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Atypical Parathyroid Tumor in an Ectopic Gland-Case Report

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Abstract: ***The atypical parathyroid tumor (formerly known as atypical parathyroid adenoma) is a novel entity introduced in the latest classification of parathyroid tumors (WHO 2022), representing a parathyroid neoplasm with uncertain malignant potential. It exhibits architectural features suspicious of malignancy but lacks unequivocal histomorphological findings of malignancy (invasion of adjacent tissues, angiolymphatic emboli, perineural invasion, and/or metastasis). We present a case of a double adenoma, with an ectopic gland whose histology revealed an atypical parathyroid tumor, and a multicentric thyroid carcinoma.***

Keywords: Atypical parathyroid tumor, Primary hyperparathyroidism, Parathyroid adenoma

1. Introduction

Primary hyperparathyroidism (PHPT) can be caused by adenoma, hyperplasia, or carcinoma of the parathyroid gland. We present a clinical case of a 78-year-old female patient with an atypical parathyroid tumor in an ectopic location**.**

2. Clinical Case

A 78-year-old female presented with several weeks of asthenia and general malaise. She had a history of arterial hypertension, smoking, and osteoporosis. She was admitted with vomiting and altered sensorium. Laboratory tests revealed a serum calcium level of 18.3 mg/dL, parathyroid hormone level of 3.834 ng/mL, vitamin D less than 5 ng/mL, and serum phosphate of 1.3 mg/dL. This was interpreted as primary hyperparathyroidism, and medical treatment was initiated. A cervical ultrasound did not reveal parathyroid tissue. A cervical MRI showed a retrothyroid formation. She underwent surgical intervention under general anesthesia, during which the right hemithyroid and an enlarged right inferior parathyroid were resected. The pathological report indicated "nodular Hashimoto's thyroiditis with 2 foci of papillary microcarcinomas and a right inferior parathyroid adenoma."**(Figures 1).**

Her calcium and parathyroid hormone levels did not decrease postoperatively, and a Choline PET scan **(Figures 2)**identified a nodular formation in the posterior mediastinum. She underwent a new cervicotomy under general anesthesia, where was found an 8 x 3 cm mass extending retroesophageal, prevertebral from the second tracheal ring to the retrosternal region. Total thyroidectomy was also performed. The pathological report showed several reactive lymph nodes, no metastases, lymphocytic thyroiditis in the left lobe, and an atypical parathyroid tumor with ectopic localization, without perineural invasion, angiolymphatic emboli, capsular invasion, or invasion of adjacent structures, with a focus of necrosis, 1 mitosis per 10 mm^2, and Ki-67 of 5%.**(Figures 3 A and B)**

Her sensorium and general malaise improved immediately after surgery, but notably, the decrease in parathyroid hormone levels took a week to occur. From that point, she required supplementation with high doses of calcium and vitamin D. She was discharged without complications, and in the 6-month follow-up, she had a parathyroid hormone level of 6, normal serum calcium with oral supplementation, and no signs of metastasis.

3. Discussion

The HPTP (Hyperparathyroidism) is generally due to a single parathyroid adenoma, which infrequently may be double.[1-4] It can also result from parathyroid carcinoma (0.5 to 15% of cases)[4] or be associated with multiple endocrine neoplasia (MEN) pathologies. An anarchic increase in parathormone production occurs, leading to hypercalcemia. Hyperparathyroidism is sporadic in 90% of cases due to a single adenoma, in 2-15% of cases due to double adenomas, and is associated with MEN 1 and 2A in 10% of cases. [1,4]Normally, there are four parathyroid glands, although the number can be higher in 14% or lower in 0.5-6% of individuals.[1,5-7]

Clinically, it is almost impossible to differentiate between a single adenoma and a double adenoma. Some authors suggest that double adenomas are more common in women in the fifth/sixth decade of life and may be associated with more pronounced bone and muscle symptoms, and higher parathormone levels than those found in single adenomas.[1-8]

Due to their embryology, parathyroids can have unusual locations. Upper glands are more frequently located in the upper half of the middle third of the thyroid gland (83% of cases) and the upper third (9% of cases).[1] Ectopic upper

parathyroids are located below the carotid bifurcation, inferiorly and posteriorly, the posterosuperior mediastinum, in the retropharyngeal and tracheoesophageal spaces.[1,9-10]

In 77% of individuals, lower parathyroids are found in the postero-lateral region of the thyroid, at the origin of the inferior thyroid artery. The rest are located in the thymus or, due to their long embryological journey, from the mandibular angle to the pericardium.[8-10]

Histologically, adenomas are typically encapsulated with proliferation of chief parathyroid cells, diffuse or nodular distribution, isolated oxyphilic cells, and few adipocytes.[1,11-12]

Atypical parathyroid tumors share clinical and histological characteristics with parathyroid carcinoma, but they differ in their course, showing a greater tendency to hypercalcemic crises, according to some authors.[4]

This new entity is a neoplasm composed of parathyroid chief cells with associated fibrous tracts containing hemosiderin, without clear evidence of infiltrative growth or necrosis. They should be considered tumors of uncertain malignant potential and require long-term close monitoring.[13-14]

There is currently conflicting evidence about whether parathyroid adenoma and parathyroid hyperplasia are separate entities, with both possibly representing asymmetric hyperplasia of more than one parathyroid.[15]

Two molecular effects are described in HPTP adenomas:[1.11.14-15]

1) Inversion of the cyclin D1 gene that induces overexpression of cyclin D1, driving cell proliferation.
2) NEM-1 mutations, found more commonly in sporadic adenomas and familial cases.

