Case Report

Challenges in diagnosis and treatment of multiple atypical parathyroid tumors in a patient with extrapyramidal symptoms: case report and literature review

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Background: Atypical parathyroid tumors (APTs) are rare entities. We report the case of a patient with multiple APT presenting with extrapyramidal symptoms and a delayed hypercalcemic crisis.

Case Description: A 72-year-old man presented to a tertiary referral center's emergency room (ER) following two episodes of temporary loss of consciousness. He had a history of ideomotor sluggishness, lethargy, extrapyramidal symptoms and dysphagia, which started 6 months prior. Serum calcium levels at presentation were normal. Four days later the patient developed a rapidly evolving respiratory failure requiring orotracheal intubation, severe hypercalcemia (up to 19.8 mg/dL) and increased serum parathyroid hormone (PTH) (151 pmol/L). A neck ultrasound (US) showed two lesions posteroinferiorly to the right and left thyroid lobe. Since hypercalcemia proved to be refractory to medical therapy, the patient underwent urgent bilateral neck exploration with subtotal parathyroidectomy for suspect parathyroid carcinoma (PC). Histopathological examination showed three nodular lesions consistent with a diagnosis of APT in each excised parathyroid. Four months after surgery, the patient is alive and well with no signs of recurrence. Neurological follow-up visits documented the absence of extrapyramidal signs.

Conclusions: Our patient showed an unusual presentation of primary hyperparathyroidism (PHPT) sustained by multiple concurrent APTs. A low suspicion threshold should be maintained to avoid delay in diagnosis. The present case adds to the body of literature on APTs, contributing to a greater understanding of this rare disease.

Keywords: Atypical parathyroid adenoma; multiple atypical parathyroid adenoma; hyperparathyroidism; hypercalcemic crisis; case report

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Introduction

Atypical parathyroid tumors (APTs) are rare entities that exhibit histopathological features of both benign parathyroid adenomas (PAs) and parathyroid carcinomas (PCs), although lacking unequivocal capsular, vascular, or perineural invasion or invasion into adjacent structures or metastases (1,2).

APTs' clinical behavior and presentation is often similar to PC, posing unique diagnostic and therapeutic challenges.

Herein we discuss a rare case of primary hyperparathyroidism (PHPT) sustained by multiple APTs presenting subacutely in an elderly patient suffering from neurologic symptoms. We present this case in accordance with the CARE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-188/rc).

Case presentation

Patient

A 72-year-old man with a mild severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and a history of chronic renal failure, type two diabetes mellitus, and arterial hypertension, was admitted to the emergency room (ER) of our hospital on November 2nd, 2022 following two temporary loss of consciousness episodes and palpitations at home.

Six months prior the patient had started experiencing ideomotor sluggishness, lethargy and dysphagia leading to significant weight loss (30 kg in four months). Said neurological symptoms had raised the suspicion of an extrapyramidal disease, prompting additional investigations. A cerebral magnetic resonance imaging (MRI) was thus performed showing vascular encephalopathy. The patient was started on oral amantadine with only partial benefit.

In the ER, cardiac ultrasound (US) revealed no structural abnormalities, whereas the electrocardiogram (ECG) highlighted several ventricular and supraventricular extrasystoles and a complete right bundle branch block.

Blood tests showed mild leukocytosis, acute kidney injury [1.88 mg/dL; reference range (rr): 0.59–1.29 mg/dL], with an estimated glomerular filtration rate of 47 mL/min, and severe hypokalemia (2.01 mmol/L; rr: 3.4–4.8 mmol/L). Calcium levels were normal (2.31 mmol/L; rr: 2.1–2.6 mmol/L). The patient was admitted to the infectious disease department for close observation.

Four days later the patient developed a rapidly evolving hypoxic-hypercapnic respiratory failure (pCO_2 >100) and severe desaturation (pO_2 78%), and became unresponsive to verbal or pain stimuli, requiring orotracheal intubation for appropriate ventilation.

