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# Enlarged thyroid gland with normal thyroid function tests

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A 41-year-old woman had a 1- to 2-cm asymptomatic thyroid mass, which had been monitored by an endocrinologist for several years with serial sonography. Noting that it had enlarged in the face of normal thyroid function tests, the endocrinologist ordered a fine-needle aspiration biopsy, which showed a cellular follicular lesion. Although some of the nuclear changes seen in papillary carcinoma were present, the cells did not fulfill all of the cytologic criteria for that diagnosis. The patient was referred to Baylor University Medical Center for surgery; she brought with her two ultrasound images *(Figure 1)* and a chest x-ray that showed a minimal leftward deviation of the trachea.

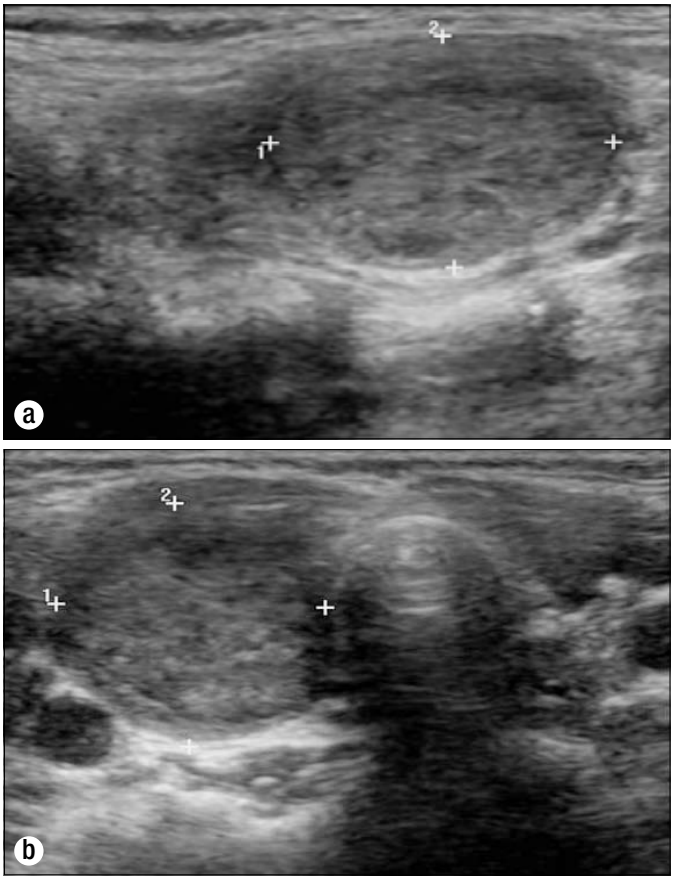


**Figure 1.** The two preoperative thyroid ultrasound images showing a well-circumscribed, solid lesion with heterogeneous echotexture. The mass was 2.4 cm (longitudinal) × 1.9 cm (anteroposterior) × 1.9 cm (transverse).

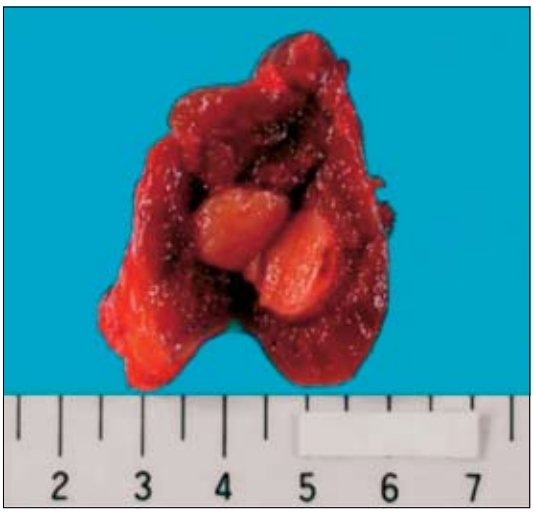


**Figure 2.** Gross features of a hyalinizing trabecular tumor of the thyroid. It has a delicately lobulated cut surface, with a yellow cast and gaping vessels.

