

Hyalinizing trabecular tumor of the thyroid gland: A case report and a brief review of the literature

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Abstract

Thyroid hyalinizing trabecular tumors (HTTs) are rare benign tumors that often mimic other malignant tumors, posing a diagnostic challenge. We report a case of a 39-year-old female with no significant past medical history who presented to her family physician for a routine annual visit. On thyroid palpation, a firm, non-tender nodule was felt in the right lobe. The patient denied awareness of the nodule or experiencing any symptoms, such as weight loss or gain, heat or cold intolerance, or neck pain. Thyroid laboratory studies were unremarkable, and thyroid peroxidase and thyroglobulin antibody tests were negative. Thyroid ultrasound revealed a solid, hypoechoic mass measuring 2.1 x 1.8 x 1.6 cm in the right lobe. There was heterogeneous echogenicity with multiple scattered microcalcifications, increased vascularity, and irregular margins, which raised suspicion for malignancy. Fine needle aspiration (FNA) was performed, and the cells were found to be aggregated in clusters, some forming trabeculae, with nuclear grooves and occasional intranuclear pseudoinclusions, which suggested papillary thyroid carcinoma (PTC). FNA results were challenging to differentiate from malignancy, given the absence of typical architectural patterns for PTC. A diagnostic hemithyroidectomy was performed. Histopathological examination and immunohistochemistry (IH) studies showed tumor cells positive for MIB-1, thyroglobulin (Tg), and TTF-1. Final diagnosis of thyroid HTT was made. Considering it is a benign neoplasm, and the patient already had a right hemithyroidectomy, there was no indication for further surgery. The patient's remaining thyroid function was normal, and she did not require any hormone replacement. Three years after initial diagnosis, the patient reported no symptoms or signs of recurrence. This case details a rare benign tumor that closely mimics malignancy, highlighting the importance of a thorough diagnostic workup to ensure accurate diagnosis

Keywords: Thyroid Hyalinizing Trabecular Tumors; Benign; Mimic; Papillary Thyroid Carcinoma; PAX8–GLIS3

1. Introduction

Hyalinizing trabecular tumor (HTT) of the thyroid is a rare thyroid tumor of follicular origin. It displays characteristics of trabecular growth and marked intra- and intertrabecular hyalinization. Prior to HTT being recognized as an independent neoplasm because of its distinct molecular and clinicopathologic features, it was initially regarded as a PTC variant due to shared nuclear features. There have been an increasing number of publications establishing HTT as a separate disease. [1] [2] Recent molecular studies have revealed that HTT is defined by specific gene fusions, most often

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PAX8-GLIS3, and less commonly PAX8-GLIS1, that set it apart from PTC and other thyroid tumors derived from follicular cells. [2] [3] [4] These gene fusions lead to increased GLIS expression and enhanced transcriptional regulation of the extracellular matrix, including type IV collagen, contributing to the thick, hyalinized stroma. [4]

On histological examination, HTTs typically appear as well-circumscribed or encapsulated nodules comprising trabecularly arranged polygonal or spindle-shaped epithelial cells, associated with variable amounts of hyaline-like material resembling amyloid. [5] Nuclear grooves or nuclear matrix elements, similar to cytoplasmic inclusions, are often found within the nucleus, which can pose challenges for pathologists diagnosing PTC through FNA cytology. [6] HTT does not express HBME1 or CK19 (both markers for PTC) and has a distinct membranous staining pattern for MIB-1 (Ki-67). [5]

Long-term follow-up after the surgical removal of HTT has shown that there is little, if any, possibility that these tumors will recur, invade, or metastasize. [1] In line with this encouraging evidence, the American Thyroid Association (ATA) currently considers HTTs to be tumors of extremely low malignant potential. It does not support the use of total thyroidectomy, lymph node removal, or radioactive iodine treatment as standard treatment for HTT patients. [7] We report this case to highlight the challenges in diagnosing HTTs and emphasize the role of molecular and immunohistochemical features in HTT classification.