During the following two days his blood exams revealed severe hypercalcemia (up to 19.8 mg/dL; rr: 8.0–10.0 mg/dL), hypernatremia (153 mmol/L; rr: 135–145 mmol/L) and increased serum PTH (151 pmol/L; rr: 1.6–6.9 pmol/L) prompting additional investigations to exclude PHPT.

Meanwhile, hydrocortisone and pamidronate were empirically started but unfortunately proved unsuccessful, given the progressive increase in serum total and ionized calcium (4.96 and 2.95 mmol/L, respectively). Consequently, an attempt at continuous venovenous hemodiafiltration (CVVHDF) was pursued, leading to a significant drop in serum calcium levels (10.9 mg/dL) and allowing for treatment with calcium mimetic (cinacalcet).

A neck US showed two solid lesions (*Figure 1A,1B*). The first one (27 mm × 23 mm) was posterior to the inferior pole of the left thyroid lobe, well vascularized and calcific. The second one (34 mm × 23 mm), similar in composition but mainly cystic, was posterior to the inferior pole of the right thyroid lobe. A head and neck computerized tomography (CT) scan confirmed US findings (*Figure 1C-1E*).

In the following days serum calcium levels persistently

Highlight box

Key findings

- Atypical parathyroid tumors (APTs) are a rare entity which can present concurrently in multiple glands.
- Clinical presentation may be subacute with neurologic symptoms and delayed hypercalcemic crisis.
- Preoperative ultrasound (US) is important in surgical planning in urgent cases.

What is known and what is new?

- APT is rare, with borderline features between a benign and malignant entity. Its multiple presentation is extremely rare in the literature.
- We suggest multiple APTs could present subacutely, with symptoms that, if misinterpreted, could let an unusual presentation of primary hyperparathyroidism (PHPT) go unnoticed. A neck US scan could be of sufficient value in urgent cases to appropriately plan surgery.

What is the implication, and what should change now?

- A high index of suspicion should be maintained while investigating patients with subacute neurological symptoms, as their condition could be metabolic in origin, as part of a PHPT secondary to multiple APTs.

