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Mixed Thyroid Carcinoma: A Clinical and Therapeutic Challenge

Zara Martínez[1], Andrea Cristiani[2], Carolina Guarneri[3], Andrés Korbut[4], Andrés Alallon[5] and Gabriela Mintegui[6]*

[1]Assistant, Academic Unit of Endocrinology and Metabolism. Hospital of Clinics, Medicine of School, UdelaR. Montevideo, Uruguay

[2]Associate Professor, Academic Unit of Pathology. Hospital of Clinics, Medicine of School, UdelaR. Montevideo, Uruguay

[3]Adjunct Professor, Academic Unit of Surgery A. Hospital of Clinics, Medicine of School, UdelaR. Montevideo, Uruguay

[4]Assistant, Academic Unit of Pathology. Hospital of Clinics, Medicine of School, UdelaR. Montevideo, Uruguay

[5]Adjunct Professor, Academic Unit of Laboratory. Hospital of Clinics, Medicine of School, UdelaR. Montevideo, Uruguay

[6]Associate Professor, Academic Unit of Endocrinology and Metabolism. Hospital of Clinics, Medicine of School, UdelaR. Montevideo, Uruguay

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***Corresponding author:** Gabriela Mintegui, Associated Professor, Academic Unit of Endocrinology and Metabolism. Hospital of Clinics, Medicine of School, UdelaR. Montevideo, Uruguay

Introduction

Thyroid cancer is the most common endocrine malignant neoplasm, with an increasing incidence in recent decades, partly attributed to greater access to sensitive diagnostic methods such as high-resolution ultrasound and fine-needle aspiration biopsy (FNAB)[1]. The vast majority of cases correspond to well-differentiated carcinomas, with papillary thyroid carcinoma (PTC) being the most common.

The synchronous coexistence of two distinct histological types in the same thyroid gland, particularly the combination of papillary and medullary carcinoma, is an exceptional finding. These mixed or combined tumors represent less than 0.15% of all thyroid carcinomas and their pathogenesis remains a topic of debate[2].

From a clinical and therapeutic standpoint, these tumors present a significant challenge due to differences in biological behavior, tumor markers, prognosis and therapeutic strategies between the two subtypes[3,4]. The medullary component, being more aggressive, often determines the predominant therapeutic approach.

In this publication, two clinical cases of patients with combined papillary and medullary thyroid carcinoma are presented, with distinct clinical, molecular and evolutionary characteristics and a review of the literature is conducted with the aim of contributing to the understanding of this rare entity and highlighting the importance of an integrated and multidisciplinary diagnostic and therapeutic approach.

Case 1

A 32-year-old male presents with a rapidly growing cervical mass with locoregional symptoms. Physical examination reveals marfanoid habitus, mucosal neuromas and grade II goiter. The FNAB reports Bethesda VI. A total thyroidectomy (TT) is performed and pathology reveals combined papillary and medullary thyroid carcinoma. Postoperative calcitonin (CT) level is 2600 pg/ml. Due to the papillary component, an ablative dose of 80 mCi of I-131 is administered. During follow-up, lymph node metastases are detected with elevated thyroglobulin (Tg) and calcitonin levels; two lateral and central lymphadenectomies are performed, confirming lymph node

metastases, including paratracheal (12 positive out of 24) mixed carcinoma metastases **(Figure 1)**. Mutated RET gene, diagnosed with MEN2B. Negative metanephrines.

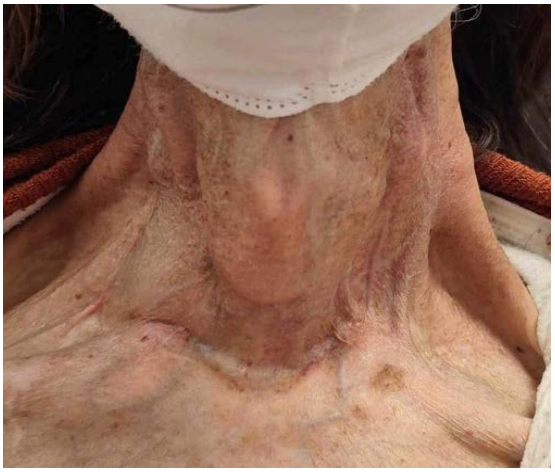

Figure 1: Neck with several scars from lymph node dissections.

