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Hyalinizing Trabecular Tumor of the Thyroid: An Update

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Abstract Hyalinizing trabecular tumor (HTT) is a rare thyroid tumor of follicular cell origin with a trabecular pattern of growth and marked intratrabecular hyalinization. This tumor is known to share morphological and architectural similarities with paraganglioma and medullary thyroid carcinoma, as well as the nuclear features and RET/PTC1 translocations of papillary thyroid carcinoma. These tumors are not associated with *RAS* or *BRAF* mutations. Whether the presence of RET alterations in HTT are sufficient molecular proof of its relationship with papillary thyroid carcinoma (PTC) is still to be defined. Of great interest is the characteristic strong peripheral cytoplasmic and membranous staining of the tumor cells with MIB1 immunostain, not seen in any other thyroid neoplasm. Although cases of malignant HTT have been recorded, HTT should be considered a benign neoplasm or, at most, a neoplasm of *extremely low malignant potential*.

Keywords hyalinizing trabecular tumor · hyalinizing trabecular adenoma · thyroid · papillary carcinoma · BRAF · RET/PTC

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Introduction

Hyalinizing trabecular tumor (HTT) of the thyroid is a unique neoplasm of follicular derivation, exhibiting prominent trabecular architecture and variably abundant hyalinization.

The so-called hyalinizing trabecular adenoma (HTA) was first described by Aidan Carney at Mayo Clinic [1], who recognized a trabecular tumor of follicular derivation with peculiar nuclear, architectural, and histochemical features, and he termed this lesion a hyalinizing trabecular adenoma based on the benign behavior of the 13 cases he originally collected. After the original proposal by some authors [2], the term adenoma was replaced by "tumor" (hyalinizing trabecular tumor) in the recent WHO Classification of Tumors of Endocrine Organs [3], which defined this lesion as "a rare tumor of follicular cell origin with a trabecular pattern of growth and marked intratrabecular hyalinization".

HTT usually occurs between the fourth and the seventh decades of life, with a reported marked female predilection. The etiology of HTT is unknown. The tumor may arise in a background of chronic lymphocytic thyroiditis, multinodular goiter, or after radiation exposure, and it may also occur in association with papillary thyroid carcinoma.

This tumor is known to share some morphological and architectural similarities with paraganglioma and medullary thyroid carcinoma (MTC) as well as some nuclear features of papillary thyroid carcinoma (PTC). HTT cells have a characteristic MIB-1 (Ki-67) reactivity at the cell membrane and cytoplasm [4]. Cytokeratin 19 and high molecular weight cytokeratin immunostains are usually negative in HTT, whereas they show a variable pattern of Galectin-3 expression. RET/PTC rearrangements (namely RET/PTC1 type) have been reported in a subset of HTT; however, neither BRAF nor RAS mutations have been identified in any case of the HTT so far investigated.

HTT of the thyroid are unique and generally follow a benign clinical course. As rare cases of malignant HTT have been recorded, it should be considered, at most, a neoplasm of *extremely low malignant potential*.

General Features

Morphological Findings

HTT is a well-circumscribed and encapsulated lesion (Fig. 1), with no evidence of capsular or vascular invasion. A uniform and diffuse solid and trabecular architecture (Figs. 2, 3a, b, 4a, b, and 5) is the hallmark of HTT, with a markedly hyalinized intratrabecular stroma containing basement membrane-type material (Fig. 2), discernible by electron microscopy from other types of basement membrane-producing tumors. Hyalinized trabecular areas, however, may be present within conventional follicular adenomas and carcinomas, and the recognition of the typical intratrabecular (as opposed to intertrabecular) hyalinization is the key point. Typically, tumor cells are elongated and contain nuclei with features comparable to that observed in PTC, including irregular shape and profile, elongation, grooves, and pseudoinclusions (Figs. 2, 3a, b, 4a, b, 5, 6). In addition, rare calcifications/psammoma bodies may be present [3, 5–13].