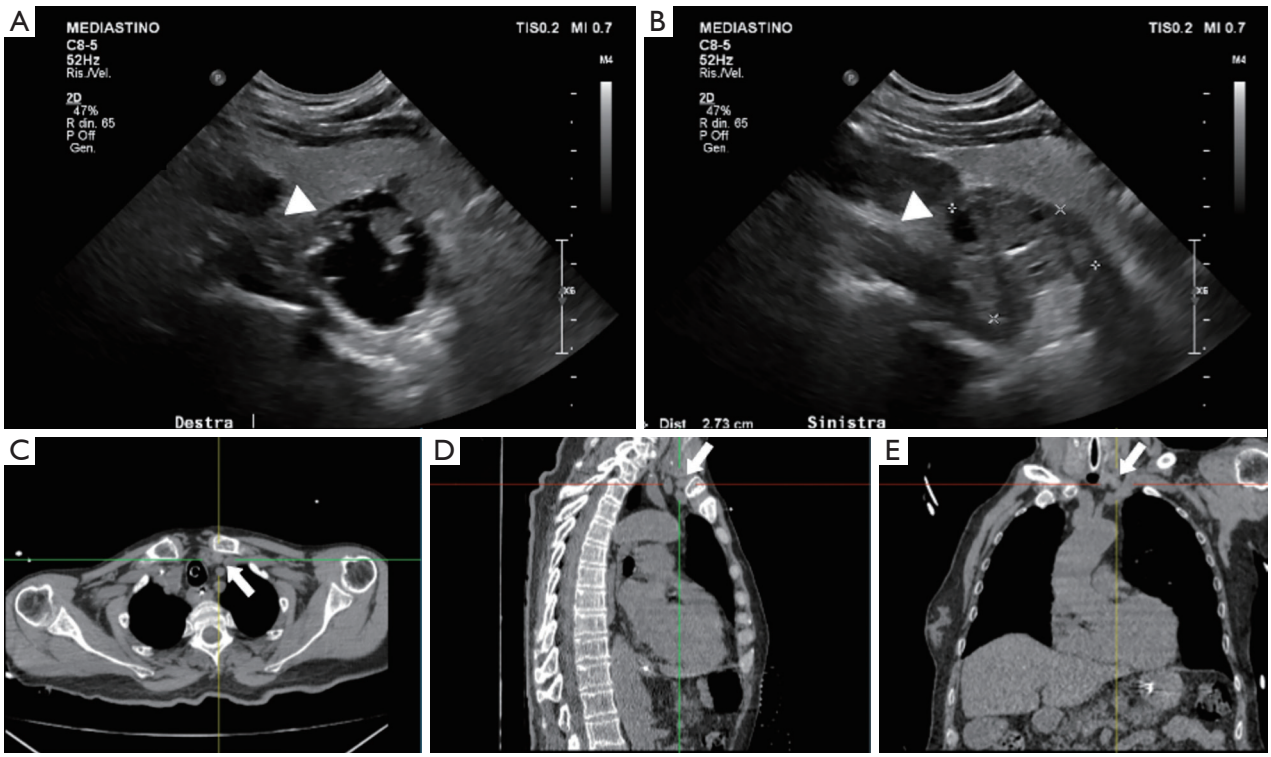

Figure 1 Diagnostic imaging, US (A,B) and CT scan (C-E) showing right inferior and left inferior parathyroid. (A) US scan showing an anechoic mass with a solid component and septa (arrowhead) posterior to the right inferior thyroid lobe. (B) US scan showing a mostly solid hypoechoic nodule with ill-defined margins and a small cystic component (arrowhead) posterior to the left inferior thyroid lobe. (C-E) Neck CT scan in the axial, longitudinal and coronal plane, respectively, showing a solid isodense mass (arrows) inferior to the left thyroid lobe. US, ultrasound; CT, computerized tomography.

tended to the upper limits, despite CVVHDF, and the patient presented significant fluctuations in consciousness, prompting an urgent surgical referral under the suspicion of PC.

Due to the patient's severely impaired clinical conditions, a scintigraphic evaluation of the cervical region was not feasible. Therefore, the patient underwent emergency bilateral neck exploration with subtotal parathyroidectomy.

Surgery

Intraoperatively, both previously identified lesions appeared tightly adhered to the thyroid parenchyma, supporting the concerns of malignancy. An indication for an associated total thyroidectomy was therefore provided along with a central compartment dissection. A third left superior enlarged parathyroid gland was identified intraoperatively and excised, while a 4th parathyroid was not identified during surgery. A venous sampling for PTH was performed 20 minutes after surgical excision, with a value of 24.8 pmol/L, thus meeting Miami criteria and confirming the complete excision of all the hyperfunctioning parathyroid tissue. A further decrease in PTH levels (1.5 pmol/L) was seen on the first postoperative day (POD).

From the 4th POD on, the patient developed postoperative hypocalcemia (nadir 6.25 mg/dL) with near normal Vitamin D levels (72.5 nmol/L; rr >75 nmol/L) responsive to oral correction with calcium carbonate (500 mg q.i.d.) and Vitamin D supplementation (calcitriol 0.5 mcg b.i.d.). The patient suffered no postoperative dysphonia.

Pathology

The histopathological examination showed three different nodular lesions, whose histopathological features were similar between each other. They were composed almost exclusively of chief cells with a predominant solid-alveolar pattern, partly encapsulated, with focal osseous metaplasia