Case 2

A 46-year-old female presents with a mass in the anterior neck region and dysphagia of one year's duration. She has grade II goiter. Ultrasound reveals a solid, homogeneous and well-defined nodule in the left lobe measuring 38×27×22 mm, with central vascularization and another similar nodule **(Figure 2)** in the right lobe measuring 10×11×7 mm. In the VI lymph node group, a hyperechoic, rounded lymphadenopathy without fatty hilum is identified. The FNAB of the larger nodule reports Bethesda VI and Tg from needle wash of the lymph node is 1050 ng/ml. With a diagnosis of PTC, TT with central lymphadenectomy is performed. Pathology reports combined, multifocal carcinoma, composed of a medullary thyroid carcinoma (MTC) measuring 35x25x24 mm and three foci of PTC, the largest being 7x5 mm with solitary central lymph vascular invasion. Postoperatively, calcitonin (5.2 pg/mL) and carcinoembryonic antigen (CEA: 18.37 ng/mL) levels were low, indicating excellent biochemical response. The patient starts treatment with levothyroxine for TSH suppression due to the papillary component, without requiring radioiodine, given the estimated low risk of recurrence **(Figure 3)**.

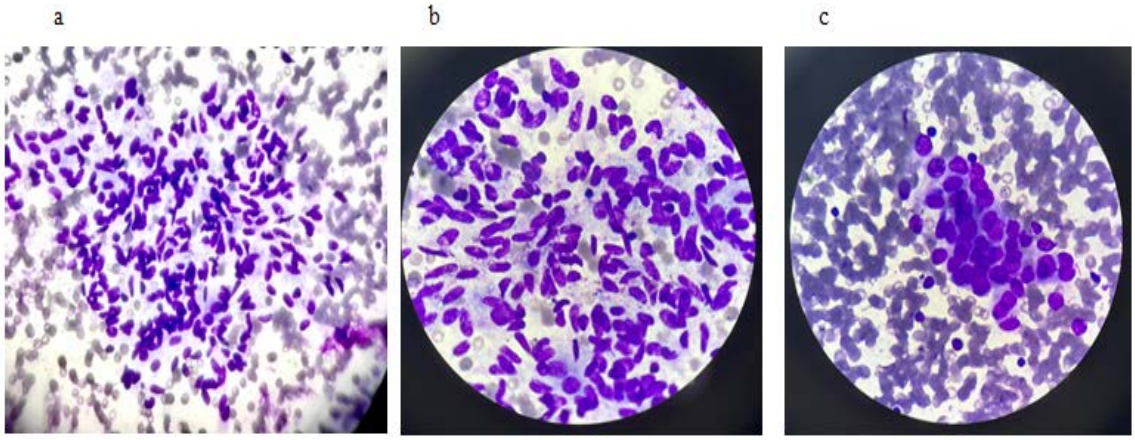

Figure 2: Cytology of thyroid nodule (a and b), adenopathy (c). High cellularity is observed with thyroid cells arranged in patches. Some have a spindle-shaped appearance.

Discussion

Thyroid cancer is the most common endocrinological tumor, with an approximate annual increase of 6.2%[1]. Its usual presentation is of a single cell lineage **(Figure 4)**, while the presence of two different subtypes of thyroid carcinomas is rare, representing only 0.15% of thyroid tumors[2]. The most common combination is the presence of MTC with PTC, followed by MTC with follicular carcinoma[3].

Jin Yao et al. report that in the last 30 years, only 18 cases have been documented in the literature and only 2 in Latin America[4,5]. The age of presentation varies between 27 and 70 years; both presented patients fall within this age range. In most cases, diagnosis is made after the appearance of a cervical mass, as in the described cases[4].

The pathogenesis is not entirely clear, as these tumors result from the conjunction of two neoplasia's of different embryonic and histological origins. PTC originates from the follicular cells of the thyroid, of endodermal origin, whereas MTC derives from parafollicular C cells, of neuroectodermal origin. Various theories have been proposed involving genetic mutations, local and environmental factors[3]. The tumor collision theory suggests the independent and contiguous development of two primary neoplasia's, while the divergent differentiation theory from a common progenitor cell proposes that a progenitor cell capable of dual differentiation gives rise to both cell lines and the metaplastic transformation proposes a trans differentiation of one subtype to another, although this is less accepted.