Because of such peculiar morphological features, the differential diagnosis of HTT includes several other thyroid tumors, including medullary carcinoma (MTC), primary thyroid paraganglioma, papillary thyroid carcinoma (PTC) with trabecular architecture and, most importantly, follicular adenomas with HTT-like patterns (Tables 1 and 2). In the latter, hyaline material accumulation generally results from degenerative changes within the lesion and appears as bands or areas of hyalinization between the trabeculae—intertrabecular, rather than within them—intratrabecular [3, 5–13] (Table 1, Fig. 7a, b).

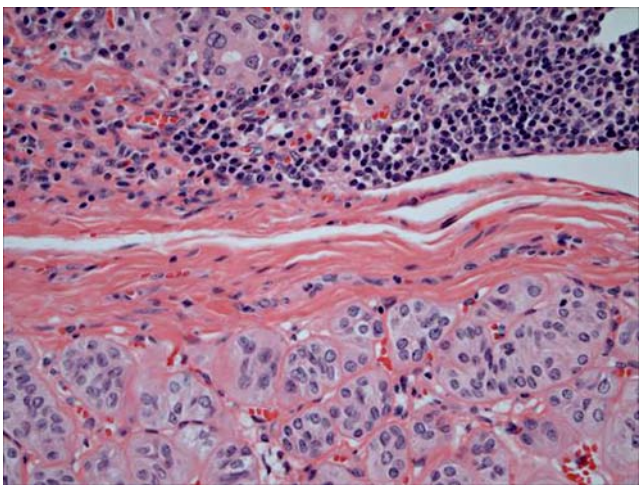


Fig. 1 Hyalinizing trabecular tumor. Hematoxylin and eosin stain; low power. A fibrous capsule separates the nonneoplastic thyroid with thyroiditis (above) from the well encapsulated trabecular-patterned neoplasm (below)

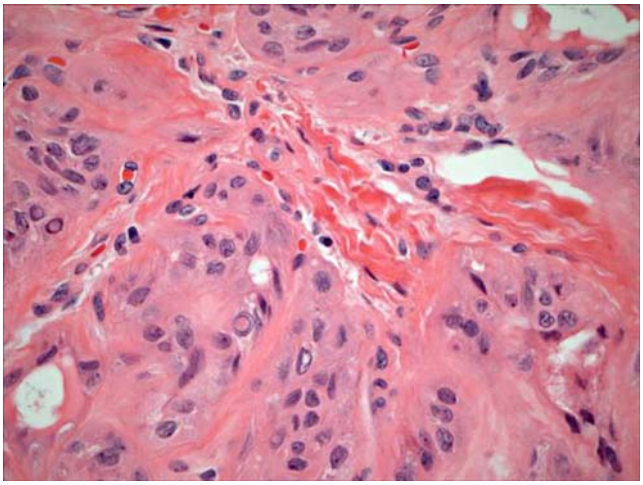


Fig. 2 Hyalinizing trabecular tumor. A prominent trabecular-patterned neoplasm with prominent intranuclear inclusions and nuclear grooves with a hyalinized stroma

Another peculiar and unique feature of HTT is the presence of cytoplasmic inclusions, seen as paranuclear cytoplasmic granules with a light yellow color (so-called "yellow bodies") [14]. These bodies are refractile and frequently have a microvacuolated or granular substructure. They appear as cytoplasmic corpuscles of a few microns having a clear halo. Their color varies from yellow to gray to pink. In some cases, they are very few and hard to see. They are claimed to be detectable even in cytological preparations [14]. Ultrastructurally, the inclusions are consistent with giant lysosomes, so-called "fingerprint" bodies. Descriptions exist of rare PTC with the presence of occasional yellow bodies [15].