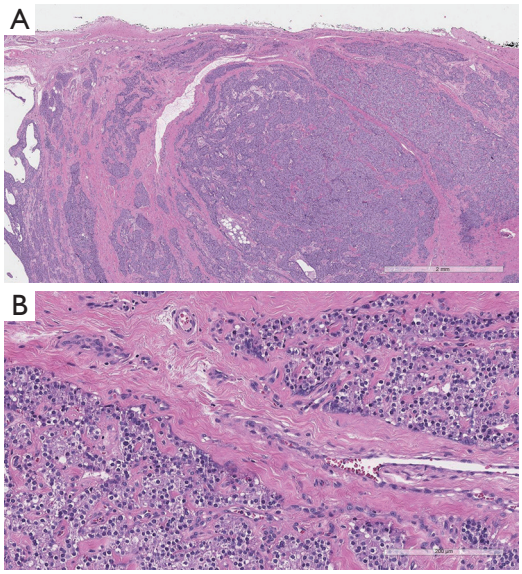

Figure 2 Histopathologic examination, hematoxylin and eosin stain. (A) Low power view on one of the atypical parathyroid tumors with areas of solid growth mixed with significant fibrosis. (B) High power view of the tumor, showing irregular growth with prominent areas of fibrosis, without definitive vascular invasion or invasion into the capsula.

and haemorrhagic areas. Focally recognizable rims of parathyroid tissue with preserved structure were identified. Neoplastic cells showed focal atypia; the architectural pattern of growth was sometimes monotonous, sheet-like or focally trabecular. The nodal capsule was irregular with multinodular growth, pseudo infiltrative aspects outside some of the nodules and architectural atypia, without clear signs of infiltrative phenomena or neoplastic embolisation (*Figure 2A,2B*). Immunohistochemical analysis showed positivity for GATA-3 and negativity for galectin-3, while the degree of nuclear proliferation of Ki67 was estimated at 1–2%.

These findings were consistent with an APT diagnosis within each excised parathyroid.

Follow-up

A multidisciplinary consensus was reached to follow the patient closely with neck US and parathyroid hormone assay at 6 months. Four months after the procedure the patient is alive and well. Serum calcium levels at 4 months follow-up were within normal range (9.4 mg/dL) under supplementation regimen (calcium carbonate 500 mg b.i.d. and calcitriol 0.25 mcg b.i.d.). The patient underwent a follow-up neurologic examination four months after surgery which found no clear extrapyramidal signs (no bradykinesia, no hypertonus, no tremor, conserved pendular movements of the arms).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

PHPT is the third most common endocrinological disorder after diabetes and thyroid diseases, occurring in approximately 0.1% to 0.3% of the general population (3,4). PHPT is more common in women (1 in 500) than men (1 in 2,000), and around 99% of patients present benign tumors (4): solitary PA are the most common cause of hyperparathyroidism accounting for about 85% of cases, followed by parathyroid hyperplasia (10–15%) (3,5) and multiple PA (3%). In contrast, PC and APT account for only 1% of cases. Given the rarity of APT, whose incidence is currently unknown, there is still no general consensus on specific treatment and follow-up (3,6). We conducted a review of the current literature through a MEDLINE database search using the following string: ((“parathyroid neoplasms”[MeSH Terms] OR “parathyroid glands”[MeSH Terms]) AND (“adenoma, parathyroid”[MeSH Terms] OR “atypical adenoma”[All Fields] OR “atypical parathyroid adenoma”[All Fields] OR “parathyroid neoplasm, atypical”[All Fields] OR “atypical parathyroid neoplasm”[All Fields])) through which we selected 31 papers until 18th February 2023 discussing single or multiple cases of APT. The results are summarized in *Table 1*. The papers included 446 patients with a mean age of 49 years at diagnosis with a pooled F:M ratio of 1.65:1. Reported signs and symptoms are heterogeneous among patients. The presence of a neck mass and renal involvement are the most commonly described clinical features. Mean calcium level at diagnosis was 3.72 mmol/L, while mean PTH at diagnosis was 100 pmol/L. The reported US features were consistent among the studies included, showing a large hypoechoic mass mostly with a cystic component and partially calcified. Predominantly reported histopathological features

Table 1 Review of papers describing at least one case of histopathologically confirmed APT published up to February 2023

