Hyalinizing trabecular tumor of the thyroid: Case report and review of the literature

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Abstract. In 1987, Carney *et al* described a rare thyroid tumor termed hyalinizing trabecular adenoma presenting characteristics consisting of a trabecular growth pattern and hyalinizing stroma. In subsequent reports, the observed nuclear features and RET alterations led this tumor to be linked to papillary carcinoma. Subsequent reports concerning hyalinizing trabecular carcinoma further complicated its classification. To avoid uncertainties, the definition of hyalinizing trabecular tumor (HTT) is more widely used. Herein, a case of HTT is reported in detail, and the circumstances are also discussed. HTT is thought to be particularly differentiated from papillary carcinoma despite the identical high frequency of nuclear grooves and cytoplasmic inclusions, and MIB-1-positive staining is one of the most accurate diagnostic methods due to the distinct membrane-positive pattern noted in HTT. It is believed that most HTTs are benign and lobectomy is the standard treatment. Pathologists should offer surgeons information concerning diagnosis overlapping with effective treatment.

Introduction

Since Carney *et al* reported a rare thyroid lesion termed hyalinizing trabecular adenoma (HTA) presenting with characteristics of a trabecular growth pattern and hyalinizing stroma in 1987, controversies concerning the classification of this entity have arisen (1). Most believe it to be a unique entity, whereas others have argued that it is a variant of papillary carcinoma. To make it even more complicated, the majority of the reported cases were benign, while a few, which were accompanied by metastasis in the lymph nodes or the lung, were named hyalinizing trabecular carcinoma (HTC) (2). Due to the uncertain malignant potential and entity of this tumor, a more general term, hyalinizing trabecular tumor (HTT), has been adopted by most pathologists and the World Health Organization classification, which reflects such controversy.

In clinical and pathological practice, HTT is frequently misdiagnosed and is managed as other thyroid neoplasms due to the similarity in morphology, mimicking papillary thyroid carcinoma (PTC) and medullary thyroid carcinoma (MTC). Although HTT has attracted the interest of pathologists, according to our knowledge such enthusiasm has not been stimulated in clinicians. In fact, it is crucial for surgeons to recognize the features of this lesion to ensure effective treatment and management of HTT. For example, currently, lobectomy is recommended for HTTs, but mistreatment may result in cases where total thyroidectomy has been undertaken. Herein, we present the diagnosis and management of a typical HTT case and general information concerning HTT is also presented.

Case report

A female patient 42 years of age presented with a single lump in the right side of the neck. Ultrasonography revealed a solid cold nodule, which was regarded as a thyroid adenoma. Thus, the intact neoplasm was surgically removed for pathological examination.

Gross investigation showed an encapsulated mass of 5x3.5x2.5 cm. The cut surface was homogeneously pale and rigid. Microscopically, the lump was surrounded by a thin capsule, and no malignant morphological features, including capsular or vascular invasions, were observed (Fig. 1A). The tumor was characterized by trabecular structures separated by minimal fibrous stroma. The intratrabecular hyalin and colloid was prominent, which consisted of basement membrane material rather than amyloid with PAS positivity (Fig. 1C) and Congo Red negativity. Alveolar and Zellballen structures were also present, partitioned by sinus vascular network, similar to those noted in paragangliomas. The tumor cells were polygonal, oval, or high columnar with an acidophilic or clear cytoplasm. The nuclei were round or oval with inconspicuous small nucleoli, with prominent grooves and less frequent pseudoinclusions (Fig. 1B). Mitosis and psammoma bodies were rare or absent.

Immunohistochemical study of these tumors showed positivity for thyroglobulin, thyroid transcription factor-1 (TTF-1)