The cytological features of HTT in fine needle aspiration biopsy material were also described by Carney, in collaboration with Goellner at Mayo Clinic [16]. In their study and in subsequent publications [9, 17–21], the relevant cytological features included moderately cellular smears in a hemorrhagic background, containing large irregular tissue fragments and single cells. The fragments may have a branching profile and abundant stromal tissue, generally amorphous and hyalinized (pink-appearing in both hematoxylin and eosin [H&E] and Giemsa stains). The cells are medium-sized and polygonal to spindle-shaped. They are arranged in loosely packed aggregates or in cords tightly associated with the amorphous tissue or even isolated in the background. The cytoplasm may be difficult to visualize. Nuclei are hyperchromatic and round, with irregular borders and nuclear holes (pseudoinclusions) and grooves, as classically seen in papillary carcinoma (Fig. 6). In cell block preparations, small fragments made of amorphous connective tissue and cords of medium-sized, uniform cells can be

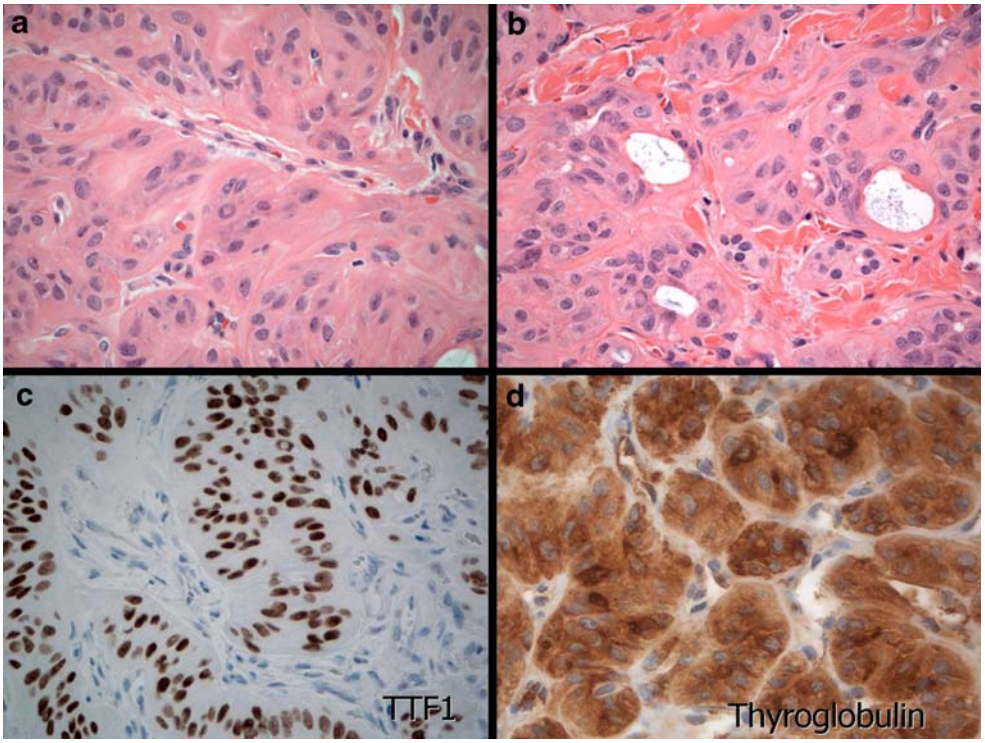


Fig. 3 Hyalinizing trabecular tumor. Typical histopathology finding with trabecular arrangement **a** and **b**. The cells are positive for TTF1 **c** and thyroglobulin **d**

observed. No colloid or necrosis are found in the background, nor are follicles present in the aspirated material.

From a practical point of view, a fine needle aspiration cytological diagnosis of HTT may not be straightforward. The recognition of a trabecular pattern in a neoplasm of follicular derivation is sufficient for referring the patient to a surgeon. Excluding the very rare thyroid paraganglioma [11] and medullary carcinomas, a trabecular patterned tumor may result in a final diagnosis of either trabecular adenoma, trabecular/solid/insular (poorly differentiated) carcinoma or of hyalinizing trabecular tumor. The cytological similarities (nuclear holes and grooves) with papillary carcinoma pose a major presurgical diagnostic dilemma, as papillary carcinoma has a much more common occurrence.

