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Trabecular hyalinizing adenoma of the thyroid (HAT): A report of two cases

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Abstract

The hyalinizing trabecular adenoma is a rare lesion of the thyroid. There is controversy in the literature about the correct name for this disease. Dr. Carney defended the benign nature of this condition and therefore continues calling it adenoma, the World Health Organization calls for the potential of tumor malignancy, and others qualify it as a variant of papillary carcinoma based on the presence of rearranged in transformation/papillary thyroid carcinoma (RET/PTC) rearrangements. In Latin America there are few reported cases. Two cases of hyalinizing trabecular adenoma are reported. The first is a 40-year-old woman with a thyroid nodule of 3 x 3 cm. The immunohistochemistry was positive for thyroglobulin and calcitonin and negative for cytokeratin 19 and chromogranin. The second case is a 36-year-old patient with a thyroid nodule of 4 x 4 cm with an immunohistochemical pattern identical to the first case. Trabecular hyalinizing adenoma is a benign disease, easily confused with papillary or medullary thyroid carcinoma. Awareness of this entity will allow a better classification and management of thyroid conditions. (Gac Med Mex. 2016;152:98-101)

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Introduction

In 1987, Carney et al. described 11 hyalinizing trabecular tumors resembling thyroid papillary or medullary carcinoma and characterized them as adenomas based on their benign behavior[1]. However, it has been proposed that Carney's adenoma should bear the name of tumor or neoplasm due to the risk for metastasis and invasive behavior in some cases; it has even been considered to be a variant of thyroid papillary carcinoma based on the presence of rearranged during transfection/papillary thyroid carcinoma (RET/PTC) rearrangements[2]. Nevertheless, the largest series to date, with 119 trabecular adenomas with a prolonged follow-up for 20 years, demonstrated that only one patient had metastatic involvement, a case that appeared to be associated with a thyroid follicular carcinoma with a trabecular component and not with trabecular adenoma[3]. However, Carney has insisted that the adequate name for this rare condition is trabecular hyalinizing adenoma (THA). Although finding this lesion in regular clinical practice is unusual, its benign behavior suggests conservative management, and, therefore, it is essential for the clinician to be aware of the disease and for the pathologist to know its features in order for

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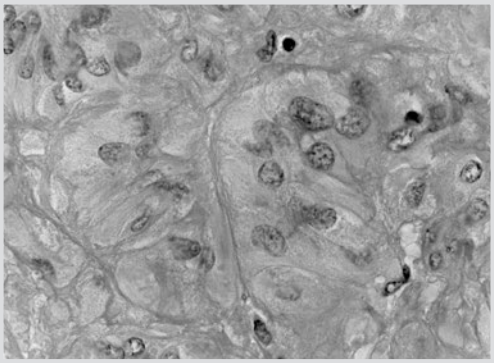

Figure 1. *Case 1: micrograph of the THA with hematoxylin and eosin staining (40 x).*

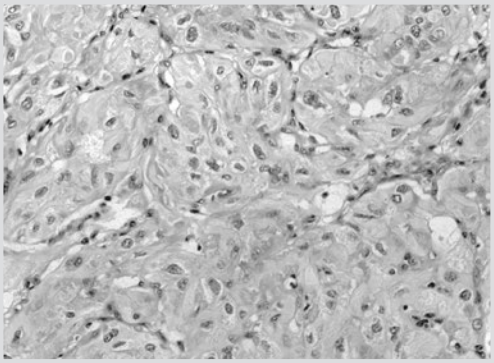

Figure 2. *Case 2: micrograph of the THA with hematoxylin and eosin coloration (10 x).*

not mistaking it with thyroid papillary or medullary carcinoma. Two cases are presented according to the CARE guidelines[4] for case reports with a review of the subject, in an attempt to cove the absence of reports on this topic in Latin America.

