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CASE REPORT

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Tertiary hyperparathyroidism masking an atypical parathyroid tumor

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Key Clinical Message

Atypical parathyroid tumors represent a group of parathyroid neoplasms of uncertain malignant potential. In view of preoperative diagnostic difficulties, suspicious features for malignancy may guide the surgeon to perform a radical surgical approach.

KEYWORDS

atypical parathyroid tumor, renal failure, tertiary hyperparathyroidism (THPT), total parathyroidectomy

1 | INTRODUCTION

By definition, THPT is caused by a prolonged period of secondary hyperparathyroidism (SHPT).[1–4] Main differences between secondary and tertiary hyperparathyroidism, despite their fundamental common point which is the increased parathyroid hormone secretion by the parathyroid glands, are observed. SHPT is characterized by adapted raised level of PTH, while THPT by non-adapted raised PTH levels.[5,6] SHPT causes buildup of 25OHVitD deficiency, renal hypercalciuria, kidney failure, malabsorption, and certain medicines, while THP is the result of prolonged stimulus under SHP.[5] In addition to their differences, it is important to mention that in SHP the serum calcium levels can be normal, depending on the cause of origin, while in THP the serum calcium levels are increased. SHP is mainly dealt with curing the underlying cause, while the THP is surgically treated by parathyroidectomy in case of symptom expression. Nearly 8% of patients with SHPT will develop THPT. Although hyperplasia of all four glands is revealed in the majority of patients with THPT, single or double adenomas and scarcely carcinomas have been reported.[2] In this paper, the unique case of an atypical parathyroid tumor in the setting of THPT is being reported. Management and follow-up strategies are also discussed.

2 | CASE HISTORY/EXAMINATION

A 64-year-old male patient was referred by the nephrologists to the outpatient department of 3rd Surgical Department of AHEPA University Hospital for the management of refractory hyperparathyroidism. The patient was under hemodialysis in the last 10 years and

was receiving oral medication with calcitriol, oral phosphate solution, and cinacalcet to manage secondary HPT. However, HPT persisted.

3 | METHODS

Current laboratory values revealed PTH of 1352 pg/mL, while serum Ca and P were at 11.67 and 6.5 mg/dL respectively. With the indication of THPT ultrasound imaging (Figure 1), technetium-99m-sestamibi scintigraphy and SPECT–CT (Figure 2) were performed. Both revealed the presence of a right upper parathyroid adenoma.

The patient was scheduled for subtotal parathyroidectomy. During neck exploration, all four parathyroid glands were recognized in their typical positions. All of them appeared enlarged and pathologic, while the right upper parathyroid gland seemed to invade the right thyroid lobe. Therefore, the surgical plan was rearranged and a total parathyroidectomy with an en bloc resection of the right superior parathyroid gland with the right thyroid lobe was performed. Part of the inferior parathyroid with healthy appearance was dissected and auto-transplanted to the left sternocleidomastoid muscle. Intraoperative parathormone (iPTH) values were measured 20 min after each resection. Only after the resection of the superior right parathyroid iPTH dropped to 5.5 pg/mL.

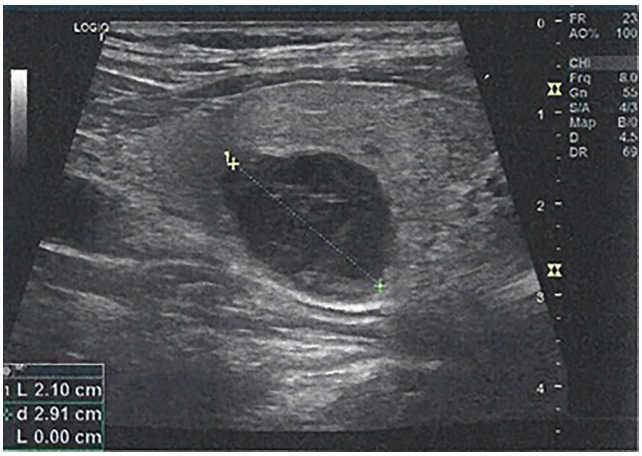

FIGURE 1 Ultrasound image depicting the presence of a hypoechoic 2.1 × 0.58 cm mass located in the area of the right anterior parathyroid gland.