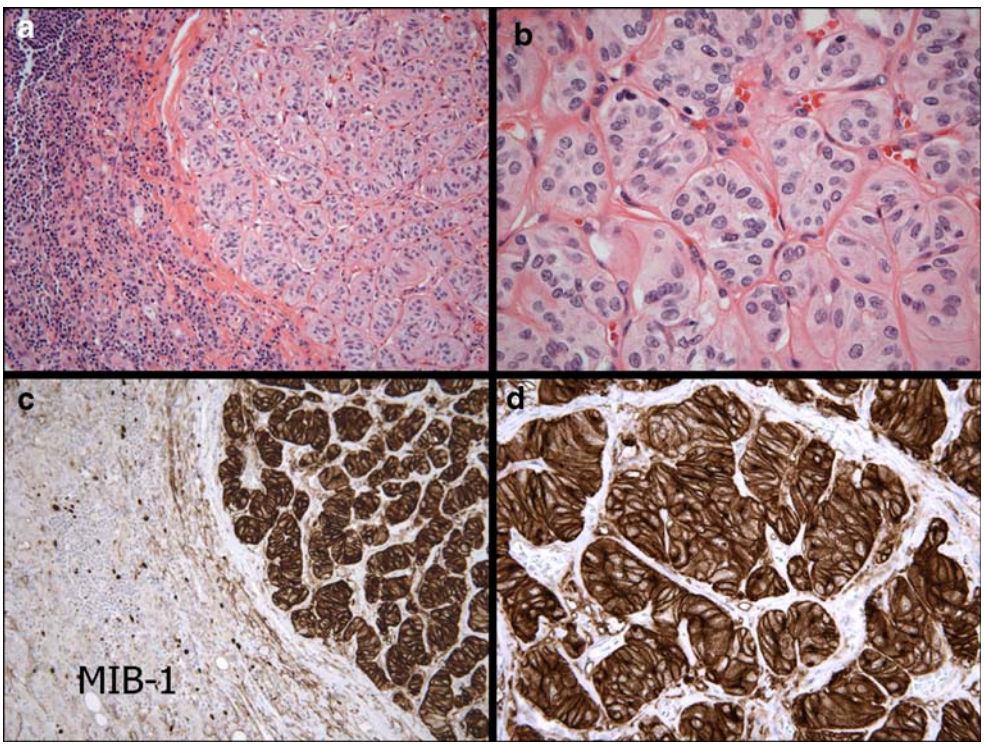


Fig. 4 Hyalinizing trabecular tumor. A low power (left; **a** and **c**) and higher power (right; **b** and **d**) of HTT, demonstrating MIB1 staining in the nonneoplastic lymphocytes (on left, **c**), and the characteristic strong MIB1 peripheral cytoplasmic and membranous staining (right, **c**, and higher power **d**)

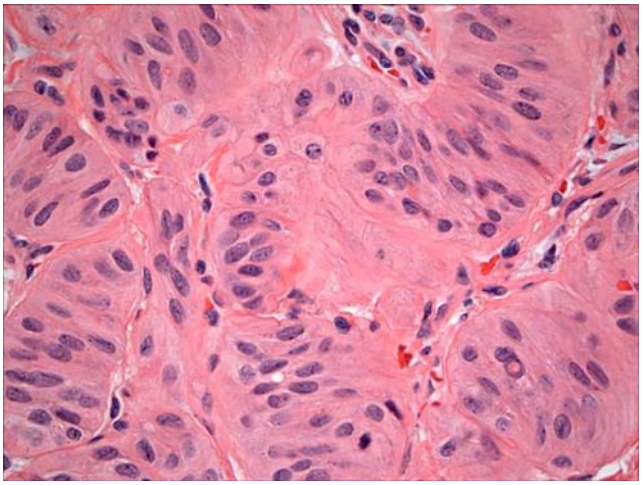


Fig. 5 Hyalinizing trabecular tumor. The characteristic trabecular growth pattern, composed by cells with prominent eosinophilic cytoplasm and oval to elongated nuclei, with nuclear grooves and intranuclear inclusions (arrow)

