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Hyalinizing Trabecular Tumor of the Thyroid Gland: A Diagnostic and Surgical Challenge

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Abstract

Hyalinizing trabecular tumors (HTTs) of the thyroid are rare benign neoplasms that often mimic papillary thyroid carcinoma (PTC) and medullary thyroid carcinoma (MTC) on cytology, creating significant diagnostic challenges. We present a case of a 38-year-old female with a 4.2 cm right thyroid nodule. Fine-needle aspiration biopsy revealed overlapping nuclei, grooves, pseudoinclusions, and stromal hyaline material, which are suspicious features of malignancy (Bethesda category V). The patient underwent total thyroidectomy. Histology showed a well-encapsulated trabecular neoplasm with extensive stromal hyalinization. Immunohistochemistry was thyroglobulin and thyroid transcription factor-1 positive, and calcitonin, chromogranin A, and carcinoembryonic antigen negative, confirming HTT. Despite these tumors being, for the most part, benign, their cytological overlap with PTC and MTC usually results in misdiagnosis and overtreatment, including unnecessary total thyroidectomy. The lack of uniform cytological or molecular markers also renders preoperative diagnosis more challenging. The current case outlines the diagnostic dilemma of HTTs and the need for improved diagnostic tools to guide appropriate management and prevent overtreatment of this otherwise benign tumor.

Categories: Internal Medicine, Endocrinology/Diabetes/Metabolism
Keywords: fine-needle aspiration biopsy, hyalinizing trabecular tumor, medullary thyroid carcinoma, papillary thyroid carcinoma, thyroidectomy, thyroid neoplasm

Introduction

Hyalinizing trabecular tumors (HTTs) are very rare thyroid tumors first described in detail by Carney et al. in 1987 [1]. These tumors usually have a slow, benign course and are more common in females, often appearing as painless, single nodules in middle-aged adults [2]. Diagnosing these tumors before surgery has been difficult because they lack distinctive cytologic features. HTTs can be mistaken for other thyroid cancers because their hyalinized stroma looks like the amyloid deposits in medullary thyroid carcinoma (MTC), and their elongated cells with nuclear grooves and pseudo-inclusions resemble those seen in papillary thyroid carcinoma (PTC) [3]. So far, no specific cytological or molecular markers have allowed for a reliable preoperative diagnosis. The presence of hyaline material in cytology samples can be misleading and does not rule out PTC or MTC.

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Case Presentation

We herein present a 38-year-old Caucasian female, a non-smoker with a disease-free medical history, who was found to have a right-sided, clearly delimited, large hypoechoic thyroid lesion measuring 4.2 cm in its greatest dimension, as detected by neck sonography. On detailed sonographic characterization, the mass was solid, hypoechoic, and sharply delimited with smooth, regular margins and a distinct peripheral halo. Color Doppler interrogation demonstrated prominent mixed perinodular and intranodular vascularity. There were no microcalcifications, macrocalcifications, or features suggestive of extrathyroidal extension, and the bilateral cervical lymph nodes showed normal fatty hilum architecture without suspicious adenopathy, consistent with an intermediate-risk Thyroid Imaging Reporting and Data System (TI-RADS) 4 pattern. Her family history was unremarkable. The patient underwent a fine-needle aspiration biopsy (FNAB), which showed overlapping elongated nuclei, nuclear grooves, pseudoinclusions, and stromatic hyaline material between the cell clusters. Based on the above-mentioned cytological features, the lesion was characterized as suspicious for malignancy (category V, according to the Bethesda System for Reporting Thyroid

Cytopathology), and the differential diagnosis included an HTT [4]. A total thyroidectomy was performed. Histologic examination confirmed a 4.2 cm encapsulated nodule on the right side of the thyroid gland. The tumor cells were polygonal to elongated with eosinophilic cytoplasm and arranged in an alveolar or trabecular pattern, while extensive hyaline material was present in the stroma. Their nuclei exhibited nuclear grooves and pseudoinclusions. Immunohistochemical staining showed positivity for thyroid transcription factor-1 (TTF-1) and thyroglobulin (Tg), and negativity for chromogranin A (CgA), calcitonin, carcinoembryonic antigen (CEA), cytokeratin 19 (CK19), and HBME-1 (Figures *1*-*4*). The Ki-67 proliferation index was exceptionally low, quantified at less than 1%, but demonstrated a highly characteristic, diffuse membranous immunoreactivity pattern (Figure *4*). These findings were compatible with thyroid HTTs. The postoperative period following total thyroidectomy was uncomplicated, characterized by the absence of surgical complications, such as hypocalcemia or recurrent laryngeal nerve injury. The patient was successfully transitioned to levothyroxine replacement therapy to maintain euthyroidism. Given the definitive diagnosis of a benign HTT and the absence of vascular or capsular invasion, no further treatment was needed. At the most recent follow-up (one year after surgery), the patient remains in clinical remission with undetectable serum thyroglobulin levels and no sonographic evidence of local recurrence.