Case reports

Case 1

This is the case of a 40-year-old female patient with a long-standing history of a thyroid nodule. Ultrasound showed hypoechoic areas with a 3 x 3 cm nodule. Fine needle aspiration biopsy was reported as papillary carcinoma. Right hemithyroidectomy was practiced, with a 3 x 3 cm cream-colored and firm consistency nodule being identified. Microscopically, it was comprised by trabeculae, elongated cells with nuclear inclusions, hyalinized areas and trabecular pattern with a thin fibrous capsule in the periphery. Immunochemistry was positive to thyroglobulin and negative to calcitonin, chromogranin and CK-19. Final diagnosis after assessment was THA (Fig. 1).

Case 2

This was the case of a 36-year-old female patient, with biopsy referred for review and immunochemistry with Carney's THA versus medullary carcinoma diagnosis. Thyroid gland was found having a 4 x 4 cm nodule with trabeculae, elongated cells with yellow bodies, hyalinized areas and trabecular pattern; immunochemistry was positive to thyroglobulin and negative to calcitonin and CK-19, Final diagnosis was THA (Fig. 2).

Discussion

Thyroid THA is an infrequent lesion: it is estimated to account for 0.44-1.3% of all thyroid neoplasms[5-7]. In 2008, Carney[1] updated his initial report of 11 THAs with 119 cases[3], and that same year he presented a review[8] explaining three previous reports (1907, 1922 and 1982) by other authors on cases unknown to him at the moment of his initial publication. THA biological behavior is controversial, since some authors support the idea that it is a papillary carcinoma variant and others suggest it is a benign tumor due to the non-invasive behavior it shows in most cases, just as reported by Carney in his series of more than 199 patients with no evidence of metastasis[3]. Defining whether it is cancer or not is essential, due to the different therapeutic approach that has to be used: an adenoma can be conservatively treated and carcinoma requires surgical and radioactive iodine management according to the patient's risk stratification[9].

Most THAs occur in middle-aged females, with a female:male ratio of 6:1[1,5]. Clinically, it is discovered as a solitary asymptomatic nodule or as part of a multinodular goiter[7]. Ultrasound findings described of this tumor are similar to those in follicular neoplasms, usually being solid, oval- or round-shaped, well defined, hypoechoic nodules, with presence of halo and with no microcalcifications[10]. Usually, these findings are not highly suggestive of malignancy[11], and average size is 2.5 cm[5]. THA etiology is unknown and has not been associated with prior history of exposure to head and neck radiation[12]. It has been described associated with Hashimoto thyroiditis, but with no certainty of causal or sporadic relationship[3,12].

Table 1. Differences between papillary and medullary carcinoma and THA

	Papillary carcinoma	Medullary carcinoma	THA
Main pathological findings	Nuclear pseudo-inclusions, papillary structures, Psammoma bodies, coffee-bean nuclear grooves, ground glass nuclei	Granular cytoplasm with round or oval-shaped nuclei, with dotted chromatin. Prominent stromal amyloid deposits	Trabeculae, elongated cells with nuclear inclusions, hyalinized areas and trabecular pattern surrounded by thin fibrous capsule; galectin 3 (–); CK-19 (–)
Genetic changes	$BRAF^{V600E}$, RAS, RET/PTC	RET	RET/PTC
Clinical features	More common in women. Thyroid nodule. 25-year survival: 95%	Thyroid nodule. 25-year survival: 79%. Sporadic: 80%. Hereditary: 20% (MEN2)	More common in women. Thyroid nodule with benign behavior. No data on long-term survival.
Treatment	– Total thyroidectomy in lesions larger than 1 cm – Radioactive iodine in high or intermediate risk patients, according to clinical characteristics	Thyroidectomy plus central compartment node dissection	Observation or lobectomy
Paraclinical follow-up	Thyroglobulin and thyroid ultrasound	Calcitonin, carcinoembryonic antigen. Imaging according to local or distant involvement.	Ultrasound

MEN2: multiple endocrine neoplasm.