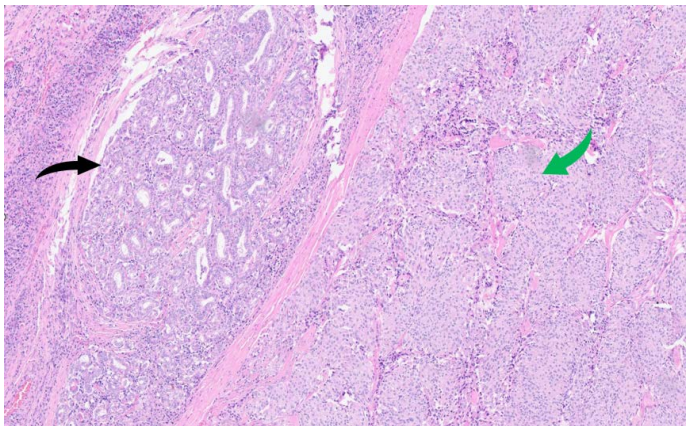

Figure 3: HE 100x microphotography shows 2 areas with very different architecture. Green arrow shows a solid, nested, proliferation and black arrow shows an area of carcinoma with follicular pattern.

Shared genetic and molecular factors: Common mutations have been found in mixed cases, such as RET, RAS or TERT, suggesting a clonal origin in some patients[3,6]. In the first case, the finding of a RET mutation and the marfanoid phenotype are consistent with a type 2B multiple endocrine neoplasia syndrome (MEN2B), which adds a relevant genetic component for diagnosis and family follow-up **(Figure 5)**.

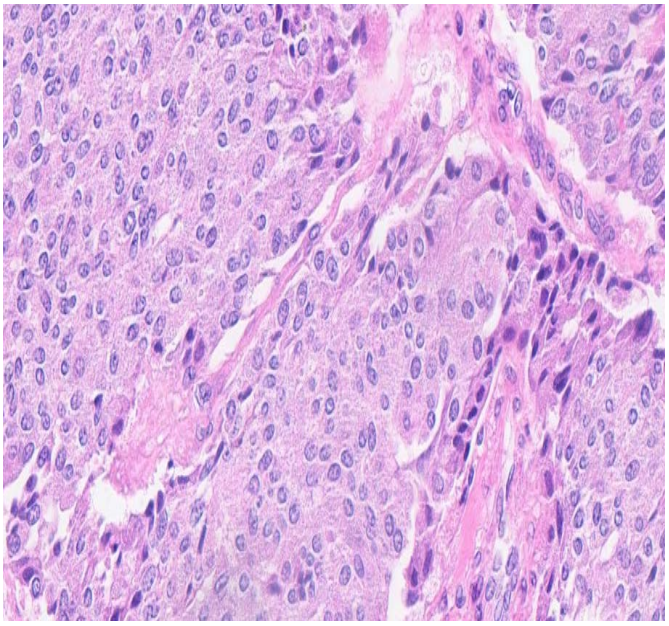

Figure 4: The solid area shows fusiform and epithelioid cells with salt and pepper chromatin nuclei and granular, eosinophilic cytoplasm. There is amyloid substance in the stroma.

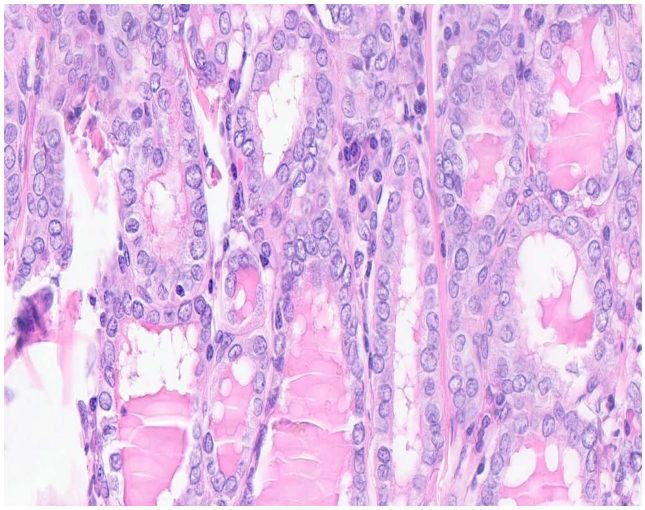

Figure 5: The follicular area shows epithelial cells with clear nuclei, grooves and pseudoinclusions. Other foci Showed papillary pattern.

