Hyalinizing Trabecular Neoplasm of the Thyroid: Controversies in Management

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Abstract

Objectives/Hypothesis: To review the clinical and pathological picture of hyalinizing trabecular neoplasm of the thyroid [HTN] and compare HTN with papillary thyroid carcinoma [PTC] in order to discuss the appropriate management of this uncommon but potentially confusing neoplasm.

Study Design: A case review of a patient with HTN treated at our institution.

Methods: Case review and MEDLINE literature search.

Results: Although recognized as a tumor of uncertain malignant potential in the pathology literature, HTN has been rarely reported in otolaryngology journals, and its management remains controversial. HTN and PTC share similar histopathological characteristics and have been described as coexistent lesions in the same thyroid. HTN's have also exhibited proto-oncogenes associated with PTC. Moreover, recent reports have described cases of HTN exhibiting vascular or capsular invasion and metastases.

Conclusions: HTN should still be considered a neoplasm of uncertain malignant potential. Criteria for the treatment of HTN have yet to be determined, and many investigators are concerned about the prudence of making broad recommendations on the basis of a few studied cases. Nonetheless, when discussing surgical treatment options and recommendations for postoperative monitoring and radionuclide ablation in patients diagnosed with HTN, physicians may be guided by the criteria for the treatment of PTC at their respective institutions.

INTRODUCTION

Hyalinizing trabecular neoplasm [HTN] of the thyroid is an uncommon but potentially confusing neoplasm originally described in 1987 by Carney et al.[1] Although recognized as a tumor of uncertain malignant potential in the pathology literature, HTN has been rarely reported in otolaryngology journals. Because HTN and papillary thyroid carcinoma [PTC] share similar histopathological characteristics and RET proto-oncogene rearrangements, HTN's classification and its management remain controversial. We review the debate about HTN's potentially malignant behavior and discuss appropriate guidelines for therapy.

MATERIALS AND METHODS

We performed a MEDLINE search to identify all the reported cases of HTN and all the published studies regarding HTN's pathologic characteristics and clinical behavior. These reports and studies provided data on HTN's histologic features, co-existence with PTC, immunostaining characteristics, genetic analysis, and clinical behavior. This data was analyzed, and suggestions regarding HTN's classification and management were generated.

RESULTS: CASE REPORT

A 41-year-old woman presented to our office with an asymptomatic 2 cm left thyroid nodule detected incidentally on a gynecological examination approximately six months prior to our evaluation. A fine needle aspirate revealed groups of follicular cells showing intranuclear inclusions suspicious for papillary thyroid carcinoma. The patient subsequently underwent total thyroidectomy. A frozen section evaluation was consistent with a follicular variant of papillary carcinoma. Final histological analysis, however, revealed a hyalinizing trabecular neoplasm in the left lobe.

No tumor was identified in the right lobe.

DISCUSSION

Hyalinizing trabecular neoplasm (HTN) of the thyroid gland was originally described as “an uncommon but potentially confusing neoplasm” by Carney and colleagues[1] in 1987. HTN typically occurs in females as either a single dominant nodule or as part of a multinodular goiter. Several cases have occurred in association with Hashimoto's thyroiditis and prior neck irradiation.[2] Grossly, HTN is a small (usually <2 cm), either encapsulated or circumscribed mass with a solid, yellow-tan appearance on fresh-cut surface. It displays a solid, lobulated appearance on light microscopy (Figure 1). The elongated spindle-shaped tumor cells are medium sized, polygonal, and oval. The finely granular cytoplasm is generally eosinophilic and is often positively immunoreactive for thyroglobulin, but non-reactive for calcitonin. The vesicular nuclei are oval, elongated and occasionally spindled. The nuclei commonly display eosinophilic pseudoinclusions as well as fine grooving (Figure 2). Perinuclear clearing is common. Mitotic figures are scarce.[1]

Figure 1

Figure 1: Lower magnification shows a well-circumscribed tumor composed of spindle-shaped cells with abundant, finely granular, eosinophilic cytoplasm. There are thin fibrovascular septae between the tumor cells arranged in a trabecular pattern.