Authors	Year	No. of patients	Gender	Age at diagnosis (years), mean	Symptoms at diagnosis	Calcium level at diagnosis (mmol/L), (number/mean)†	PTH level at diagnosis (pmol/L), (number/mean)†	Ultrasound features	Ultrasound dimensions (cm × cm × cm)	Histopathological features	Multiple parathyroid pathology	Recurrent disease
Goshen *et al.* (7)	2000	1	F	20	Expanding mandibular mass, nephrolithiasis	3.1	13.2	–	–	Cells arranged in wide sheets, trabecular growth pattern, broad fibrous bands, fibrous capsule	–	None
Poppe *et al.* (8)	2001	1	M	31	Laterocervical neck mass	2.4	5.2	–	–	Invaded capsule with no perforation	–	None
Ippolito *et al.* (9)	2007	16	11 F, 5 M	58	Palpable lesion	–	–	Large exophytic mass	–	Trabecular growth, broad fibrous bands, nuclear atypia, mitosis, pseudo-capsular invasion, absence of capsule	–	None
Fernandez-Ranvier *et al.* (4)	2007	7	3 F, 4 M	55.8	Bone pain, fatigue, anorexia, abdominal symptoms (pain, dyspepsia, reflux), psychiatric symptoms	3.4	31.5	–	–	Fibrous trabeculae 5, trabecular pattern 2, mitotic features 2, nuclear polymorphisms 1	1 concurrent adenoma	1
Yener *et al.* (10)	2007	1	F	26	Asymptomatic	2.9	155.4	Low-echogenic	2×2.4×3.2	Nuclear polymorphism: fibrous bands	–	None
Juhlin *et al.* (11)	2010	5	3 F, 2 M	52.4	–	3.4	21.5	–	–	Fibrous bands, trabecular growth, nuclear atypia, capsular enlargement, Ki67 index	–	None
Guarnieri *et al.* (12)	2012	14	7 F, 7 M	54	–	3.3	30.5	–	2.3	–	–	1
Mishra and Newman (13)	2014	1	M	36	Neck mass, muscle soreness, joint pains, constipation	5.8	354.0	–	–	Encapsulated-cells showed mild atypia with mild nuclear enlargement and pleomorphism, rare mitotic figures	–	None
Brown *et al.* (14)	2014	1	M	70	Hypercalcemic crisis, acute kidney injury, constipation, weakness, fatigue, depression, weight loss	4.9	175.0	Enlarged parathyroid with cystic component	4.8×4.0×2.9	Oncocytic cells in a solid, nested, and trabecular growth pattern	–	None
Razavi *et al.* (15)	2014	1	F	42	Asymptomatic	2.8	38.7	–	1.7×1.7×2.2	Hypercellular parathyroid gland, solid and follicular pattern, thick capsule, acellular fibrous bands, infiltrative pattern	–	–
Quinn *et al.* (16)	2015	34	17 F, 17 M	56.5	Chronic kidney disease, GERD, kidney stones, hypercalcemic crisis, weakness, fatigue, depression, weight loss	3.3	28.2	Heterogeneous mass with cystic and vascular solid components	–	Capsular invasion, intratumoral fibrous bands splitting tumor, diffuse cellular atypia, nuclear atypia, loss of parafibromin staining	–	None
Favere *et al.* (17)	2015	1	F	62	Diffuse bone pain, asthenia, weight loss, depressed mood, neurofibromas, café au lait spots	13.5	205.0	–	–	Irregular capsule, islands of neoplastic tissue trapped in the fibrous capsule, trabecular pattern	–	–
McCoy *et al.* (18)	2015	51	31 F, 20 M	56	–	3.3	172.0	–	–	Fibrosis 40, trabecular growth pattern 19	–	None
Schneider *et al.* (19)	2015	68	39 F, 29 M	58	Urolithiasis, bone alterations, depression, palpable neck mass	3.3	55.4	–	–	Grayish/white/grossly enlarged tumor 16, adherence 50	–	1 recurrent adenoma
Christakis *et al.* (20)	2016	1	F	32	–	2.9	53.0	–	–	Thick bands lobular feature	1 recurrent adenoma	None
Rodrigues *et al.* (21)	2016	1	F	34	Lumbar pain, multiple osteolytic lesions with fluid-fluid levels, neck mass, arterial hypertension	3.2	134.1	–	–	Banding fibrosis	–	–
Cakir *et al.* (22)	2016	23	12 F, 11 M	51.3	–	3.3	47.5	Hypoechoic 15, isoechoic 5, cystic 3	2.2	–	–	1
Krishna Mohan *et al.* (23)	2017	1	F	21	Bone lesions	2.6	33.4	Hypoechoic nodule	1.8×0.6	Pleomorphic nuclei minimal mitotic features partial capsular invasion	–	None
Clark *et al.* (24)	2017	1	M	65	Renal calculus, osteoporosis, neurocognitive symptoms	–	146.1	Hypoechoic nodule	–	Thickened capsule, extensive acellular fibrous tissue with embedded nests of cells, expansile sheets of tumor cells	–	–
Dobrinja *et al.* (25)	2017	5	4 F, 1 M	–	–	–	42.9	–	–	–	–	–