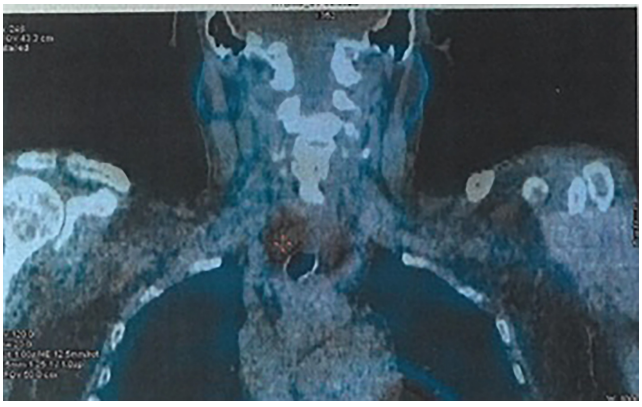

FIGURE 2 SPECT–CT images.

4 | CONCLUSION AND RESULTS

Histological examination revealed a 3.5 × 2 × 1.2 cm atypical neoplasm surrounded by thick fibrous capsule confirmed to be the right inferior parathyroid gland specimen. (Figure 3A). Neoplastic cells were small in size containing small nuclei and clear or eosinophilic cytoplasm. Nuclear atypia was mild, with only two mitoses in 10 mm.[2] No necrosis was found (Figure 3B,C). Although neoplastic cells were occasionally infiltrating the thyroid capsule, penetration through it was not revealed, highlighted by immunohistochemical staining for CD31 (Figure 4A–C). Immunohistochemically, the neoplastic cells were focally positive for galectin-3, occasionally focally positive for p53, and only focally negative for BCL2. The mitotic index Ki67 was estimated below the critical point of 5%, being usually 1%–2% with rare hot spots of 4% (Figure 4D). Taking all the above under consideration, an atypical parathyroid tumor was diagnosed. The pathology report confirmed, also, the presence of diffuse parathyroid hyperplasia in all the other resected tissues.

Postoperatively, 2000 mg of calcium carbonate was administered as daily therapy due to a significant drop in serum calcium levels (6.0 mg/dL). The patient was discharged on the third postoperative day in good condition. Currently, at 12 months of follow-up, he is free of disease without any sign of locoregional recurrence or distant metastases, as well as optimized values of calcium and parathyroid hormone.

5 | DISCUSSION

The combination of hypercalcemia with autonomous proliferation of parathyroid glands seen after long-standing SHPT refers to THPT.[3]

The pathophysiology of THPT remains unclear. It is hypothesized that a monoclonal expansion of parathyroid cells in which the set point of the Ca-sensing receptors (CaSRs) has been altered such that semi-autonomous secretion of PTH occurs despite high serum calcium levels.[3]

CaSR is a G protein-coupled receptor which is expressed in a plethora type of cells. It is widely known that CaSRs occupy a fundamental multifunctional role in the