In the authors' experience with over 15 cases of hyalinizing trabecular tumors, the identification of the entity originally described by A. Carney is difficult because of the occurrence in the thyroid of several other "trabecular" lesions, which are distinct from HTT (e.g., MTC, paragangliomas, parathyroid tumors, metastases), and have a different architecture. Therefore, a strict diagnostic algorithm is needed (see diagnostic algorithm proposed by the authors; Table 3) to exclude all alternative diagnoses (trabecular/fetal adenoma, poorly differentiated insular carcinoma, solid variant PTC, medullary carcinoma, etc.). Indeed, all such alternative conditions are not really similar to the structure of true HTT cases, and the only real mimicker of HTT is paraganglioma, which in the thyroid is an exceptional occurrence and fortunately has different immunoprofile.

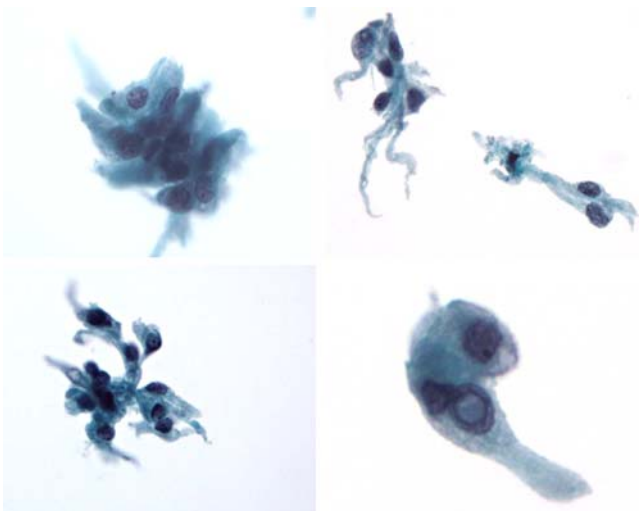


Fig. 6 Hyalinizing trabecular tumor. Cytology findings demonstrating moderately cellular smears containing large irregular tissue fragments with a branching profile, and spindle-shaped single cells. Of note is a cell with an intranuclear inclusion

Immunohistochemistry

To exclude two of the major mimics of HTT, medullary thyroid carcinoma and paraganglioma, neuroendocrine markers such as chromogranin A or calcitonin, in the case of medullary carcinoma, may be useful, although neuroendocrine differentiation in HTT has been reported [22]. Markers of HTT are TTF-1 and thyroglobulin (Fig. 3c, d), a profile shared by most follicular-derived thyroid tumors [1].

In addition, a unique Ki-67 (MIB1) membranous staining pattern is considered characteristic of HTT within thyroid neoplasms [4] (Fig. 4c, d), and a diagnostic impact of this finding has been proposed by some authors [20–21] and rejected by others [23]. Ki-67 membranous pattern is not restricted to HTT, but has also been rarely reported in sclerosing hemangioma of the lung [24]. No cell membrane or cytoplasmic MIB-1 reactivity has been reported in MTC or PTC and its variants. The primary antibody used routinely is MIB-1/Ki67 antibody clone, 1:600 dilutions, and the cellular conditioning used is heat-induced epitope retrieval in citrate buffer at pH 6.0, in an electrical pressure cooker for a total time of 30 minutes (Fig. 4c, d). Very recently it was found that the use of certain Ki-67 staining protocols may dramatically affect the membranous staining pattern, this feature being restricted to the MIB-1/Ki67 antibody clone used (as opposed to other Ki67 antibodies), and to the incubation temperature [25].

Discrepant results have been reported concerning the cytokeratin profile in HTT [9, 13, 26], thus limiting its diagnostic application.