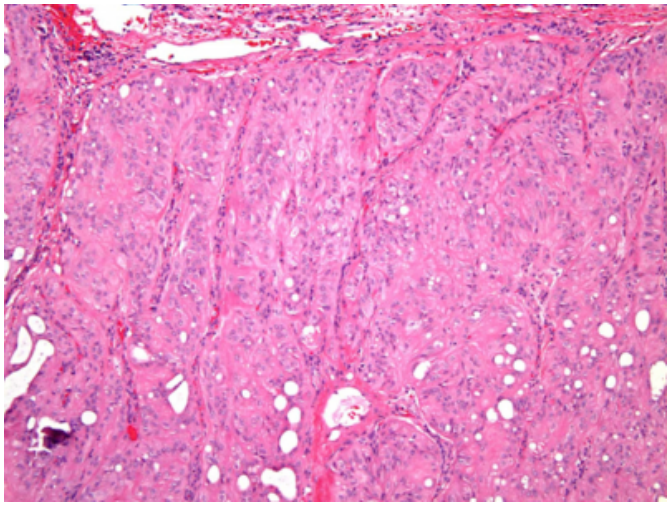
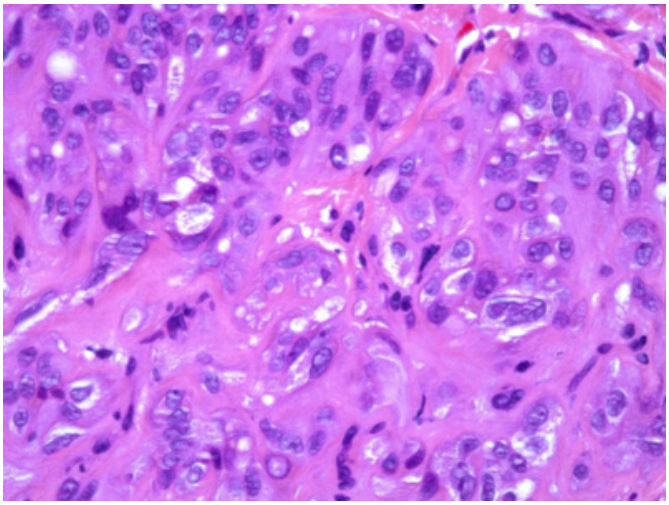


Figure 2

Figure 2: Higher magnification shows the vesicular chromatin distribution within enlarged nuclei.



Tumor cells are arranged in a trabecular or alveolar pattern. They are inserted vertically into capillaries that compose the delicate intertrabecular fibrovascular stroma, which is markedly hyalinized. Epithelial cells adjacent to the hyalinization are often non-viable ghost cells. In many cases the trabeculae feature internal spaces (pseudofollicles) that contain material similar to thyroid colloid. This colloid-like material is occasionally calcified in a laminated fashion, making it indistinguishable from a psammoma body. Rarely, true follicles are also seen.[1]

HTN may be misinterpreted as the encapsulated variant of medullary thyroid carcinoma. This confusion arises due to the presence of elongated spindle cells and a stromal hyaline fibrosis that mimics amyloid. However, these tumors can be distinguished from medullary carcinomas by Congo-red negativity, positive thyroglobulin immunoreactivity and negative calcitonin immunoreactivity.[2]

HTN may also exhibit features typical of paraganglioma. These features include a nested Zellballen architecture coinciding with a delicate vascular network. HTN may be differentiated from paraganglioma by the presence of pseudofollicles and colloid material, and by characteristic spindle shaped nuclei. In addition, Bronner and coworkers[3] note that paragangliomas, unlike HTN, are typically non-reactive for thyroglobulin and reactive for neurofilament. Finally, there has been no conclusive evidence proving the existence of intrathyroidal paragangliomas[3,4].

