Hyalinizing Trabecular Tumor of the Thyroid: A Case Report

P. Caraci · A. Fulcheri · C. Ondolo ·
F. Laino · M. Volante · S. Aversa

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Abstract Hyalinizing trabecular tumor (HTT) of the thyroid is a rare neoplasm that was first described by Carney in 1987. It is a tumor of follicular derivation with peculiar nuclear, architectural, histochemical, and immunohistochemical features. We report a case of HTT in a 69-year-old woman with a multinodular goiter. Since the clinical and ultrasonographic features were nonspecific, fine needle aspiration biopsy (FNAB) of the left lobe-dominant node was performed that resulted in an indeterminate cytologic diagnosis (category THY-3). The patient underwent total thyroidectomy, with a histologic diagnosis of HTT. We discuss the clinical and diagnostic approach, including the role of FNAB, and the pathologic features of HTT with special reference to the possible differential diagnosis. Total thyroidectomy or hemithyroidectomy represent adequate treatments, while radioiodine ablation is not standard. Although rare cases of malignant HTT have

been documented, this tumor should be considered a benign neoplasm or, at most, a neoplasm of extremely low malignant potential. As a consequence, once this diagnosis is rendered, clinical management should be conservative, which may include a precautionary annual follow-up in order to exclude the very rare possibility of recurrence, as exceptionally reported.

Keywords Hyalinizing trabecular tumor · Fine needle aspiration biopsy · Thyroid tumor

Introduction

Well differentiated thyroid tumors commonly present follicular and/or papillary growth patterns. Less frequently, both benign and malignant lesions may have a nonfollicular, nonpapillary architecture. Among these, the solid/trabecular architectural pattern is the most common.

These cases yield the widest range of differential diagnoses, which may represent a challenge for the pathologist, who must carefully consider this broad variety of lesions [1], each of which is to be treated with specific surgical and/or medical protocols. The differential diagnosis of the solid/trabecular pattern includes, but is not limited to, trabecular adenoma, medullary thyroid carcinoma (MTC), the solid variant of papillary thyroid carcinoma (PTC), hyalinizing trabecular tumor (HTT), and even other tumors, such as paraganglioma [2].

HTT is a very rare neoplasm, which was first described as hyalinizing trabecular adenoma in 1987 by Carney et al. [3] at the Mayo Clinic. HTT is a tumor of follicular derivation with peculiar nuclear, architectural, histochemical, and immunohistochemical features [4]. Since HTT was first reported, some authors [5] considered this tumor to be a

P. Caraci · F. Laino
Section of Internal Medicine, San Luigi Hospital,
regione Gonzole 10, Orbassano (Torino) 10043, Italy

A. Fulcheri · C. Ondolo · S. Aversa (✉)
Section of Otolaryngology – Head and Neck Surgery,
Department of Clinical and Biological Sciences, University
of Turin, San Luigi Hospital, regione Gonzole 10,
Orbassano (Torino) 10043, Italy
e-mail: salvatore.aversa@unito.it

M. Volante
Section of Pathology, Department of Clinical and Biological
Sciences, University of Turin, San Luigi Hospital,
regione Gonzole 10, Orbassano (Turin) 10043, Italy

variant of PTC. However, several subsequent reports considered HTT as a separate entity and highlighted the unique features that distinguish it from other well-recognized thyroid lesions, including PTC and MTC [6–10].

In this paper, we report the clinical and pathologic features of a female patient presenting with HTT and discuss the differential diagnosis with other mimickers within the thyroid, as well as in the head and neck area.

Case Report

Clinical History

A 69-year-old woman with a familial history of autoimmune thyroid disease (chronic lymphocytic thyroiditis) was admitted to our hospital because of a progressively increasing nodule in the left lobe of the thyroid in the setting of a multinodular goiter. The nodule was diagnosed two years before by ultrasonographic (US) examination and was now 1 cm larger in size. Fine needle aspiration biopsy (FNAB) performed at that time was nondiagnostic due to insufficient cellular material (cytological category THY-1 according to the British Thyroid Association Guidelines) [11]. On admission, the patient was clinically euthyroid: circulating free thyroxine (FT4) and thyroid stimulating hormone (TSH) were in the normal range. US examination confirmed the diagnosis of multinodular goiter and revealed that the dominant left nodule was increased up to 1.7 cm, oval shaped, hypoechoic, with well-defined margins and a “halo” sign, and without intranodular calcifications. Echo-color Doppler showed a peri-intranodular vascular pattern.