A thyroidectomy was performed in the patient, and 15 lymph nodes in her neck were dissected from the central compartment of the neck. The excised mass was like a small rock *(Figure 2)*. The patient's surgery was uneventful, and she was discharged home. She had no postoperative complications and has been started on a replacement dose of levothyroxine. She has resumed all normal activities.

Pathological evaluation showed a 2.0 cm encapsulated nodule in the right lobe with a distinctly trabecular pattern, elongated tumor cells with enlarged nuclei with longitudinal grooves, occasional intranuclear cytoplasmic intrusions, and eosinophilic hyalin stroma. The features were strongly in favor of a hyalinizing trabecular tumor (HTT). There was advanced lymphocytic thyroiditis in the nonneoplastic right lobe parenchyma and in the left lobe *(Figure 3)*. The resected lymph nodes revealed no metastatic disease. The differential diagnosis

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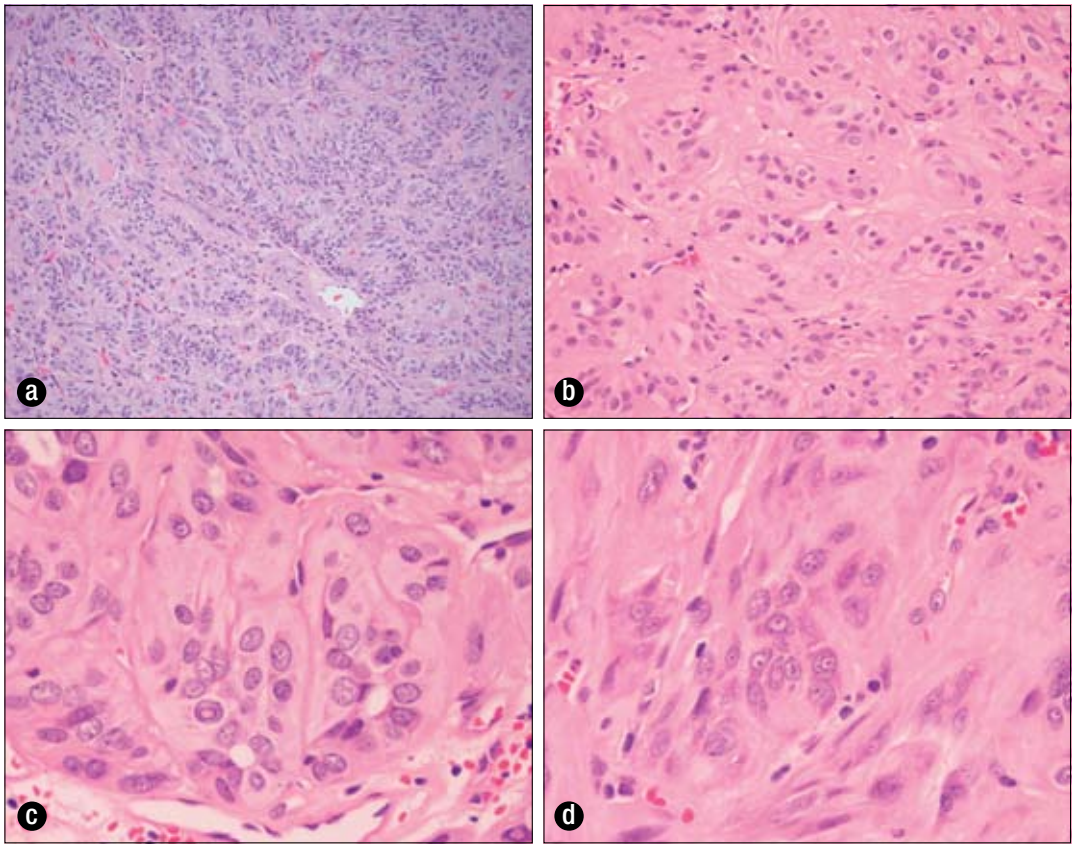