The most recent and controversial debate surrounding HTN concerns its potentially malignant behavior and the possible

relationship to papillary carcinoma of the thyroid [PTC]. Both HTN and PTC lesions share several characteristics, such as fine nuclear grooving, intranuclear inclusions, psammoma bodies, and occasionally, coarse papillations that project into large intratrabecular cystic spaces. When Carney and colleagues[1] first described HTN, they stressed its benign course. In a follow-up period of many years, they found no cases demonstrating capsular invasion, vascular invasion, recurrence or metastases. In more recent years there have been numerous reports of HTN displaying vascular or capsular invasion, and even metastases. [5,6,7,8,9] However, there is new debate over whether the lesions described in these later reports are the same lesions originally described by Carney in 1987.[10]

In addition to histological and cytological similarities, the frequent coexistence of HTN and PTC has also led to speculation about their classification. For example, a third of thyroid glands containing HTN also contain PTC.[10] Furthermore, areas with a hyalinizing trabecular pattern have been identified within both primary and metastatic PTC lesions. This hyalinizing trabecular pattern can also be found within otherwise typical follicular neoplasms and other thyroid lesions, including multinodular goiter. Some suggest that HTN's coexistence with, and histological similarity to PTC, should lead to its reclassification as a variant of PTC.[11]

Another means employed to compare HTN and PTC is cytokeratin immunostaining. Fonesca and coworkers[11] reported that HTN has similar patterns of expression to PTC, expressing stratified cytokeratins 1, 5/6 and 13 as well as simple epithelial type cytokeratins 7, 8, 18 and 19. This evidence may support the claim that HTN is a variant of PTC. In contrast, Hirokawa and colleagues[12] found that HTN and PTC have different patterns of expression of CK 19 and HMW-CK. These workers suggest that this data provides further evidence to distinguish HTN from PTC as a discrete pathologic entity.

The pathogenesis of HTN may be explored through genetic analysis. Papotti and his group[13] analyzed HTN for the presence of rearrangements of RET, the proto-oncogene associated with papillary carcinoma of the thyroid. They discovered that almost 30% of HTN lesions contained RET/PTC rearrangements. In a similar study, Cheung and coworkers[14] detected RET/PTC rearrangements in 75% of the HTN lesions studied. Both investigators support the theory that HTN is a subtype of PTC rather than a discrete thyroid lesion.

Livolsi[10] has argued that these studies do not conclusively refute the classification of "pure HTN lesions," without co-existing thyroid cancers as neoplasms of "very low malignant potential". Livolsi argues that the cases studied by Papotti[13] do not necessarily represent the same entity that Carney once described. Moreover, other workers have described RET/PTC rearrangements in other benign thyroid conditions. In 1997 Wirtschafer and colleagues[15] showed that 95% of cases of chronic lymphocytic thyroiditis displayed RET/PTC rearrangements. Furthermore, Bunone and his group of investigators[16] showed expression of RET proto-oncogene in normal thyroid follicular cells. This implies that RET/PTC rearrangements may not be as specific to PTC as previously assumed, and that the identification of these rearrangements in HTN does not necessarily suggest potential malignant behavior.

The classification of HTN as a variant of PTC, rather than as a discrete lesion of low malignant potential, has therapeutic consequence. If HTN is classified as a variant of PTC, then total thyroidectomy will be recommended for lesions meeting appropriate criteria. If HTN is a benign lesion, then lobectomy alone would be recommended, and the greater surgical risk of total thyroidectomy could be avoided.

CONCLUSION

Many investigators are concerned about the rarity of HTN and the prudence of making broad recommendations on the basis of a few cases. Currently, the most conservative treatment approach is to treat HTN as PTC. Total thyroidectomy may be recommended for HTN lesions meeting the same criteria as PTC for such surgery. HTN should still be considered a tumor of uncertain malignant potential. There have been no cases described nor recommendations made for post-operative radionuclide ablation in the treatment of HTN. Further study with adequate follow-up will continue to delineate the behavior and natural history of the lesion.

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