2. Case presentation

2.1. Clinical presentation

A 39-year-old female presented to her primary care physician for a routine annual examination. During thyroid palpation, a solitary, firm, non-tender nodule measuring approximately 2 cm was detected in the right thyroid lobe. The patient reported no compressive symptoms such as dysphagia, dyspnea, or voice changes. She had not noticed the nodule herself and was entirely asymptomatic. There was no history of neck pain, weight changes, heat or cold intolerance, palpitations, or other thyroid dysfunction symptoms. The nodule had been present for an unknown duration, given its size. Following detection, the primary care physician ordered thyroid function tests, which returned to normal limits, and referred the patient to endocrinology for further evaluation. The incidental nature of the discovery and the need to exclude malignancy prompted a comprehensive workup, including imaging and fine-needle aspiration.

2.2. History, physical examination, and laboratory studies

The patient's past medical history was unremarkable, with no previous thyroid disease, neck irradiation, or autoimmune conditions. She had regular menstrual cycles and no symptoms of hormonal imbalance. Family history was significant for hypothyroidism in her mother (diagnosed in her 50s) but negative for thyroid cancer, multiple endocrine neoplasia syndromes, or other familial thyroid disorders. She denied radiation exposure during childhood, did not reside in iodine-deficient areas, and had no occupational exposures. She was a non-smoker and consumed alcohol occasionally.

On physical examination, vital signs were stable with blood pressure 118/76 mmHg, heart rate 72 bpm, and temperature 36.8°C. The general appearance was well-nourished and in no distress. Head and neck examination revealed a palpable, firm, smooth, mobile nodule in the right thyroid lobe, measuring approximately 2 cm in maximum dimension. The nodule moved with swallowing. No cervical lymph nodes were found to be enlarged on either side. The left thyroid lobe appeared normal on palpation. Cardiovascular and respiratory examinations were unremarkable, with no signs of thyrotoxicosis or hypothyroidism.

Laboratory studies included thyroid-stimulating hormone (TSH) 1.8 mIU/L, free T4 1.2 ng/dL, and free T3 3.1 pg/mL, all within normal limits. Thyroid peroxidase antibodies and thyroglobulin antibodies were negative. Complete blood count, comprehensive metabolic panel, and calcium levels were all within normal limits.

2.3. Radiographic studies

Thyroid ultrasonography demonstrated a 2.1 × 1.8 × 1.6 cm solid, hypoechoic nodule in the right thyroid lobe with well-defined but irregular margins. The nodule showed heterogeneous echogenicity with scattered internal microcalcifications. Color Doppler imaging revealed increased intranodular vascularity with a central vascular pattern. No notable cystic areas or large calcifications were found. The left lobe appeared normal without nodules. No pathologically enlarged cervical lymph nodes were detected.

The sonographic features raised concern for malignancy, including hypoechogenicity, microcalcifications, irregular margins, and increased vascularity. The differential diagnosis included PTC (given microcalcifications and hypoechogenicity), follicular neoplasm, medullary thyroid carcinoma (less likely without lymphadenopathy), or potentially a HTT. However, HTT cannot be reliably distinguished sonographically from papillary carcinoma. The Thyroid Imaging Reporting and Data System (ACR TI-RADS) scoring suggested moderate-to-high suspicion warranting Fine-needle aspiration (FNA). Cytology evaluation of the FNA slides demonstrated cellular smears with cells arranged in clusters and occasional trabeculae. The cells displayed elongated nuclei with prominent nuclear grooves and occasional intranuclear pseudoinclusions, features that raised concern for PTC. However, the chromatin pattern appeared different from that of classic papillary carcinoma, and the cytoplasm was amphophilic to eosinophilic. Numerous regions showed extracellular hyaline material. The cytological impression was "suspicious for malignancy, favor papillary thyroid carcinoma, recommend surgical excision."

2.4. Tumor board discussion

The case was presented to the multidisciplinary endocrine tumor board, which included endocrinologists, head & neck surgeons, pathologists, and radiologists. Discussion centered on the cytological ambiguity of the FNA results. The imaging characteristics and cytology findings together raised suspicion for malignancy.