**Figure 3.** Hyalinizing trabecular tumor ("adenoma"). **(a)** A distinctive trabecular pattern is seen from low power in this encapsulated tumor. **(b)** Eosinophilic hyaline material is seen surrounding the tumor cells in many areas. **(c)** The nuclei are enlarged and elongated, with occasional intranuclear cytoplasmic inclusions. **(d)** Perinucleolar halos are a peculiar feature of hyalinizing trabecular tumor. Hematoxylin-eosin stain, ×10.

of HTT is chiefly medullary thyroid carcinoma and papillary thyroid carcinoma, since several histologic features are shared with these two entities. Immunohistochemical studies were positive for thyroglobulin and thyroid transcription factor-1 and negative for calcitonin, confirming the follicular cell origin of the tumor and excluding medullary thyroid carcinoma. An immunostain for the tumor proliferation marker MIB-1 demonstrated a distinctive cell membrane pattern that has been described in HTT but not in papillary carcinoma *(Figure 4)*. A test for the mesothelial cell surface protein recognized by monoclonal antibody HBME-1 was invalid, as it demonstrated patchy staining of the tumor and the nonneoplastic thyroid tissue in this case. Cytokeratin 19 was negative in the tumor cells.

**DIAGNOSIS:** Hyalinizing trabecular tumor.

## DISCUSSION

Since solitary thyroid nodules are present in nearly 10% of adults—and since 95% of these nodules are benign—it is important to be able to distinguish between thyroid cancer and benign growths. It is also important to better understand the implications of a diagnosis of an unusual thyroid neoplasm such as HTT. Although original descriptions of this lesion utilized the term "hyalinizing trabecular adenoma" and it was considered to be a variant of follicular adenoma, a significant controversy still surrounds HTT: it has been variously viewed as a variant of follicular adenoma, an indolent variant of papillary thyroid carcinoma, and a nonspecific growth pattern of thyroid neoplasia rather than a distinct clinicopathological entity (1–3).

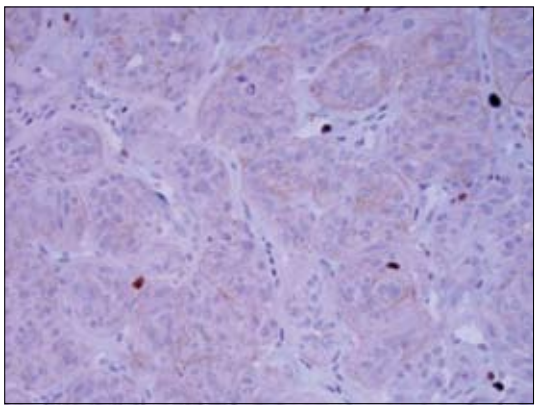

**Figure 4.** MIB-1 staining in the specimen demonstrates a very low proliferative index; the rare positive nuclei in this field are endothelial cell nuclei—no tumor cells are staining.

HTT occurs more often in women than in men, as do most thyroid neoplasms. It is unusual in patients under age 30, with incidence equally distributed in the fourth through seventh decades of life. HTT typically presents as a single, asymptomatic neck mass and appears as a "cold" nodule on thyroid scans (4). Grossly, the tumor is solitary, solid, and encapsulated, usually measuring ≤2.5 cm. Gross calcification is rare, though fine calcifications may be seen. The differential diagnosis includes papillary carcinoma, medullary

**Table 1. Microscopic features of hyalinizing trabecular tumors**

- A trabecular-alveolar growth pattern of medium-to large-sized cells
- Finely granular, acidophilic, or clear cytoplasm
- Round yellow paranuclear cytoplasmic bodies
- Polygonal and fusiform cells
- Nuclei with prominent grooves, small nucleoli, and cytoplasmic pseudoinclusions and with occasional mitotic figures
- Intratrabecular hyaline (Periodic acid Schiff–positive basement membrane material); this resembles amyloid but has a negative amyloid stain
- Arrangement of cells in sinuous or straight trabeculae supported by a delicate fibrovascular stroma (ranging from minimal to modest)
- Scant to absent colloid
- The possible presence of psammoma bodies
- The possible association of lymphocytic thyroiditis