Table 1 *(continued)*

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Authors	Year	No. of patients	Gender	Age at diagnosis (years), mean	Symptoms at diagnosis	Calcium level at diagnosis (mmol/L), (number/mean)†	PTH level at diagnosis (pmol/L), (number/mean)†	Ultrasound features	Ultrasound dimensions (cm × cm × cm)	Histopathological features	Multiple parathyroid pathology	Recurrent disease
Sungu *et al.* (26)	2018	14	–	–	–	–	–	–	–	Thick fibrous band, nuclear atypia, mitosis, Ki67 >5%	–	None
Florakis *et al.* (27)	2019	1	M	44	Arthralgias, myalgias, nephrolithiasis, osteopenia	3.1	119.9	Hypoechoic mass	2.6×3.6	Solid and cystic areas with fibrosis and partial capsular invasion	–	None
Song *et al.* (28)	2020	2	2F	51.5	Nephrolithiasis, pain-induced restricted movement, GERD, melena	3.3	115.9	–	–	Lobular features, fibrous bands, focal active growth and mitoses, thick bands	1 hyperplasia, 1 adenoma	None
Faulkner *et al.* (29)	2020	1	F	80	Neck swelling	2.9	21.9	–	–	Cystic change, dense acellular fibrous bands infiltrated by large, and small nests of chief tumor cells	3 APT	–
Knappe *et al.* (30)	2021	1	F	77	Nephrolithiasis, vertebral osteoarthritis	2.9	17.9	–	–	–	–	–
Saponaro *et al.* (31)	2021	58	37 F, 21 M	56	–	3.1	14.9	Heterogeneous ultrasound pattern 18, calcifications 5, cystic features 3	1.54	Thick fibrous bands, pseudocapsular invasion, mitotic activity, trabecular growth pattern, nuclear atypia, cystic features, prominent nucleoli, cellular pleomorphism	1 papillary thyroid microcarcinoma, 2 adenoma, 2 hyperplasia	2 recurrent, 4 persistent
Schulte *et al.* (32)	2021	17	–	–	–	2.9	63.7	–	–	Fibrous capsule invasion, intralesional fibrous bands, necrosis, solid growth, infiltrative soft tissue invasion	–	2 parathyromatosis, 1 parathyroid carcinoma, 1 lung
Galani *et al.* (6)	2021	10	5 F, 5 M	62	Nephrolithiasis, peptic ulcers, pancreatitis, cardiovascular disease, hypertension, osteoporosis, fragility fracture, neuropsychiatric/neurocognitive symptoms, neuromuscular symptoms	3.4	127.1	–	2.5	Pseudocapsular invasion, bands of fibrosis, trabecular growth, mitotic rates of >1/10 HPFs, tumor necrosis, nuclear pleomorphism, cystic degeneration, thick capsule	None	None
Boro *et al.* (33)	2022	1	F	16	Musculoskeletal pain, proximal-distal muscles weakness, weight loss, graveluria, constipation, acute pancreatitis, facial dysmorphism, GERD	4.6	530.0	–	–	Adherent capsule, focal nuclear atypia, focal intratumoral, fibrous bands, mitosis (1–2/10 HPF) focal oncocytic metaplasia, trabecular growth, intratumoral thick septae, cystic changes	2 APT	–
Saraydaroglu *et al.* (34)	2022	32	23 F, 9 M	54.8	–	–	–	–	–	Nuclear enlargement 24, cellular atypia 15, mitotic rates of >1/10 HPFs in 2, fibrous bands 6, areas of solid growth pattern 2	–	1 (bone metastasis)
Chen *et al.* (3)	2023	79	57 F, 22 M	46.9	Bone involvement, fragility fracture, urolithiasis, gastrointestinal symptoms, hypercalcemic crisis	3.0	62.9	–	–	–	9	4
Present case	2023	1	M	72	Weight loss, lethargy, dysphagia, hypercalcemic crisis, respiratory insufficiency, temporary loss of consciousness, ECG anomalies, long-standing ideomotor sluggishness	2.3	16.0	Hypervascularization, calcified, cystic	2.7×2.3–3.4×2.3	Cells with a solid-alveolar pattern, partly encapsulated, focal bone metaplasia, irregular nodal capsule, multinodular growth, pseudo infiltrative aspects outside the nodule, architectural atypia	3 APT	–