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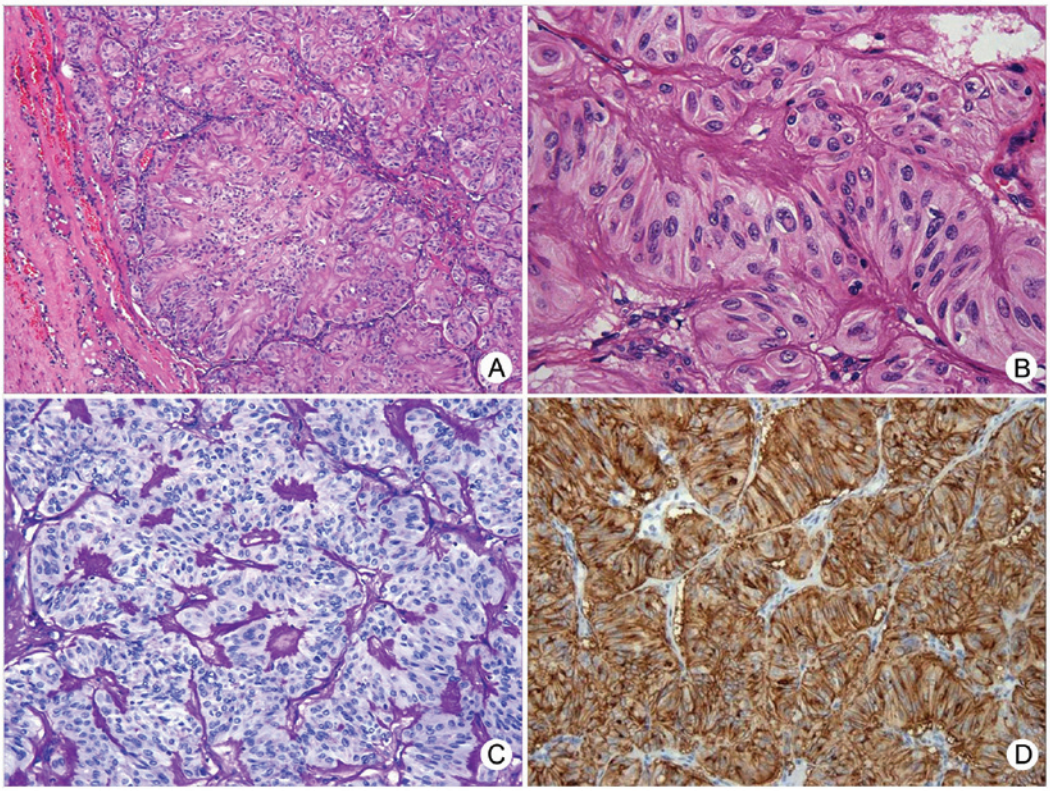

Figure 1. (A) HTT, surrounded by a thin capsule without capsular or vascular invasions, was composed of trabecular structures separated by minimal fibrous stroma and the intratrabecular hyalin and colloid was prominent (magnification, x100). (B) Nuclei were round or oval with inconspicuous small nucleoli, with prominent grooves and less frequent pseudoinclusions (magnification, x400). (C) The intratrabecular hyalin exhibited PAS positivity (magnification, x200). (D) MIB-1 staining showed a distinctive membranous pattern (magnification, x200).

and gelactin-3, and negativity for calcitonin, cytokeratin-19, synaptophysin and chromogranin A. Staining with the MIB-1 antibody showed a distinctive membranous pattern (Fig. 1D), whereas other clones of Ki-67, such as SP2 or 7B11, showed a common nuclear pattern, with an index of <1%. Staining for the anti-P53 antibody was negative. After a follow-up of 4 years the patients was alive without local recurrence or metastasis.

Discussion

HTT is a rare and controversial thyroid lesion, prevalent in females between the fourth and fifth decades of age. The entity remains controversial as HTT was originally believed to be a distinct neoplasm, but others regard it as a variant of PTC as some similarities are noted in nuclear features. RET/PTC rearrangements, which are characteristic of a specific molecular event of PTC, were noted in HTT samples by immunohistochemistry staining and reverse transcription-polymerase chain reaction, and the ratio was nearly identical to that of PTC (3,4). All of these observations reinforced the fact that HTT is a variant of PTC. However, as previously pointed out, the conclusion was arbitrary as RET rearrangements may also occur in other thyroid lesions, such as lymphocytic thyroiditis which is frequently associated with HTT. Moreover, cytokeratin-19 and gelactin-3, which are expressed strongly in PTC, were expressed at weak levels in HTT. MIB-1 staining of HTT samples exhibits a distinctive membrane-positive pattern rather than nuclear positivity; however, this finding has not been observed in PTC samples. In contrast to the high prevalence for mutations of the BRAF and N-ras genes in PTC, such have not been detected in HTT patients (5). The five microRNAs, which have been found to be upregulated in PTC, were verified to be downregulated in HTT (6). These provide evidence that HTT is distinct from PTC. Thus, to date, HTT is diagnosed as an independent neoplasm, rather than one variant of PTC.