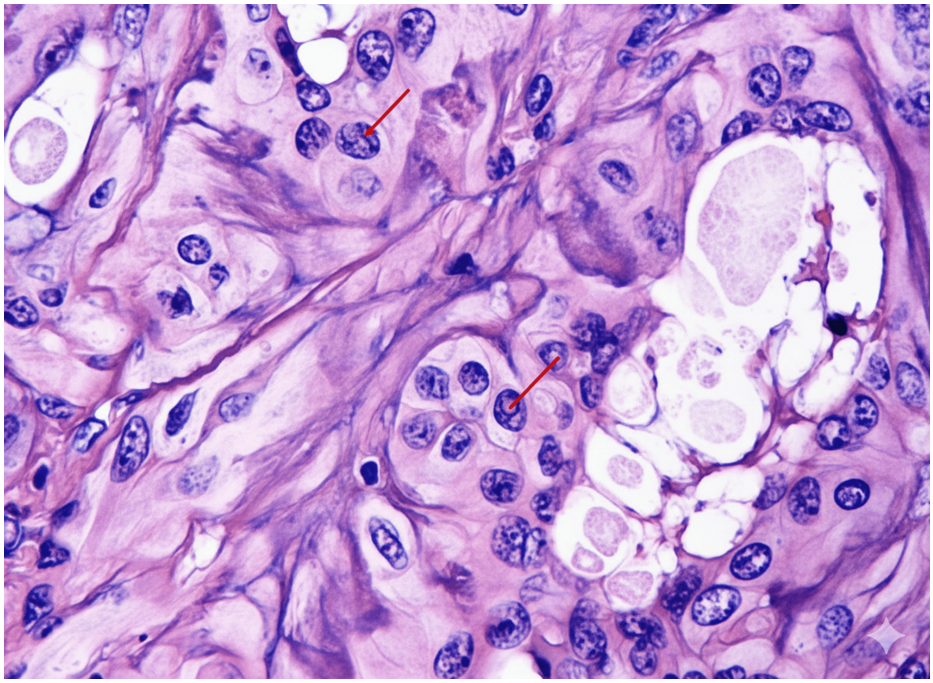


FIGURE 1: Hyalinizing trabecular tumor of the thyroid gland (hematoxylin and eosin, x400).

Large, polygonal to fusiform cells with abundant cytoplasm surrounding oval to elongated nuclei. Nuclear grooves and intracytoplasmic inclusions are easily identified (arrows).