The board discussed diagnostic challenges, noting that HTT frequently mimics PTC on both cytology and frozen section. Given the diagnostic uncertainty and the possibility of malignancy, the recommendation was diagnostic hemithyroidectomy (right lobectomy) to obtain PTC examination, immunohistochemical (IHC) studies, and molecular testing if needed, while avoiding overtreatment if the lesion proved benign. The patient was informed about the risks of surgery and advised that total thyroidectomy might be necessary depending on the final pathology results.

2.5. Tissue diagnosis

The right hemithyroidectomy specimen revealed a well-circumscribed, encapsulated tan-yellow tumor measuring 2.2 cm in greatest dimension. The cut surface was solid and homogeneous without necrosis or hemorrhage. The tumor did not extend beyond the capsule, and surgical margins appeared clear. Microscopic examination showed a well-demarcated neoplasm composed of polygonal to elongated cells arranged in trabecular and nested patterns. The trabeculae were encased in notable hyalinized stroma that contained abundant type IV collagen. Tumor cells exhibited elongated nuclei with fine chromatin, nuclear grooves, and occasional intranuclear cytoplasmic pseudoinclusions mimicking papillary carcinoma. No capsular or vascular invasion was identified. No psammoma bodies were present. (Figure 1 A, B, C)

IHC studies showed strong membranous positivity for MIB-1 (Ki-67 <2%, low proliferative index). The tumor was positive for thyroglobulin and TTF-1, confirming thyroid follicular cell origin. Critically, the tumor was negative for cytokeratin 19 and galectin-3, markers typically positive in papillary carcinoma. Hector Battifora Mesothelial-1 (HBME-1) showed weak focal staining. Molecular studies revealed that the BRAF V600E mutation was not found. RET/PTC rearrangements were absent.

The key differential diagnoses included PTC (excluded by IHC pattern and molecular findings), follicular adenoma (different architecture), and medullary carcinoma (calcitonin-negative). The final diagnosis rendered was hyalinizing trabecular tumor (HTT) of the thyroid.

2.6. Treatment, Outcome, Follow-up, and Patient Status

Following definitive diagnosis of HTT, the multidisciplinary team reviewed the case. Since HTT is classified as a benign neoplasm by the WHO and was completely removed with clear margins, further surgery was not advised. It was determined that thyroidectomy completion was unnecessary. The patient did not require radioactive iodine therapy or thyroid hormone suppression therapy.

Postoperatively, the patient recovered uneventfully. Since her remaining thyroid lobe was working properly, she did not require any thyroid hormone replacement. She was placed on active surveillance with clinical examination and neck ultrasonography every 6-12 months initially, then annually.

At three years post-diagnosis, the patient remained clinically well and disease-free. Serial thyroid ultrasounds showed a normal left thyroid lobe without nodules or suspicious features. There was no evidence of local recurrence at the surgical site, and no cervical lymphadenopathy was present. Thyroid function tests remained within normal limits throughout follow-up. She required no medical or surgical interventions beyond the initial hemithyroidectomy.

The patient expressed satisfaction with her care and outcomes. She maintained regular follow-up appointments and continued annual surveillance imaging. Her case exemplified the importance of accurate pathological diagnosis in distinguishing HTT from thyroid malignancy to avoid unnecessary aggressive treatment while ensuring appropriate monitoring.