US-guided FNAB was adequate for cytologic examination and showed the presence of noncohesive cellular sheets, with nuclear clearing and irregular borders—although not sufficiently diagnostic of papillary carcinoma—and absence of colloid in the background. These findings supported the cytologic diagnosis of (an indeterminate) follicular neoplasm (category THY-3, Fig. 1) [11]. Galectin-3 immunocytochemistry revealed strong cytoplasmic staining (Fig. 2). Four months later, the patient successfully underwent total thyroidectomy, without post-surgical complications. Intraoperative frozen section examination was not performed.

Pathologic Findings

Macroscopic examination revealed a dominant encapsulated nodule in the left lobe, 1.3 cm in size, with a solid and whitish appearance. Colloid nodules less than 1 cm in size were present in the same and contralateral lobes. On light microscopic examination, the lesion showed a trabecular architecture, with marked inter- and intra-trabecular

Fig. 1 Cytologic smears of the lesion had scarce material, whereas the cell block showed groups of cells with trabecular growth and inconclusive nuclear changes (original magnification, 400×)

Fig. 2 Galectin-3 immunohistochemistry of the FNAB: the cells showed strong cytoplasmic positivity for galectin-3 (original magnification, 200×)

deposition of hyalinized PAS-positive amorphous material. Small follicular structures were rarely present. The nuclei were diffusely enlarged, with clearing, grooves and rare pseudoinclusions (Fig. 3 a–c). By immunohistochemistry, neoplastic cells were strongly positive for thyroglobulin and showed a diffuse and intense membrane staining with MIB-1 (Ki-67) monoclonal antibody. Together, these findings were consistent with the diagnosis of HTT.

Post-Surgical Therapy and Follow Up

Following thyroidectomy, L-thyroxine replacement therapy was begun, without the need to achieve TSH suppression. Post-surgical US neck examination excluded residual disease and/or cervical metastatic lesions. During the following 2 years, serial follow-up US tests were

Fig. 3 The lesion was encapsulated (a), with a predominant trabecular growth pattern lacking follicle formation and prominent inter- and intra-trabecular hyalinization (b); nuclear abnormalities included clearing, irregular shape and borders, frequent grooves, and occasional pseudoinclusions (c); [H & E stained sections, original magnifications: **a** 100 $\times$, **b** 200 $\times$, **c** 400 $\times$]

repeatedly negative. In addition, thyroglobulin levels were monitored, as a specific serum marker for differentiated thyroid cancer, and were detectable only at very low concentrations, thus excluding residual or progressive neoplastic disease.

Discussion

In the World Health Organization (WHO) classification of Tumors of Endocrine Organs, HTT is defined as “a rare tumor of follicular origin with a trabecular pattern of growth and marked intra-trabecular hyalinization” [12].

In the present paper, we report a clinically unexpected case of HTT, which underwent surgical intervention because of the initial “indeterminate” (category THY-3) cytologic diagnosis [11].

The pre-surgical diagnosis of HTT might be worrisome for both pathologists and clinicians. The US features of HTT are non-specific [13]. Lee et al. [14] recently reported a retrospective study involving ten patients with the histologic diagnosis of HTT, assessing and comparing the preoperative US and cytologic features. The characteristic US findings supported a follicular lesion (indeterminate behaviour) and did not show features to suggest a malignancy: the absence of microcalcifications and the presence of well-defined margins with a hypoechoic “halo” are not typically seen in malignant nodules. In contrast, a substantial percent (80%) of HTT nodules were cytologically misdiagnosed as PTC, due to the overlapping nuclear features with classic PTC.

In our case, the hypoechoicity and peri-intranodular vascular patterns were interpreted as nonspecific US features, and FNAB was considered to be strongly indicated for categorization of the lesion, which would determine subsequent therapeutic interventions.