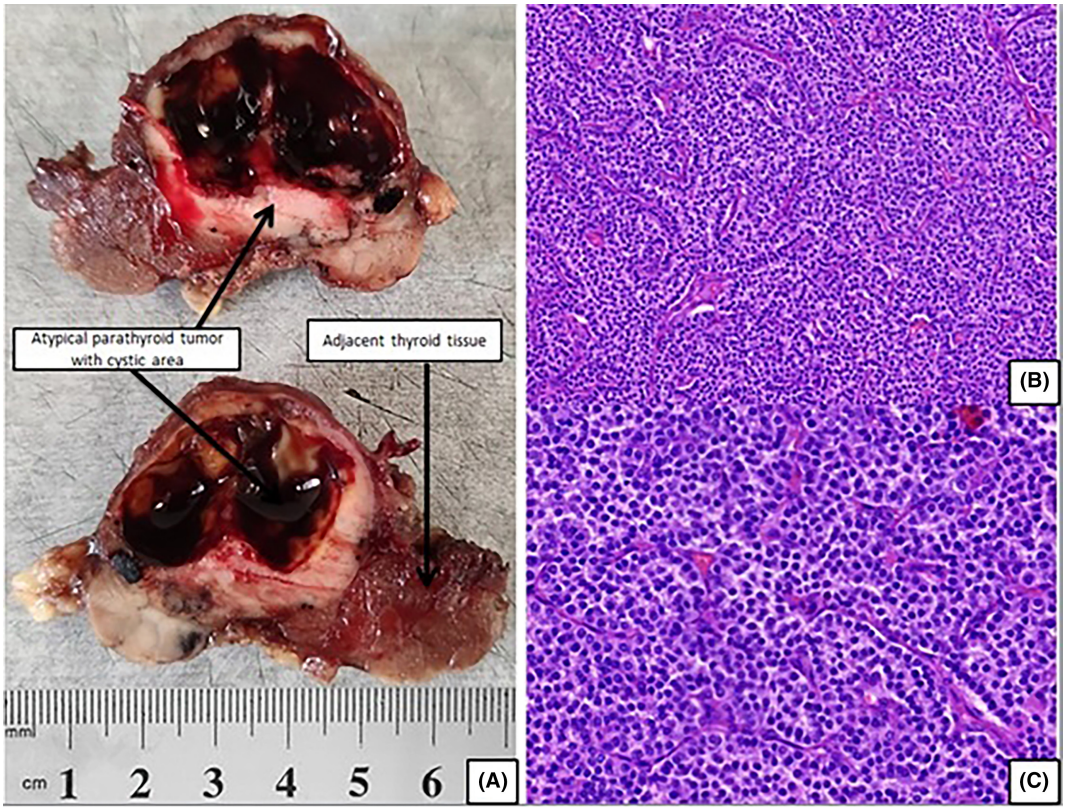

FIGURE 3 (A) Upon dissection, right thyroid lobe and a cystic hemorrhagic area of the atypical parathyroid tumor. (B, C) Diffuse arrangement of small neoplastic cells with small nuclei and clear or eosinophilic cytoplasm. Mild nuclear atypia without any substantial mitotic activity can be seen (H&E ×200 and H&E ×400).

body system, participating in blood coagulation, muscle and nerve conduction, skeletal mineralization, and signal transduction as well. CaSR protein expression is quite prevalent in parathyroid chief cells and thyroid c cells, where they can be found in affluence.[4] Detection of CaSR can be noticed in renal tubules, dealing with the regulation of calcium reabsorption and in other body systems. CaSR pathophysiology helps in maintaining calcium levels in normal limits. Parathormone (PTH) secretion is regulated by CaSR, which depends on the extracellular ionized calcium. PTH production is blocked preventing the release of increased serum calcium by binding to CaSR. That leads to renal calcium excretion and blocking of PTH secretion occur and calcinuria, due to CaSR activation, following calcitriol synthesis inhibition, preventing the high serum calcium by reduced calcium mobilization and absorption from small intestine. On the other hand, in case of low serum calcium levels the effect is the exact opposite.[5]

In SHP, the role of calcium is not always dominant, because in some cases it can be within normal limits. The mechanism of CaSR function is still not clear. Increasing serum phosphorus (P) may stimulate CaSR activation, despite the physiological serum calcium levels. In addition, the PTH calcemic effect must be noted, which contributes to hypocalcemia following parathyroid hyperplasia, due to phosphorus, which is the generation of skeletal resistance to that effect.[6]