**Table 2. Comparison of typical morphological and molecular features of benign and malignant thyroid lesions***

| Feature | Benign† | Hyalinizing trabecular tumor | Papillary thyroid carcinoma | Medullary thyroid carcinoma |
|---|---|---|---|---|
| Circumscription | + | + | –/+ | + |
| Predominant trabecular growth pattern | – | + | – | –/+ |
| Nuclear grooves | – (rare in adenomas) | + | + | Rare |
| Intranuclear pseudoinclusion | – | + | + | Rare |
| Hyaline material | – | + | – | + |
| Cytoplasmic yellow bodies | – | + | – (very rare) | – |
| Calcification/psammoma bodies | – | Rare | + | Rare |
| MIB-1 membranous and cytoplasmic | – | + | – | – |
| Cytokeratin 19 | –‡ | Usually – | + | – |
| Galectin 3 | –‡ | + 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 | + | + |

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†The benign category includes lymphocytic thryoiditis, nodular hyperplasia, and adenomas.
‡Positive in Hashimoto's thyroiditis.

carcinoma, paraganglioma, and follicular carcinoma with trabecular architecture.

In fine-needle aspiration samples, HTT is often interpreted as papillary carcinoma or occasionally as medullary carcinoma. Evenson and colleagues showed that of seven patients diagnosed with HTT, all had preoperative fine-needle aspiration biopsy findings that mentioned papillary carcinoma: in one case, papillary carcinoma was noted as "positive," in four cases, "suggestive," and in two cases, "suspicious" (5). Although a definitive diagnosis of HTT, with exclusion of papillary carcinoma, is often not possible on cytologic material, the high cellularity of the specimen in such cases is generally sufficient evidence to proceed with surgery with a presumptive diagnosis of a neoplastic thyroid nodule.

Microscopically, there are differences as well as similarities between HTT and papillary carcinoma, particularly for postoperative specimens. Some key microscopic features of HTT are summarized in *Table 1*.

Immunohistochemistry results for HTT are similar to those reported in our patient: i.e., positive results for thyroglobulin and thyroid transcription factor-1; a distinctive cell-membrane staining pattern for MIB-1; negative results for calcitonin and HBME-1; and either positive or negative results for cytokeratin 19, which is strongly and diffusely positive in papillary carcinoma (2, 3). Cheung and colleagues recently reported that HBME-1 positivity could be a marker of malignancy in nodules of follicular epithelial derivation (6). Unfortunately, the many reports of immunohistochemical studies in HTT, as well as in papillary carcinoma and follicular neoplasms in general, yield disparate results, making it impossible to rely on such ancillary studies for a definitive diagnosis or to answer the larger question of classification of HTT as a papillary or a follicular tumor.

Efforts have also been made to differentiate HTT from papillary carcinoma and other thyroid tumors based on molecular genetics. For instance, Baloch and colleagues reported that *BRAF* mutations were not present in two cases of classic HTT but were present in one case of trabecular papillary carcinoma (7). In general, *BRAF* mutations are present in 36% to 69% of cases of papillary carcinoma (8). RET/PTC1 somatic translocations have been reported by two independent groups in 21% to 62% of cases of HTT (9, 10). Doubt has been cast on the validity of these findings due to the presence of classical papillary carcinoma in some lesions, the lack of specificity of reverse transcriptase polymerase chain reaction for the RET/PTC1 transcript, and the fact that Hashimoto's thyroiditis can be shown to have the same rearrangement (11). Some of the differentiating morphological and molecular features of benign and malignant thyroid lesions are summarized in *Table 2*.

In the end, morphology remains the gold standard for making a diagnosis of HTT. A lesion with the classic histologic features of HTT, without capsular or vascular invasion, almost invariably behaves as a benign neoplasm. In light of the lingering controversy, however, patients with HTT should receive clinical follow-up.


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