Table 1 Histopathological Differential Diagnosis of HTT

Type of Tumor/ Disease	Morphological Features
Paraganglioma	Very rare; strikingly similar morphology; expresses neuroendocrine markers
Papillary thyroid carcinoma	Similar cytological features, but generally papillary or follicular structure; more problematic in case of solid/trabecular variants
Medullary thyroid carcinoma	Amyloid-like amorphous material and medium sized round or elongated cells with eccentric dark nucleus; expresses neuroendocrine markers
Trabecular adenoma/ carcinoma	Solid nests and cords of uniform cells, generally smaller than HTT; stromal hyaline material having an intertrabecular location; no yellow bodies; signs of malignancy (vascular invasion, capsular penetration, etc)
Regressive changes in goiter	Abundant dense connective tissue and amorphous/fibrinous material mimicking hyaline material of HTT, however is extratrabecular; follicular areas

Table 2 Comparison of Typical Morphological and Molecular Features of Benign Thyroid Lesions (Such as Lymphocytic Thyroiditis, Nodular Hyperplasia, and Adenomas), HTT, PTC, and MTC

Feature	Benign	HTT	PTC	MTC
Circumscription	+	+	−/+	+
Predominant trabecular growth pattern	−	+	−	−/+
Nuclear grooves	− (Rare in adenomas)	+	+	Rare
Intranuclear pseudo−inclusion	−	+	+	Rare
Hyaline material	−	+	−	+
Cytoplasmic yellow bodies	−	+	− (Very rare)	−
Calcification/psammoma bodies	−	Rare	+	Rare
MIB−1 membranous and cytoplasmic	−	+	−	−
CK 19 (cytokeratin 19)	− (+ in Hashimoto's thyroiditis)	Usually −	+	−
Galectin 3	− (+ in Hashimoto's thyroiditis)	+ in about 40% of cases	+	+
RET/PTC	+/−	+/− (Up to 60%)	+ (Up to 40%)	−
RAS	−	−	+ (15%, only in follicular variant)	−
BRAF	−	−	+ (30–70%)	−
Metastatic potential	−	Unknown	+	+
Lymph node metastases	−	Unreported	+	+

HTT: Hyalinizing trabecular tumor; PTC: Papillary thyroid carcinoma; MTC: Medullary thyroid carcinoma

Markers described in follicular neoplasms of the thyroid, such as galectin-3, have been tested in HTT and shown to be variably expressed [27]. Galectin-3 immunostaining showed that 60% of the HTT were negative or had weak staining and 40% had strong staining, an immunophenotype, which is intermediate between that of benign and malignant thyroid tumors, with special reference to PTC. In this same study, follow up data revealed absence of metastatic disease in all 58 HTT patients investigated, supporting the view that HTT has very low, if truly any, metastatic potential, as has also observed in many papillary microcarcinomas.

Other immunohistochemical markers related to specific genetic alterations, such as ret protein, have been found to be present in HTT, but are of limited usefulness in diagnostic practice (Table 2). The hyaline material present in the neoplastic trabeculae has been largely investigated and found to contain basement membrane type proteins, such as laminin and collagen-type IV [9, 12].

Molecular Profiles

Cytomorphological similarities between HTT and PTC suggest an association [3, 12, 28, 29] that has also been supported by a few molecular studies aimed at a common genetic background.

RET protooncogene rearrangements are common in PTC and are believed to be tumor-specific. However, RET/PTC rearrangements have also been reported in HTT, ranging from approximately 20 to 60% of the cases, which is close to what has been observed in PTC [30–32]. The RET/PTC type present in HTT is exclusively the RET/PTC1, which is usually associated with biologically less aggressive cases of PTC, as opposed to the RET/PTC3 type. In very few cases of mixed HTT-PTC tumors studied by RET immunohistochemistry [31], the expression of RET was restricted to the PTC component, possibly indicating RET rearrangement as part of a progression rather than as an initiating event. As RET rearrangements may also be found in lymphocytic thyroiditis and oxyphilic tumors [33, 34], it remains to be defined whether RET alterations in HTT are sufficient molecular proof of its relationship with PTC.

