molecular mechanisms with PC.[9] APA has higher rates of symptomatic hypercalcemia and fragility fracture, higher preoperative serum calcium, higher 24-hr urinary calcium and higher pre and postoperative PTH than typical adenoma.[4] The clinical and biochemical differences between APA and PC are nil, making

differential diagnosis difficult without histopathological analysis.[10]

It has been reported that the differences between APA and PC by imaging studies are minimal: parathyroid adenomas are generally solid, hypoechoic lesions with well-defined margins and dimensions usually not >2 cm. In contrast, PCs are lesions with irregular and poorly defined margins, large dimensions (>2-3 cm), and increased vascularity.[11] In our cases, we observed ultrasonographic patterns that included features of both, which is an interesting research topic for future studies in patients with APA.

Histologically, PC are characterized by sheets or lobules of tumor cells with interspersed thick fibrous bands, a pattern of trabecular growth, mitotic figures/high mitotic index, cell pleomorphism, nuclear atypia, necrosis, invasion beyond the capsule and vascular invasion.[3,12] APA is a parathyroid tumor with surrounding fibrous tissue and some of the histological features of PC, but it is not sufficient to make a diagnosis of malignancy.[8] Compared to PC, APA has a lower proportion of fibrous bands (77% vs. 100%), less cellular atypia (18% vs. 33%), less necrosis (12% vs. 17%), and less tissue infiltration (23% vs. 83%).[10] These findings are compatible with what was observed in our patients. In the first case, cell pleomorphism, nuclear atypia, and vascular invasion were evidenced, while the second case showed cell pleomorphism and focal capsular invasion; in both cases, a giant adenoma (>4 cm) was evident.

APA is a challenge for the differential diagnosis of PC, and it could represent an early stage of a PC that is excised before the development of the molecular signature of malignancy responsible for the invasive properties.[3] The importance of a proper diagnosis of APA lies in the prognosis. The prognosis in PC is poor, with a 5-year survival of 86.5%, while the 5-year survival in APA is 93.3% with a disease-free recurrence of 90.9%. [13]

The relevance of these 2 cases lies in the clinical presentation of parathyroid crisis, highlighting in the first case the presence of constitutional syndrome, an extremely rare entity and unreported in PHPT, and the second case the alteration of renal function with acute deterioration of chronic kidney disease. Biochemically, we highlight the elevated levels of calcium and PTH, as well as imaging studies with characteristics of both PC and parathyroid adenoma. Furthermore, we highlight the heterogeneity of the

clinical context of the patients: one patient with a previous normal renal function who developed HBS after PTX but with disease cure at 6 months post-surgery and another patient with impaired renal function attributed to long-standing recurrent nephrolithiasis, with a high probability of long-standing PHPT but with a risk factor for secondary hyperparathyroidism, who had persistent disease at 6 months after surgery.

The main reported clinical manifestations of APA are nephrolithiasis (approximately 30%) and osteoporosis (18%-22%), rarely presenting with parathyroid crisis [3,4]; however, information about outcomes in patients with APA is scarce, even null in specific populations such as cyclin-dependent kinase. This represents an interesting topic for future research.

When PC is suspected in patients with hypercalcemic crisis, en bloc resection (PTX, resection of the surrounding capsule and concurrent hemithyroidectomy) has been recommended. In the case of APA, there are no specific guidelines for the first-choice surgical approach. The most frequent initial surgery in APA is selective PTX (resection of affected parathyroid) (56%), followed by en bloc resection (24%).[3] The cure rate of PHPT in APA is 96%, similar to that of typical adenoma, with a recurrence of 3% and persistence of 1% [3]; however, information about the cure, persistence, or recurrence rate according to the type of surgery is still scarce. The factors associated with the persistence of PHPT in the specific context of APA have not yet been elucidated.

In our cases, it is important to note that in the patient with curative criteria (Case 1), en bloc resection was performed, while in the patient with persistent PHPT, selective PTX was performed, which raises the question: could the type of surgery be a determining factor in the successful outcome of PHPT in patients with APA?

Added to this is the possibility of having patients with complications of PHPT, such as long-standing nephrolithiasis and subsequent chronic kidney disease, which is a risk factor for persistent hyperparathyroidism, further justifying the need for more stringent and individualized surgical management by an expert surgeon.

It is important to consider that parathyroid surgery concurrent with thyroidectomy carries an 8-fold increased risk of complications compared to PTX alone, mainly hypocalcemia,[14] which is consistent with our first cases, noting

that this complication was transient. HBS is a rare but serious complication of PTX for PTH, characterized by profound and prolonged hypocalcemia. Risk factors for HBS include advanced age, very high preoperative serum calcium, alkaline phosphatase, and PTH levels, osteitis fibrosa cystica, and high volume and weight of the resected pathological parathyroid gland(s).[15]

We propose that when PC or APA is suspected, surgical treatment (individualized and performed by an expert surgeon) should be more stringent to improve the patient's prognosis, as histopathological analysis is decisive in diagnosing APA. APA should be closely monitored because of the likelihood of a premalignant stage of PC.[13]

CONCLUSION

We present 2 cases of PHPT that represented a diagnostic challenge due to their rare clinical presentation (parathyroid crisis), with a heterogeneous spectrum of target organ damage, with infrequent symptoms (constitutional syndrome and 'acute on chronic renal disease'), caused in turn by a rare pathology (APA). The clinical and biochemical presentation in these patients may be indicative of PC; however, histopathological diagnosis was the key point for the diagnosis of APA. These data highlight the need for a differential diagnosis of APA vs. PC in our clinical practice during the approach to patients with severe manifestations of PHPT, the need for a multidisciplinary team in its treatment and the generation of prospective studies oriented to long-term results in APA. We propose that surgical treatment be more stringent in patients with suspected PC vs. APA to improve the prognosis of patients with PHPT, as APA has been considered by some experts as a premalignant lesion.

DECLARATIONS

Ethics approval and consent to participate

Both patients signed a written consent to be part of this case report (Protocol no. R-2022-3601-006 of Local Ethics and Research Committee).

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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