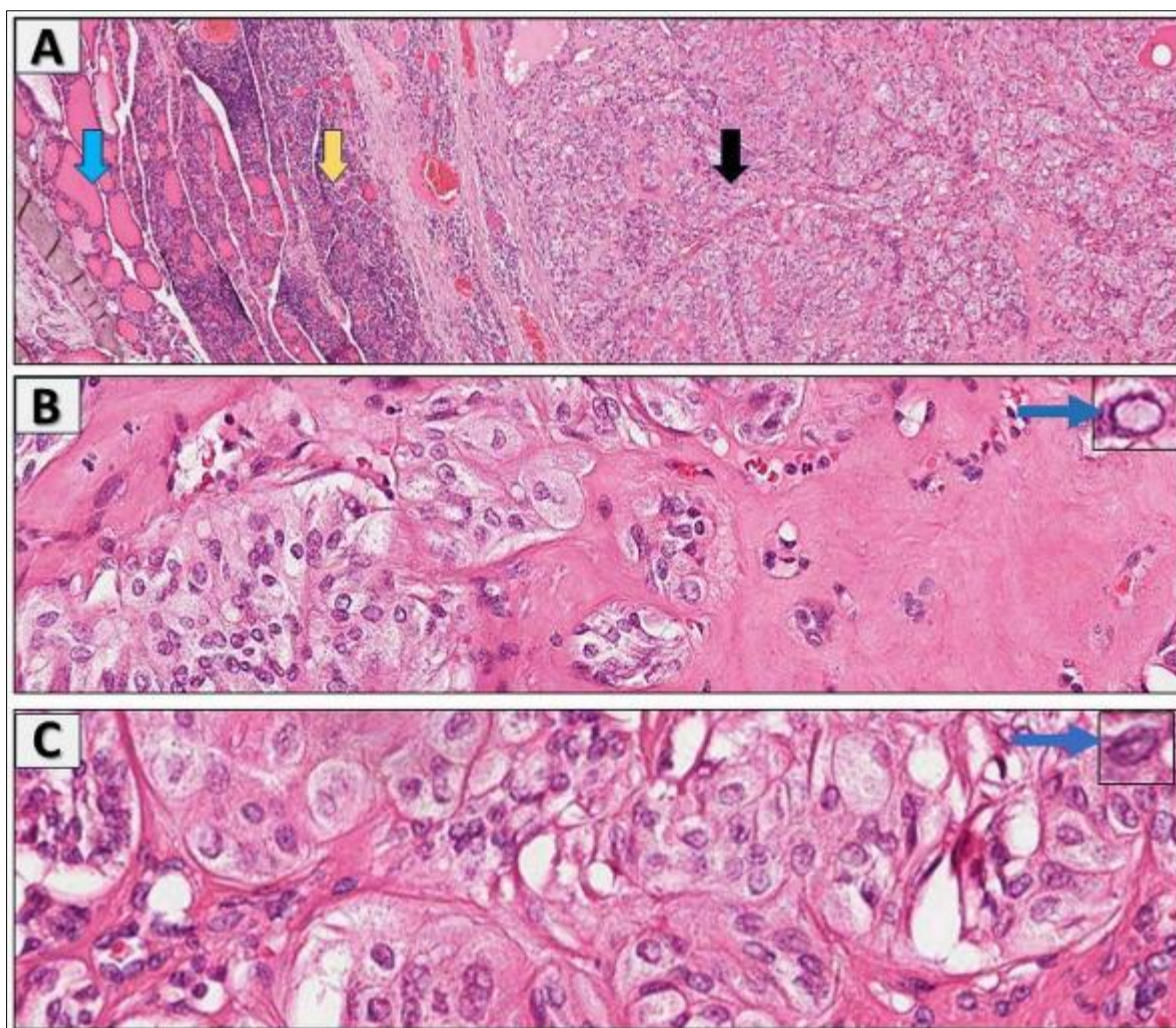


Figure 1 Microscopic features of the excised hyalinizing trabecular tumor of the thyroid gland

- **1A:** Low power view showing normal thyroid tissue (blue arrow), chronic inflammation of thyroid tissue (yellow arrow), and the well-defined tumor of hyalinized trabecular tumor (black arrow) (H&E X20).
- **1B:** High power view showing strong hyalinized stroma (right side). Blue arrow showing intranuclear inclusion (H&E X40).
- **1C:** High power view showing eosinophilic granular cytoplasm. Blue arrow showing nuclear groove (H&E X60)