On microscopy, a neoplasm with trabeculae and hyalinized material accumulation is observed[13]. The nucleus is rounded with some pseudo-inclusions and Psammoma bodies can be appreciated. Immunohistochemically, tumors are positive to thyroglobulin, transcription termination factor 1 (TTF-1) and cytokeratins, except for CK-19, which is negative or minimal in comparison with thyroid papillary carcinoma, which is strongly positive for this marker[1,14]; however, other authors have found positivity for CK-19[15]. Some authors propose that, if there is positivity for CK-19, the neoplasm is not THA, but some papillary carcinoma variant[6,16]. It should be remembered that in Carney et al. initial description, these neoplasms were negative for CK-19[1]; therefore, THA has to be, *stricto sensu,* negative for CK-19. These tumors do not express calcitonin[17], and staining with Congo red is negative. Galectin 3 expression is negative or feebly positive in most THAs (60%); in those cases where it is positive, it is diffuse and predominantly cytoplasmic[18]. Biological behavior of galectin 3-positive THAs does not appear to be aggresive[18]. Additionally, THA exhibits cytoplasmic and cell-membrane reactivity to the methylation-inhibited binding protein 1 (MIB-1)[19] antibody that targets Ki-67[20,21], a finding that will allow differentiating it from thyroid papillary carcinoma[22].

Given the histological similarities with thyroid papillary carcinoma, several molecular genetics studies have been carried out in order to clarify THA molecular biology[2,13, 17, 23-29]. In patients with thyroid papillary carcinoma, variable prevalence (up to 50%) of Rearrangement During Transfection (RET) protooncogene somatic rearrangements has been found[2] and, hence, this finding in a THA would be consistent with a variant of papillary carcinoma. One of the initial studies assessed the presence of RET/PTC rearrangements[28] in 14 THAs by RT-PCR or immunochemistry. 28.6% of THAs expressed RET/PTC rearrangements, although in one of the cases it was only by immunochemistry and not by RT-PCR; in two positive cases by immunochemistry, positivity was focal, and in one further case with a THA/papillary carcinoma mixed tumor, positivity for RET/PTC was found by real-time polymerase chain reaction (RT-PCR) and immunochemistry only in the papillary component[28]. In another study, the presence of RET/PTC rearrangements was of 47%[24]. However, the presence of RET/PTC rearrangements is not specific of thyroid papillary carcinoma, since it has been described in benign conditions such as Hashimoto's thyroiditis[30] and, therefore, presence of these arrangements cannot be claimed with certainty as being a proof of thyroid papillary carcinoma.

On the other hand, the search for BRAF (V600E) mutations, present in 29-83% of patients with papillary carcinoma and central to the pathogenesis of this

neoplasm, has been negative[17,23,25,31,32]. RAS mutations have neither been found[24,29,31]. Additionally, in a multi-center study for thyroid nodule presurgical molecular diagnosis validation with a 167-gene expression test (Afirma®), two THA cases were found[33], with their molecular profile indicating a benign nature.

In Latin America, there are only few case reports or studies on this entity. In a search carried out in Scielo, Medline and Google Scholar, a report from Argentina[34] and another from Colombia[35] were found. There is another Argentinean report published at the Sociedad Argentina de Citología website[36]. It is possible that THA is poorly recognized in our part of the world, or maybe its frequency is lower than reported. Multi-center studies need to be conducted in order to know the epidemiological features of this neoplasm in our region and differences with the rest of the world.

Given that most reports indicate minimal malignant potential, management should be conservative, with hemithyroidectomy, with no need to use radioactive iodine or thyrotropin suppression, or with clinical and ultrasound surveillance if the tumor has been diagnosed by fine needle aspiration. Continued medical education is required in the field of thyroidology for better recognition of this tumor, of its benign nature and on how easily it can be mistaken with thyroid papillary or medullary carcinoma (Table 1) if there is no awareness of its existence and, consequently, to manage it according to its benign nature.

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