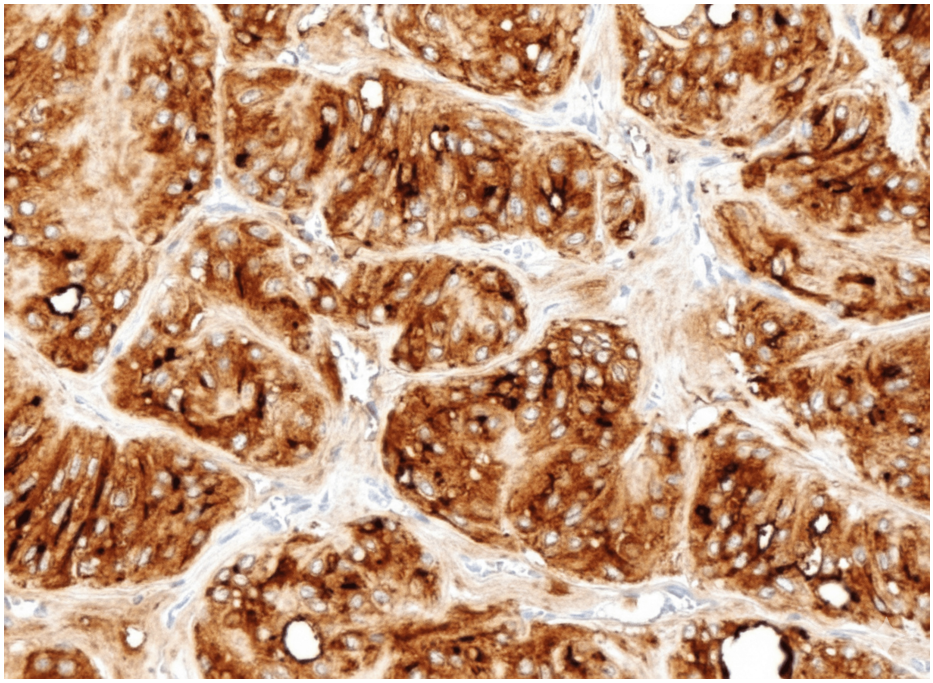


FIGURE 2: Hyalinizing trabecular tumor of the thyroid gland with diffuse strong thyroglobulin immunohistochemical expression (hematoxylin and eosin, x400).

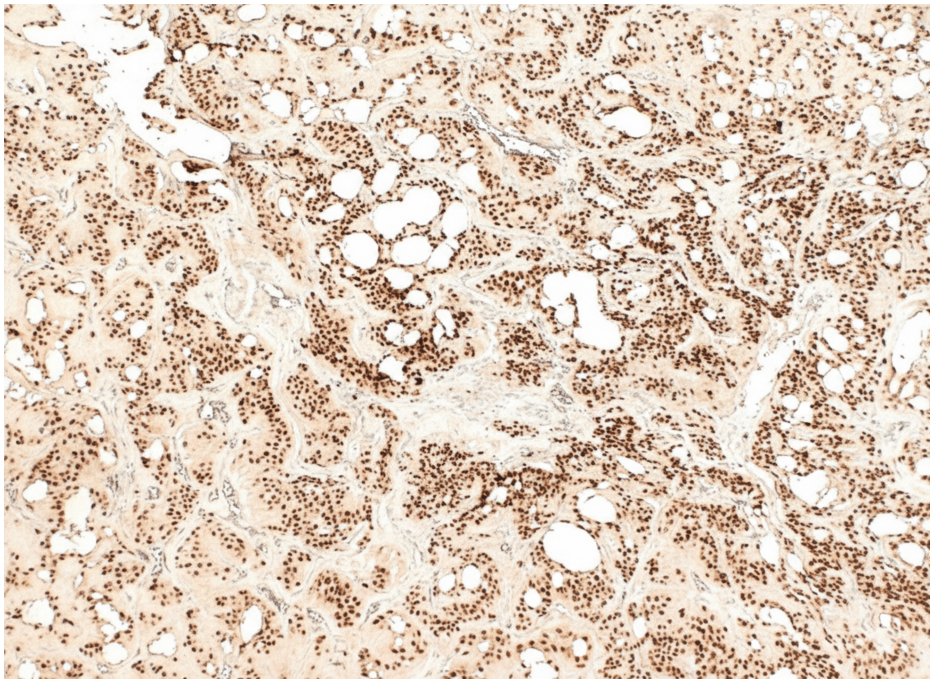


FIGURE 3: Hyalinizing trabecular tumor of the thyroid gland with diffuse strong nuclear thyroid transcription factor-1 (TTF-1) immunohistochemical expression (hematoxylin and eosin, x100).