†, where a single case is described, the number refers to the single case value, whereas if multiple cases are described, the number refers to the mean of the cases' values. APT, atypical parathyroid tumor; PTH, parathyroid hormone; F, female; M, male; GERD, gastroesophageal reflux disease; HPF, high power field; ECG, electrocardiogram.

include fibrous bands and trabeculae, nuclear atypia and pseudocapsular invasion. Unlike glandular hyperplasia, or, less frequently, PCs, APT generally involves a single gland (19,29). To the best of our knowledge this is the second reported case of PHPT with an acute presentation due to multiple APTs. However, unlike the case reported by Faulkner *et al.* (29), our patient did not show any anterior neck swelling, his serum corrected calcium was initially normal, and the APT presented subacutely with indirect signs and symptoms. Moreover, Faulkner *et al.*'s patient was female (29). Conversely, we presented a case of multiple APTs in a 72-year-old man. This occurrence is unusual and more consistent with a PC. Indeed, APT is more frequent in women, with a female: male ratio reaching 2.59:1 (3) and an average age of onset around the sixth decade of life, although in familial forms it can occur as early as in the fourth decade (30±17 *vs.* 55±13 years in sporadic forms) (31).

Our patient presented to the ER with two temporary loss of consciousness episodes, ECG anomalies, and long-standing ideomotor sluggishness, lethargy and dysphagia, while a hypercalcemic crisis occurred only later in his course, once renal failure arose.

This presentation is indeed insidious and differential diagnosis is troublesome, thus requiring a high index of suspicion.

Patients with APT are slightly more symptomatic (about 60%) than patients with benign adenomas. The most common signs are renal manifestations (nephrocalcinosis, nephrolithiasis, and renal insufficiency) and bone involvement (osteitis fibrosa cystica, osteoporosis and rarely pathological fractures), followed by gastro-oesophageal reflux disease (GERD), weakness and fatigue. Rarely, clinical presentation can be more severe, with arrhythmias, hypercalcemic crises and neurological involvement (35,36). Saponaro *et al.* reported that 15% (5/34) of patients with symptomatic APT had hypercalcemic crises, while in the cohort of APT patients studied by Quinn *et al.* 5.6% presented ECG anomalies (16,31,37).

Our patient exhibited normal serum calcium levels at presentation with a late-onset hypercalcemia without a history of long-standing PHPT.