In THP the mechanism is also changed, but it is still unclear. The CaSR expression in not activated, but it acts autonomously, probably due to parathyroid cell monoclonal expansion, where the set point of CaSR protein has been changed.[5] Monoclonal chief cell growth results in the formation of nodules. Nodular glands have less vitamin D receptor (VDR) and CaSRs compared to diffusely hyperplastic glands and this exacerbates parathyroid gland resistance to calcitriol and calcium.[3,7] In the reported patient THP resulted from prolonged stimulus under SHP.[6] The triad of high serum PTH, calcium and phosphorus levels were indicative.[8]

Usually, in THP hyperplasia of the three glands with a single or double adenoma, and in rare cases with a carcinoma coexists.[2,9] In this case, the thyroid specimen was easily recognized as a part of a goiter with degenerative lesions while the three of the received parathyroid glands showed diffuse parathyroid hyperplasia compatible with the history of the patient. Regarding the right upper parathyroid specimen, the diagnosis was challenging enough and finally the diagnosis of an atypical parathyroid tumor according to the WHO 2022 criteria was reached.

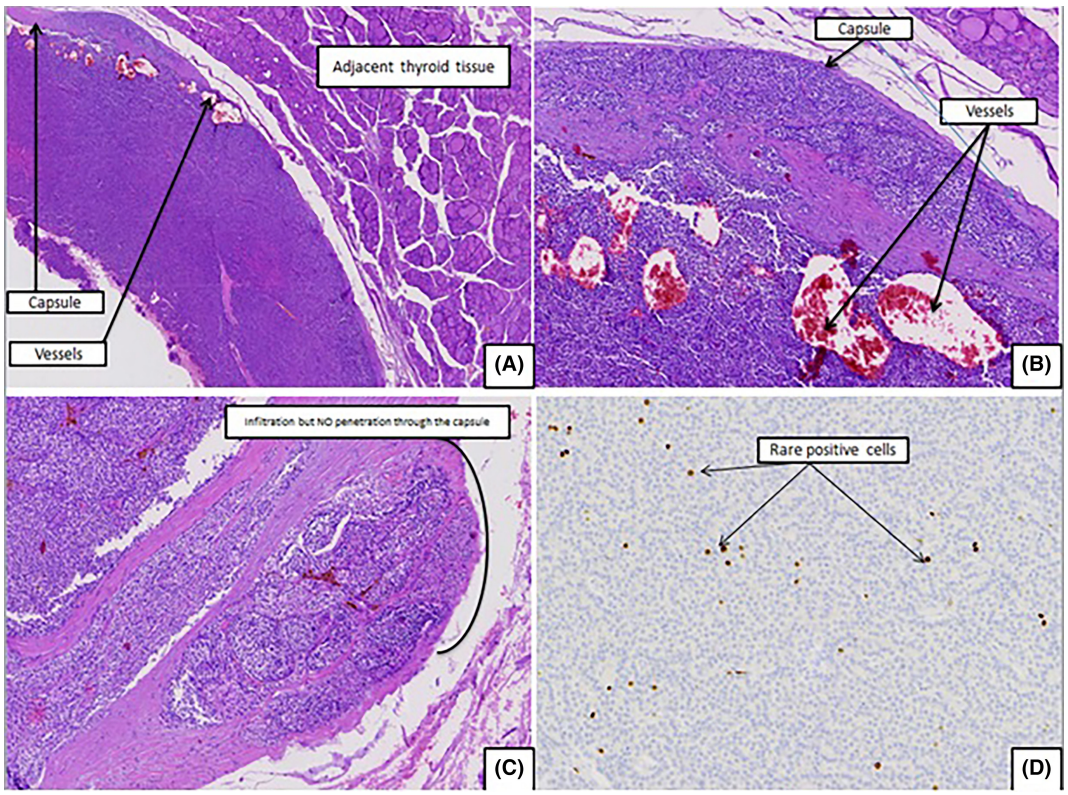

FIGURE 4 (A, B) The neoplasm is surrounded by a thick fibrous capsule and the cells are separated by fibrous band-like tissue. No neoplastic infiltration of the adjacent thyroid gland and of the capsular vessels is found (H&E ×100). (C) The neoplastic cells are occasionally found to infiltrate the capsule but never to penetrate through (H&E ×200). (D) The mitotic index is estimated below the critical point of 5% (Ki67 stain ×200).