Preoperative diagnosis is crucial as it influences surgical methods and prognosis It requires a thorough clinical evaluation, including history, physical examination, blood tests (TSH, calcitonin) and imaging studies (ultrasound)[4,7]. Cytological diagnosis via FNAB is complex, as medullary carcinoma can mimic other neoplasia's and histology is variable[2]. Immunohistochemical staining for calcitonin is essential to confirm or rule out medullary carcinoma[4]. In the two presented cases, a definitive diagnosis was established in the postoperative histopathological analysis, reinforcing the difficulty in identifying this entity at the preoperative stage. In our setting, routine measurement of baseline calcitonin is not requested for all nodules, aligned with what most guidelines suggest.

Lymphatic metastases are often present at the time of diagnosis, as in the second case presented. These lymph nodes may present pure cell populations or mixed components within the same node[2]. This coincides with observations in the described cases, where the first patient presented mixed metastases and the second patient had pure papillary metastases **(Figure 6)**.

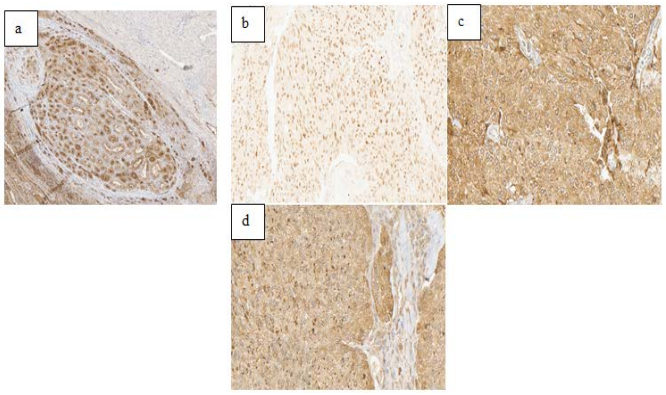

Figure 6 (a): Immunohistochemistry for thyroglobulin was positive in the papillary carcinoma and negative in the medullary carcinoma (solid). INSM1 (b), synaptophysin (c) and calcitonin (d) were positive in the medullary carcinoma.

Chromogranin and TTF1 were also positive in the medullary component. TTF1 was positive in the papillary component.

Understanding the synchronous coexistence of these tumors is important for appropriate therapeutic management, although preoperative diagnosis is difficult due to low incidence and diagnostic complexity, as occurred in both cases, where the definitive diagnosis was made post-thyroidectomy[2,7].

Treatment is primarily guided by the medullary component, as it is the most aggressive and determinant of prognosis. Total thyroidectomy and central lymphadenectomy constitute the standard[4,7]. Preoperative identification of lymph node metastases is key to planning surgery. Total thyroidectomy with central lymphadenectomy is the surgical approach of choice for MTC and should also be considered when mixed variants or multifocality are suspected.

From a pathological standpoint, the medullary component presents tumor cells with disordered arrangement, granular cytoplasm and organization in sheets, nests or rows and may present a papillary pattern. The papillary component does not differ from classical papillary carcinoma[2].

Although radioactive iodine ablation and TSH suppression are not effective for medullary carcinoma due to the absence of iodine uptake in parafollicular cells, they are useful for the coexisting papillary carcinoma[8]. The indication for radioiodine treatment is based on the assessment of recurrence risk, as observed in the first case (moderate risk) that received radioiodine and in the second case (low risk) that did not require it[4,8].

It is difficult to comment on the prognosis of these combined thyroid carcinomas, as few cases have been reported[4]. Patients with papillary carcinoma have the highest 10-year relative survival, while MTC is considered to have a worse prognosis, difficult to cure and with a higher likelihood of recurrence[4]. However, according to the WHO[4], the prognosis of mixed medullary and follicular thyroid carcinoma depends on the medullary component. Therefore, the presence of the medullary component worsens the prognosis compared to pure papillary carcinoma.

The prognosis is determined by the presence or absence of metastases and age (older age, worse prognosis). In this case, there is a young middle-aged patient who has lymph node metastases of large proportions and in large numbers, which persist to date[10].

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