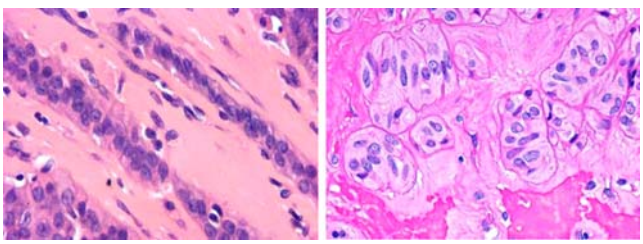
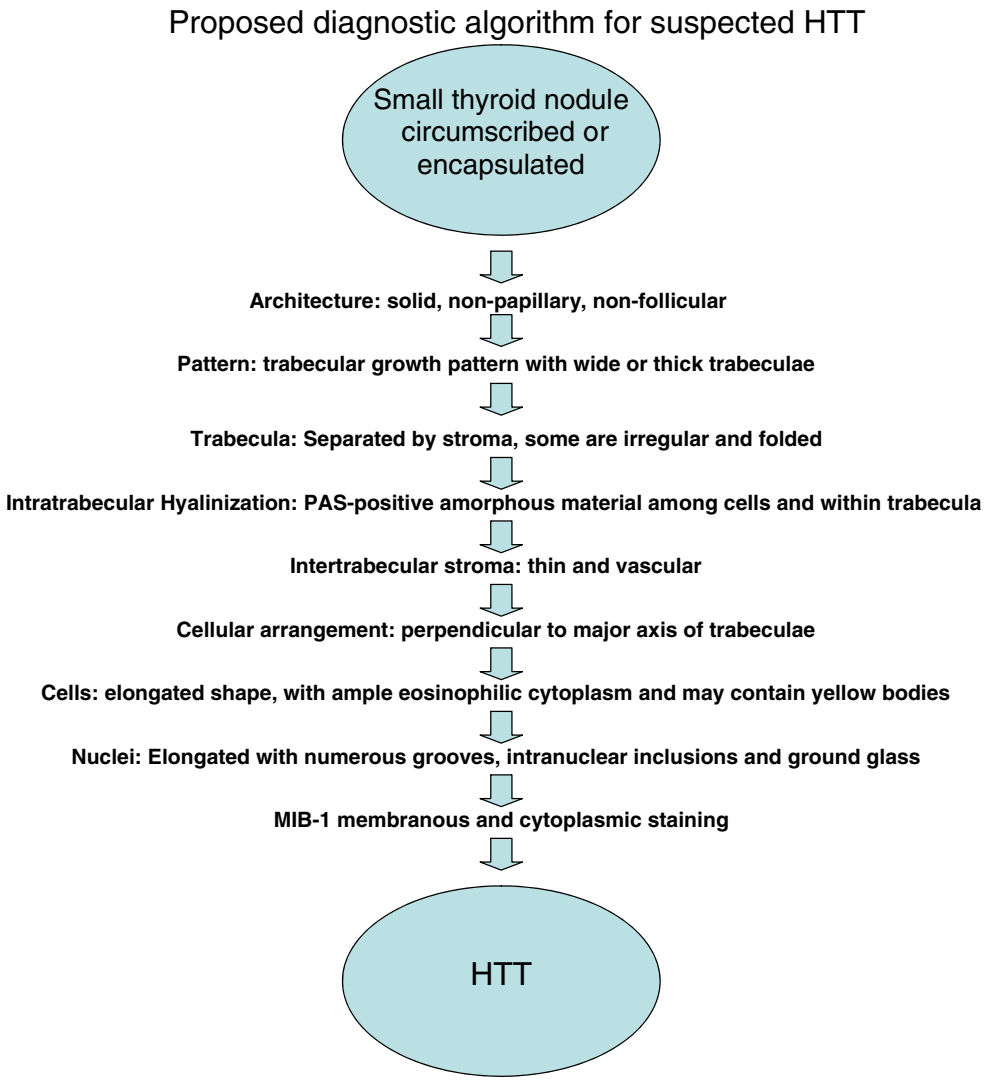