According to the most recent diagnostic criteria,[14,16-18]parafibromin is a nuclear protein encoded by the CDC73 gene with a tumor-suppressor role in the development of hereditary and sporadic parathyroid carcinomas. It is considered a regulator of genes involved in cell growth and survival. Parafibromin immunohistochemistry is recommended in atypical parathyroid tumors and carcinomas to detect a possible CDC73 gene mutation (germline or somatic).[17]Parafibromin deficiency could be a predictor of progression, recurrences, and metastasis risk, although long-term follow-up is required to assess recurrent disease.[17-19]

Atypical parathyroid tumor is defined as a parathyroid neoplasm with uncertain malignant potential, representing 1.2 to 1.3% of HPTPs, and the epidemiology is currently unknown.[20] It exhibits histological and cytological features suspicious of carcinoma, but the diagnostic criteria are not identifiable despite sufficient tumor samples being studied.

The atypical parathyroid tumor, as defined by WHO 2022[14] should exhibit:

- Cellular nests in a dense fibrous stroma, atypical cells with enlarged nucleoli
- Neoplastic cells invading the capsule
- Adhesions without clear invasion of adjacent tissues
- Band-like fibrosis
- Trabecular growth pattern
- Atypical mitotic figures (5 per 10 mm^2)
- Coagulation necrosis
- Negative parafibromin
- Ki67 > 5%
- Clinical and laboratory data suspicious of malignancy are not definitive criteria for parathyroid carcinoma diagnosis
- Differential diagnosis with carcinoma must be based on unequivocal histopathological criteria of malignancy
- Complete post-surgical processing of the pathological parathyroid gland is necessary.

No relationship has been found between unilateral or multicentric papillary thyroid carcinoma, (as in our case), and atypical parathyroid tumor.[21]

4. Conclusion

Primary hyperparathyroidism is primarily caused by a single adenoma, less frequently by a double adenoma, and it is a rarity for a double adenoma with an ectopic gland to have atypical tumor histology. The definitive diagnosis of carcinoma often only occurs when metastasis and/or recurrence take place. Long-term studies are needed to assess the malignant biological potential and determine the risk of metastatic disease among patients with atypical parathyroid tumors (Parafibromin+ or -).

5. Future Scope

Long-term studies are needed to assess the malignant biological potential and determine the risk of metastatic disease among patients with atypical parathyroid tumors.

Figures

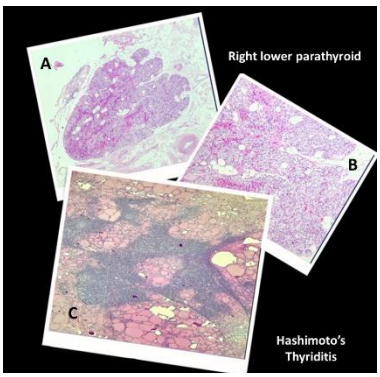

Figure 1: Histological sections of material obtained during the first surgical intervention. A and B: lower right parathyroid gland. C: Hashimoto's thyroiditis

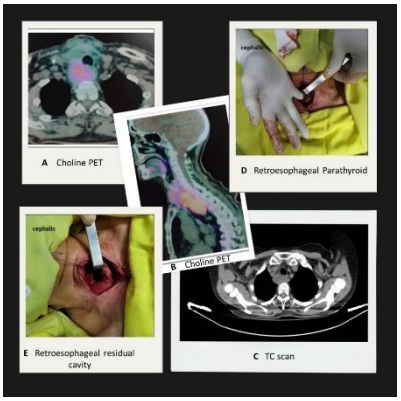

Figure 2: A and B: Choline PET images. C: Retroesophageal image visualized in tomography. D and E: Retroesophageal parathyroid and residual cavity

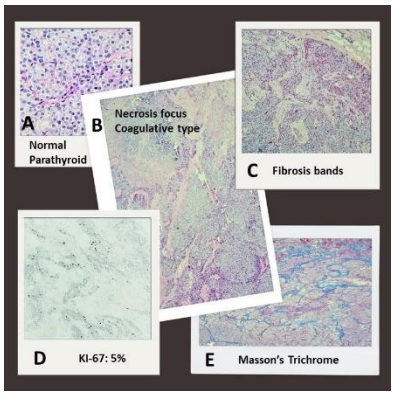

Figure 3: Histological sections of material obtained during the first surgical intervention. A: Normal parathyroid gland. B: Focus of coagulative necrosis. C: Band of fibrosis with hematoxylin and eosin staining. D: Ki-67%. E: Masson's trichrome staining to observe fibrotic bands

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