As reported in the literature, the diagnosis of HTT can be made on FNA alone [15, 16]. Casey et al. [17] provided a detailed cytologic profile of HTT on a series of 29 cases, and compared it with that of PTC and MTC. Important features to discriminate HTT from PTC included a bloody background, and the presence of cells with ample cytoplasm arranged in cohesive aggregates often radially oriented around hyaline material [17], combined with the characteristic membrane immunoreactivity with MIB-1 antibody [18]. However, the diagnosis of HTT by FNA remains challenging [19, 20] because the cytologic features can be similar to those of malignant neoplasms—not only PTC but other solid neoplastic lesions. Nonetheless, from a practical point of view, the recognition by cytology of a trabecular pattern in a follicular lesion is sufficient for referring the patient to surgery for a definitive histologic diagnosis, as occurred with our patient.

Once histologic sections are available for examination, a definitive diagnosis can be made by the hallmark finding of a uniform and diffuse solid/trabecular pattern with marked hyalinized deposits containing basal membrane-type material, typically located within the trabeculae (rather than in the interposed stroma) [1, 3, 6]. Clear nuclei with grooves and pseudoinclusions are commonly found in

HTT; as a matter of fact, they have been considered a morphologic histogenetic link with PTC and represent a potential pitfall in the differential diagnosis.

In addition to these morphologic similarities, immunophenotypic and molecular data suggested that HTT may represent a variant of PTC. In fact, HTT shows patterns of cytokeratin expression similar to PTC [5] and has been reported to harbor the RET/PTC (type 1) translocation in a proportion of cases, similar to PTC [21, 22]. However, whether these observations are sufficient proof of its relationship with PTC is still a matter of debate [2], since other differences have been described, such as a specific Ki-67 (using the MIB-1 clone) membrane immunoreactivity [23] and the absence of BRAF and RAS mutations [24] in HTT.

In addition, a recent study of the patterns of microRNAs expressed by PTC, HTT, and other thyroid lesions, concluded that there was no evidence to support the concept that HTT represents a variant of PTC [9]. Moreover, although HTT variably (40% of cases) expresses the malignancy-related marker galectin-3 [25], as in the present case, other similar markers, such as HMBE-1, are negative in HTT [26], thus calling into question the malignant biologic behavior of this tumor entity.

It has been suggested that HTT is associated with other thyroid diseases, particularly chronic lymphocytic thyroiditis, as in the present case, as well as papillary/follicular neoplasms. This association was claimed since its original description [3] and was confirmed in a recent study of 199 cases of HTT that presented, in a subset of cases, with concurrent chronic lymphocytic thyroiditis (41%), follicular adenomas or multinodular goiter (37%), and papillary thyroid carcinomas (5%), respectively [27]. However, the nature of each of these associations remains to be defined, largely due to the rarity of HTT.

Among primary thyroid neoplasms not derived from the follicular epithelium that enter into the differential diagnosis, MTC and primary thyroid paraganglioma deserve a special comment. The former may be a diagnostic pitfall due to the presence of a trabecular growth pattern and a well-defined tumor “capsule” secondary to amyloid stroma that might be misinterpreted as hyalinization. The latter entity is a very rare disease that shows several architectural and cytologic similarities with HTT. Usually confined to the thyroid gland with well circumscribed margins, primary thyroid paraganglioma is composed of neoplastic cells arranged in a trabecular/lobular growth pattern with an interposed, supporting fine connective tissue network [28]. Nuclear atypia is usually mild, with round to oval nuclei that may show cytoplasmic pseudoinclusions. Features of both MTC and paraganglioma that are distinct from HTT include the absence of intra-trabecular hyalinization, and their specific immunophenotypes, which show a lack of

follicular derivation and neuroendocrine (plus calcitonin reactivity in medullary carcinoma) marker expression.

Concerning the biologic and clinical behaviour, HTT should be considered as a benign neoplasm or, at most, a neoplasm of extremely low malignant potential [27], although rare cases of malignant HTT have been recorded [29–31]. Consequently, when this diagnosis is rendered, the clinical management of HTT should be conservative, with only a precautionary follow-up warranted. Radioiodine ablation should not be performed and total- or hemithyroidectomy can be considered as adequate treatments. Our patient has had precautionary annual follow-up, including physical examination, thyroglobulin plasma determination, and neck US. This will be continued in the future to exclude the very rare event of tumor recurrence, as exceptionally reported.

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