WHO-defined atypical features in parathyroid tumors include cellular nests in thickened connective tissue, tumor cells in capsule, adherence to adjacent structures without frank invasion, band-like fibrosis, trabecular growth, increased mitotic activity (>5/10 mm^2), atypical mitotic figures, coagulative necrosis, parafibromin loss, Ki-67 >5% and other immunohistochemical findings.[10] WHO-defined clear-cut criteria of malignancy include angioinvasion, lymphatic invasion, perineural invasion, invasion of adjacent structures, and histologically confirmed mestastasis.[10,11] Regarding the use of immunohistochemistry, data are not as clear for atypical parathyroid tumors, as they are for adenomas and carcinomas. Whereas parathyroid adenomas display positivity for parafibromin and APC, they often are negative for galectin-3 and PGP9.5, with a Ki67 index often below 1%. In contrast, parathyroid carcinomas usually show the opposite immunophenotype and have a Ki67 index >5%.[12,13] As expected, atypical parathyroid tumors display immunophenotypical features variable between the above two categories. Therefore, WHO suggests a judicious use of immunohistochemical markers, considering negativity for parafibromin, APC, RB, e-cadherin, p27, BCL2, MDM2, and 5-HMC, and positivity for PGP9.5, galectin-3, hTERT, p53, and Ki67>5% more consistent with malignancy.[12,13] Considering all the above, in our case no clear-cut sign of malignancy was established, but enough atypical features were found in order to reach the diagnosis of an atypical parathyroid tumor. According to the new criteria of WHO, atypical parathyroid tumors are considered neoplasms of uncertain biological behavior exhibiting atypical histological and immunohistochemical findings, that occasionally relate to malignant biological behavior but without showing clear-cut criteria of malignancy.[11] Patients with atypical parathyroid tumors show no specific clinical profile, while their biochemical profile is more similar to that of patients with carcinoma than classic adenoma.[14] Imaging techniques, such as neck ultrasound and 99mTc-sestamibi scintigraphy, are useful for tumor localization but cannot reliably discriminate benign from malignant hyperparathyroidism.[10,13] In such cases, surgery has both a therapeutic and a diagnostic role. The macroscopic appearance at surgery is of limited help; however, firm and adherence to the adjacent structural lesions should raise the suspicion for malignancy and may dictate a more radical surgical approach. En bloc resection with ipsilateral thyroid lobectomy is

considered the gold standard in patients with suspected parathyroid carcinoma.[15] Taking into account the high suspicion of malignancy and the setting of THPT in our patient total parathyroidectomy with autotransplantation thus en block right lobectomy was performed.

Most atypical parathyroid tumors behave similarly to parathyroid adenomas and do not recur after excision. However, recurrences and metastases have been reported, especially in the context of parafibromin deficiency. In such cases, genetic screening of CDC73 is also recommended.[16,17] Due to the lack of specific guidelines for the surveillance of patients with atypical parathyroid adenomas, some authors suggest a close follow-up based on their own experience.[17,18] while others follow up only patients with atypical tumors of large size and/or complete loss of parafibromin expression.[16,19–21]

As far as our patient is concerned, he is followed up by nephrologists and endocrinologists evaluating both biochemical testing and neck ultrasound.

AUTHOR CONTRIBUTIONS

Styliani Laskou: Conceptualization; writing – original draft. **Ismini Kountouri:** Writing – original draft. **Eleni Paschou:** Writing – review and editing. **Christos Topalidis:** Writing – review and editing. **Georgios Petrakis:** Investigation; writing – review and editing. **Paraskevi Axi:** Writing – review and editing. **Christoforos Kosmidis:** Supervision. **Konstantinos Sapalidis:** Supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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