Fig. 7 **a**: Trabecular adenoma: Intertrabecular fibrous or hyaline bands seen in trabecular adenoma or carcinoma, do not represent a diagnostic feature of HTT. **b** HTT: The diagnosis is confirmed by the recognition of the hyaline material within the trabeculae (intratrabecular hyalinization)

Table 3 Diagnostic Algorithm for Suspected Hyalinizing Trabecular Tumor Proposed by the Authors



Mutations in the *BRAF* gene have recently been detected in a wide range of neoplastic lesions, with a particularly high prevalence in PTC. The hot-spot mutation in BRAF (V600E) is frequently detected in PTC and its variants (36–69%), in contrast to its absence in other benign or malignant thyroid lesions. Recently, one study showed a 47% prevalence of RET/PTC rearrangements in 28 cases of HTT, but detected neither *BRAF* nor *N-ras* mutations in any of the studies [32]. Moreover, no *BRAF* mutations were detected in 10 cases of HTT studied by others [35,36].

Although RET/PTC, N-ras, and BRAF proteins may act along the same signaling cascade, the biological and morphological outcome of their activation in HTT is unique from that of PTC.

With regard to possible genetic susceptibility of HTT, two cases were described in members of a family affected by oxyphilic thyroid tumors related to alterations of TCO gene in chromosome 19p13.2 [37], whereas another case with HTT features was observed in a patient affected by Cowden disease [38].

Prognosis

The original publication on HTT included all benign cases [1]. In the series of cases so far collected by Carney and partially published in molecular studies [27, 32], none of the cases had morphological signs of malignancy (e.g., vascular invasion or capsular penetration), nor did any of the cases develop malignant behavior.

The benign nature of HTT has been questioned because of subsequent descriptions of possible vascular invasion in aggressive cases of tumors having hyalinizing trabecular patterns [2, 9, 39, and 40]. Comparing the original images and description of HTT with those of published so-called “malignant hyalinizing trabecular carcinomas”, a major concern is related to the diagnostic criteria used by the

various authors to label a case as HTT or "hyalinizing trabecular carcinoma". It seems that the published thyroid tumors with hyalinized trabecular growth pattern are rather heterogeneous, and the cases reported to follow a malignant course are often characterized by trabecular growth patterns having a remarkable *inter*trabecular accumulation of hyaline material (rather than *intra*trabecular, as typically observed in HTT. Likely, they represent cases of trabecular carcinoma with prominent (intertrabecular) hyalinization.

Having so far excluded the existence of a true malignant HTT in the follicular adenoma/carcinoma spectrum, the question remains whether the HTT is a variant of PTC. So far, no HTT case meeting all the originally described diagnostic criteria [1] has been reported to follow a malignant course. It is, however, of note that many PTCs often follow a benign course and are, nevertheless, considered malignant tumors, albeit with low malignant potential. Only careful longitudinal studies of this rare tumor entity will definitively address its malignant potential, perhaps restoring the monicker of adenoma, according to the original description. From current data, both cytomorphological features and the molecular profile of HTT share features of PTC, and therefore, a definitive link between these entities cannot be entirely excluded.

Conclusions

HTT represents a rare and peculiar type of thyroid tumor with a debated histogenesis and largely benign clinical behavior. It shares morphological similarities with other thyroid neoplasms and falls within the differential diagnosis of trabecular-patterned lesions, such as MTC and PTC, based on overlapping nuclear features. Genetic features, as well as the immunophenotypic markers related to malignancy (such as galectin-3), are intermediate between benign follicular adenoma and follicular/papillary carcinoma. From a practical standpoint, HTT that fulfill the classical morphological characteristics listed in the original paper [1] should be considered to be benign neoplasms, or at most, to be of low malignant potential.

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