Patients with APT have significantly higher preoperative serum levels of calcium and PTH compared to patients with PAs, but less markedly than carcinomas (11.8 *vs.* 13.0 mg/dL) (16). These findings further support the hypothesis that APT is a neoplastic entity that exhibits features and behaviors that straddle the line between a malignant and a benign form (16).

Specifically, Saponaro *et al.* observed that both serum calcium and PTH concentrations were significantly higher in symptomatic patients than in asymptomatic patients (12.8±3.1 *vs.* 11.5±1.2 mg/dL and 204 *vs.* 65 pg/mL, respectively) (31). Normal calcaemia at presentation should not, however, mislead diagnostic efforts delaying diagnosis, as our case highlighted, and a high index of suspicion should be maintained to improve patient's prognosis.

Although single photon emission computed tomography (SPECT)/CT and parathyroid scintigraphy are mainstays for preoperative disease localization in PHPT, their use could be problematic in emergency situations as they may not be widely and promptly available. In our case, we relied on neck US color-Doppler imaging (neck US-CD) for diagnosis and disease localization, which allowed for a quick assessment of disease burden in the neck.

Cakir *et al.* found that the diameter of the largest adenoma was higher in the APT and PC groups than in the PA group. Additionally, there were significant differences in the ultrasonographic appearance of the adenomas among groups. APT and PC had more frequently an isoechoic or cystic appearance. In addition, the latter was an independent predictor of aggressive disease (22).

In our case, a cystic appearance was demonstrated by US scan for each pathological adenoma suggesting multiglandular involvement without the support of a scintigraphic evaluation, thus allowing for an upfront emergency bilateral exploration strategy.

Due to intraoperative concerns of malignancy, the patient underwent total thyroidectomy along with a 3/4 parathyroidectomy and central compartment dissection.

While the mainstay of treatment for PC is *en bloc* resection of parathyroid and involved adjacent structures (38), optimal treatment for APT is still debated. APT generally behaves anatomically like PC being adherent to surrounding structures (39) and diagnosis can only be made histopathologically. Consequently, the surgical treatment of choice is generally an oncologically radical *en bloc* resection to avoid surgical re-excision, to reduce the risk of incomplete resections and the risk of recurrence. However, APT seems to have a more benign course than PC, with a reported five-year disease-free survival rate after complete excision of 59.6% *vs.* 90.9% for PC *vs.* APT, respectively (20).

Even though the better prognosis of APT over PC may theoretically justify a more conservative surgical approach, there are currently no reliable means to predict the neoplasm's histopathological features preoperatively. When there is a great suspicion for malignancy, a prudential

approach is therefore currently warranted for this kind of disease (7).

In our case, parathyroids showed atypical features (i.e., sheet-like or focally trabecular architectural growth pattern, irregular capsule with multinodular growth and pseudo-infiltrative aspects, among others) without clear signs of infiltrative phenomena or neoplastic embolization, distinctive of PC. The histological diagnosis of APT poses indeed several challenges. Firstly, the paucity of widely shared data due to the rarity of the disease makes accurate characterization problematic. Overlapping features between APT and PC add to the difficulty of specimen examination, limiting the value of intraoperative frozen section analysis. Moreover, molecular tests and specific immunohistochemical markers are currently expensive and of limited availability. In light of these well-known challenges, clinicopathological correlation and the integration of molecular techniques are pivotal to improve diagnostic accuracy and APT's management. Further research is needed to expand our knowledge of these rare neoplasms.

Conclusions

This case depicts an unusual presentation for APT which posed unique challenges, both clinical and therapeutic. A low suspicion threshold should be maintained to avoid delay in diagnosis and provide the patients with the best chances for cure. To the best of our knowledge, this is the first reported case of multiple concurrent APTs presenting subacutely with a delayed hypercalcemic crisis. There are currently no clear indications or guidelines on how to manage APT. The present case adds to the body of literature on APTs, hopefully contributing to a greater understanding of this rare disease.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-188/rc

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-188/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-188/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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