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

HTT of the thyroid is a rare neoplasm of follicular cell origin, first described in detail by Carney and colleagues in 1987 as "hyalinizing trabecular adenoma". Initially considered a benign adenoma due to its circumscribed nature and indolent behavior, its classification has been a subject of debate. [8] The presence of nuclear features overlapping with PTC, such as nuclear grooves and pseudoinclusions, led to the more neutral term "hyalinizing trabecular tumor". [8] [9]

HTT is an uncommon tumor, accounting for less than 1% of all primary thyroid neoplasms. It demonstrates a significant female predominance, with a female-to-male ratio of approximately 6:1. The tumor typically affects middle-aged adults,

with a mean age at diagnosis in the fifth decade of life. [10] Most patients are asymptomatic, and the tumor is often discovered incidentally as a solitary, well-circumscribed thyroid nodule during physical examination or neck ultrasonography. [11] There are no well-defined genetic, environmental, or occupational risk factors. [12] However, a few cases have been reported following radiation exposure, and they can arise in thyroids with chronic lymphocytic thyroiditis or multinodular goiter. [13]

The 2022 World Health Organization (WHO) classification of thyroid tumors categorizes HTT as a "low-risk neoplasm". This classification acknowledges its overwhelmingly benign clinical course, with metastases being exceptionally rare. [14] Despite this, the potential for malignancy, though very low, is recognized, and rare cases of "hyalinizing trabecular carcinoma" with invasion or metastasis have been reported. [15]

3.2. Pathogenesis, Pathophysiology

The biological relationship of thyroid HTT to PTC was suggested by two publications reporting that HTT frequently harbors RET/PTC rearrangements, a characteristic genetic feature of PTC. However, these reports themselves sparked controversy due to concerns about the histologic criteria for tumor selection and the use of highly sensitive assays for RET/PTC detection, which are prone to false-positive results. [2] [4] A subsequent study revealed no RET/PTC rearrangements in a series of 18 HTT analyzed by reverse transcription polymerase chain reaction (RT-PCR). Furthermore, these tumors were found to harbor no BRAF or RAS mutations, which are highly prevalent in classic PTC and the follicular variant, suggesting that HTT is a distinct tumor and not a variant of PTC. [2] [4]

A 2019 study, followed by another study in 2025, found that GLIS fusion is a genetic hallmark of HTT. The tumor is driven by recurrent chromosomal rearrangements that generate gene fusions between PAX8 and either GLIS3 or GLIS1. The predominant fusion, identified in approximately 93% of cases, is, which results from an interchromosomal rearrangement involving PAX8 on chromosome 2q14.1 and GLIS3 on chromosome 9p24.2. PAX8-GLIS1 is a less common fusion identified in about 7% of cases and results from an interchromosomal rearrangement involving PAX8 and GLIS1. PAX8 is a transcription factor that is prominently present in differentiated thyroid follicular cells and is essential for normal thyroid development and function. GLIS1 and GLIS3 belong to the GLI-similar zinc finger transcription factor family, and they act as either transcriptional activators or repressors. In the thyroid, GLIS3 is an important regulator of thyroid hormone biosynthesis. The PAX8-GLIS gene fusions result in marked overexpression of the 3' regions of the GLIS genes, while preserving the DNA-binding zinc finger domain. As a result, PAX8-GLIS3 fusion-positive tumors demonstrate consistent upregulation of extracellular matrix-related genes, including multiple collagen genes such as COL4A1, which encodes the $\alpha 1$ chain of collagen IV. This molecular alteration likely underlies the excessive production and deposition of collagen IV and other collagens in HTT, leading to the prominent hyalinization, a hallmark microscopic feature of these tumors. [2] [10]

3.3. Comparative analysis of our case with the existing literature. (Clinical-radiology-pathology, lab, diagnosis-management, and outcome)

Our case aligns with existing literature in several key aspects. The patient's presentation with an asymptomatic thyroid nodule, discovered incidentally, is the most common clinical scenario reported for HTT. [11] The diagnostic challenge we faced, particularly the difficulty in distinguishing HTT from PTC on FNA, is a recurrent theme in the literature. [16] Several reported cases are initially diagnosed as "suspicious for PTC" on cytology due to overlapping nuclear features such as grooves and pseudoinclusions, with the correct preoperative diagnosis achieved in fewer than 10% cases. [12] [13] [17] This often leads to a more extensive surgical approach, such as total thyroidectomy, which may not be necessary for a low-risk lesion.