Moreover, one additional controversy is whether HTT is a benign or malignant neoplasm. In early reports, malignant phenotypes such as vascular or capsular invasion, or a high index of mitoses were not observed in histological studies. However, the benign nature of these tumors has been challenged in subsequent descriptions of vascular invasion in aggressive cases or with metastases to the lymph nodes and lung (2). In his most recent report, Carney *et al* investigated 119 cases of HTT for invasion, recurrence and metastasis, and obtained follow-up for 96% of the cases (7). In their biggest series to date, only one case showed vascular and capsular invasion and pulmonary metastasis. Thus, it was confirmed that the overwhelming majority of HTTs behave as benign neoplasms. Thus in clinical practice, sufficient dissection and careful observation of vascular, capsular and parenchymal invasion is essential to eliminate the minute possibility of malignancy.

Despite the fact that the entity of HTT is not entirely clear, it is frequently misdiagnosed as a malignant thyroid lesion. Surgeons should be aware that HTT can be mistaken for PTC

or MTC following pathological evaluation, particulary when using cytological or frozen sections, whereas it may be considered as a benign lesion in ultrasonography (8,9). Preoperative cytology using fine needle aspiration biopsy of thyroid nodules is the most effective and widely used method to distinguish the nature of these lesions. However, the features of hypercellularity and grooves, pseudoinclusions and hyperchromaticity of the nuclei, which are the main diagnostic clues for HTT, are also often observed in patients with classical PTC (10-13). In most reported cases, these tumors are diagnosed as 'suspicious or even diagnostic for PTC' in cytological evaluations, and few tumors are diagnostic or suspicious for HTT, partly since cytologists are not familiar with HTT. Similarly, frozen sections are seldom useful for the diagnosis of HTT. In our experience with the 42-year-old patient, we initially diagnosed the patient as 'suspicious for PTC' based on the nuclear features observed in the frozen section, but we made no recommendations for further treatment until we had obtained a definite pathological diagnosis. Thus, surgeons should be aware that the preoperative cytological or frozen sectional diagnosis may not necessarily agree with the final pathological diagnosis due to the overlapping nature between HTT and PTC. In addition, surgeons can inform the patients that most cases of HTT are benign and are associated with a much more favorable outcome than PTC.

The differentiation of HTT from other thyroid tumors, such as MTC or PTC and occasionally, primary thyroid paraganglioma with trabecular architecture, can be achieved by histochemistry and immunohistochemistry besides morphology. HTT usually stains positive for thyroid follicular epithelial markers, such as thyroglobulin and TTF-1, and negative for calcitonin, NSE, chromogranin A or synaptophysin. The hyalinizing material is PAS-positive and Congo Red-negative in special staining, and is positive for collagen type IV in immunostaining, which has been demonstrated for basal lamina-like substance ultrastructurally (14). On the contrary, MTC often expresses calcitonin and neuroendocrine markers and exhibits positive staining for Congo Red. Thyroid paraganglioma is a rare lesion which expresses neuroendocrine markers.

Differentiating HTT from PTC is more challenging due to the similarities in cellular morphology and origin. PTC often displays strong positive staining for CK19 and galectin-3, whereas these markers are weakly expressed in HTT (15). MIB-1 staining pattern is useful as the membrane-positive reactivity is a distinctive feature of HTT, however, no such pattern appears in PTC. Notably, it has been reported that the membrane-positive pattern is observed for the MIB-1 clone only but not other clones of Ki-67, which was also confirmed in our present study (16).

To date, the etiology of HTT remains to be fully clarified. This tumor may arise in the background of chronic lymphocytic thyroiditis and multinodular goiter, or in association with PTC. The link between HTT and lymphocytic thyroiditis may be significant due to similarities in molecular genetics and age or gender distribution. However, this remains to be addressed in future studies. The prognosis of most HTT cases is favorable, therefore, lobectomy treatment is sufficient; however, when HTT is accompanied by metastasis, we require further knowledge regarding treatment and prognosis.

In summary, HTT represents a rare and controversial thyroid tumor. It has a characteristic trabecular growth pattern and hyalinizing stroma. The differentiation of HTT from other thyroid tumors such as PTC and MTC can be achieved using histochemistry and immunohistochemistry in addition to morphology. In general, the prognosis of HTT is favorable, whereas a few cases may be accompanied by morphological malignant features or metastases.

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