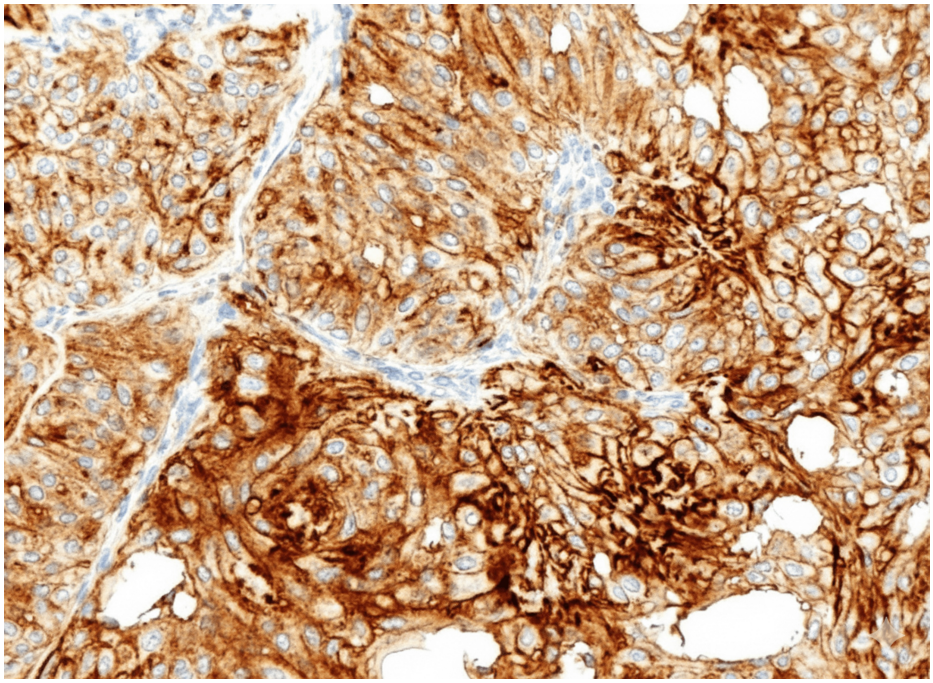


FIGURE 4: Hyalinizing trabecular tumor of the thyroid gland with diffuse strong membranous Ki-67 immunoreactivity (hematoxylin and eosin, x400).

Discussion

Even though HTTs are classified as sporadic benign thyroid neoplasms, there is an ongoing debate about the benign or malignant potential of such neoplasms. Some authors consider these neoplasms as a variant of PTC because of the detection of cytological features such as nuclear overlapping, grooves, and pseudoinclusions, as well as expression of RET/PTC rearrangements [5]. In our case, FNAB demonstrated suspicion of PTC or the possibility of an HTT, and thus we proceeded to total thyroidectomy.

Recent advances in molecular analysis have distinguished HTT from PTC, confirming HTT as a distinct genetic entity. While classical PTC is primarily associated with the BRAFV600E mutation, RET/PTC gene rearrangements, or RAS mutations, next-generation sequencing (NGS) has demonstrated that HTTs lack these alterations. Instead, HTT is characterized by specific fusions in the GLIS family of transcription factor genes, including PAX8-GLIS3 and PAX8-GLIS1. These GLIS1/3 translocations serve as definitive biomarkers for HTT and are absent in PTCs, follicular thyroid carcinomas, and MTCs. Incorporating these fusions into preoperative molecular panels, such as ThyroSeq, enables reliable differentiation of HTT from malignant mimics, thereby reducing the risk of misdiagnosis and unnecessary total thyroidectomies for this benign tumor [6].

The histology after thyroidectomy did not show vascular invasion or invasion into the surrounding thyroid tissue. Due to the uncertain malignant potential of the neoplasm, the initial terminology has changed, and finally, these neoplasms are described as HTTs [3]. On the other hand, HTTs can be confused with MTC, especially the encapsulated variant. Stromal hyalinization and the presence of spindle cells are microscopic features of the MTC [7]. In our case, immunohistochemistry showed positivity for TTF-1 and Tg and negativity for calcitonin and CEA, so the diagnosis of MTC was excluded. Furthermore, although Ki-67 is typically a nuclear marker, the unique and intense membranous staining observed in this case is a well-documented paradoxical feature of HTT. This finding further supports the definitive diagnosis, despite the low proliferation index. Given the fact that HTTs of the thyroid gland are benign and cytological findings based on FNAB cannot safely and with a high degree of certainty distinguish them from PTC and MTC, patients are still overtreated with thyroidectomy (total or subtotal) [8]. Thus, novel cytologic features, including molecular panels unique for HTTs, would be of great value for pre-surgery recognition and prevention of overtreatment with thyroidectomy for treating an almost benign disease.

Conclusions

Treatment of HTTs remains conservative. The patient's follow-up after thyroidectomy remains the same as that followed after surgical removal of a thyroid neoplasm with low malignant potential.

We present this unusual case to emphasize that, because of the lack of clear diagnostic criteria for HTTs, patients are often treated with total thyroidectomy, which could have been avoided if the results of the initial cytological examination were specifically diagnostic for HTT.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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