The definitive diagnosis in our case, relying on the characteristic histopathology of a trabecular growth pattern with intratrabecular hyalinization, and confirmed by IHC, is consistent with the diagnostic pathway described in numerous studies. [5] [10] [12] The use of MIB-1 (Ki-67) staining, which shows a distinctive membranous pattern in HTT, is highlighted in the literature as a key feature for differentiating it from PTC. [12] Furthermore, the absence of BRAF and RAS mutations and the presence of a PAX8-GLIS fusion, if evaluated, would be another point of concordance with the now well-established molecular profile of HTT. [10] [18]

One of the most important lessons from comparing our case with literature is the value of considering HTT in the differential diagnosis of thyroid nodules, especially those with FNA results suspicious for PTC but lacking other malignant ultrasound features. This consideration can help prevent overtreatment. The literature strongly supports a conservative surgical approach, such as a lobectomy, for confirmed HTT, given its overwhelmingly benign course. [7] Our case reinforces the knowledge that while HTT can mimic more aggressive cancers cytologically, its clinical behavior is indolent, and the prognosis is excellent with complete excision. [9]

4. What have we learned from this case?

This case offers useful clinical insights. The primary diagnostic lesson is the importance of maintaining a high index of suspicion for HTT when faced with a thyroid nodule cytologically suspicious for PTC but with benign ultrasound features. Clinicians should recognize the red flag of this discordance between cytology and imaging. This case reinforces that the classic nuclear features of PTC are not exclusive to it and can be a pitfall leading to an initial misdiagnosis and potential overtreatment.

The implications for management are significant. An intraoperative frozen section can be misleading, and a definitive diagnosis often requires permanent sections and ancillary studies, such as MIB-1 IHC and molecular testing for PAX8-GLIS fusions. This case highlights that a conservative surgical approach, such as a thyroid lobectomy, is often sufficient for HTT, thereby avoiding the risks and lifelong hormone replacement associated with a total thyroidectomy. This has a direct impact on future practice by encouraging a more nuanced approach to surgical decision-making. Some studies even suggest that active surveillance can be a valid strategy for tumors cytologically diagnosed as HTT with high confidence. [19] The case reinforces the existing knowledge that a subset of these tumors is low risk, such as HTT, and can be managed more conservatively.

Abbreviations

- Thyroid hyalinizing trabecular tumors (HTTs);
- Fine needle aspiration (FNA);
- Papillary thyroid carcinoma (PTC);
- Immunohistochemistry (IH)

5. Conclusion

Hyalinizing Trabecular Tumor (HTT) of the thyroid is a rare, low-risk neoplasm that presents a significant diagnostic challenge due to its cytological and histological mimicry of more aggressive thyroid malignancies, particularly papillary and medullary thyroid carcinomas. This case aims to highlight the typical clinicopathological characteristics of HTT and emphasize why it should be considered when evaluating thyroid nodules with uncertain or suspicious cytology. The value of this case to the medical community lies in its reinforcement of the need for a comprehensive diagnostic approach that integrates clinical, radiological, cytological, histological, and ancillary findings to arrive at an accurate diagnosis. Recognizing the characteristic features of HTT, such as its unique MIB-1 staining pattern and pathognomonic PAX8-GLIS gene fusion, can prevent overtreatment and lead to more appropriate, conservative management, ultimately improving patient outcomes.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

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- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

Ethical review and approval were not required for this study involving human participants. The paper has been sufficiently anonymized to maintain the patient's confidentiality.

Statement of informed consent

This study was conducted as a retrospective review of archival pathology material collected during routine clinical care. All data were fully de-identified prior to analysis. No patient contact or intervention was involved, and informed consent was not required in accordance with institutional policies.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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