Hyalinizing trabecular tumor of the thyroid: A case report

LUYAO ZHANG[1], QIANG MA[2], ZHIXIN SHEN[1] and LU GUO[3]

[1]Department of Thyroid and Breast Surgery, Affiliated Hospital of Shandong Second Medical University, Weifang, Shandong 261042, P.R. China; [2]Department of Pathology, Sunshine Union Hospital, Weifang, Shandong 261000, P.R. China; [3]Department of Oncology, Affiliated Hospital of Shandong Second Medical University, Weifang, Shandong 261042, P.R. China

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Abstract. A hyalinizing trabecular tumor (HTT), characterized by a trabecular growth pattern and notable hyalinization within the trabeculae, occurs at a rate of ~1%. As patients with HTT may be asymptomatic, accurate diagnosis is a challenge. Due to its resemblance to other tumors, such as papillary thyroid carcinoma and medullary thyroid carcinoma, a precise diagnosis necessitates both pathological and molecular examinations. Additionally, HTT is potentially malignant. The present study described the clinicopathological diagnosis of a patient with HTT; highlighting how an understanding of the clinical and pathological features of HTT is needed to provide an accurate differential diagnosis and thus tailor the treatment approach in order to effectively manage the disease.

Introduction

Rare follicular epithelium-derived hyalinizing trabecular tumor (HTT) comprises 1% of thyroid tumors and is often associated with favorable prognosis (1,2). Previous studies indicate that HTT constitutes only 1% of all thyroid tumors and can occur in individuals aged between 40-70 years (3,4). Due to its clinical rarity, there are several uncertainties in the diagnosis and treatment of this disease.

Whether HTT is benign or malignant remains controversial. Although HTT is typically benign, it is considered a borderline tumor with malignant potential due to reports of invasion and metastasis in a number of cases (4,5). HTT can transform malignantly into PTC (6).

HTT exhibits a prominent trabecular pattern, abundant intratrabecular hyalinized stroma and characteristic nuclear features of papillary carcinoma (7).

The cytological and histopathological diagnosis of HTT is challenging (8) and it is necessary to differentiate HTT from other diseases such as papillary thyroid carcinoma, medullary thyroid carcinoma and non-invasive follicular thyroid neoplasm with papillary-like nuclear features as it guides the treatment process. Due to the predominantly benign biological characteristics of HTT, surgical resection followed by long-term follow-up is sufficient for its management (9). Using ultrasonography, histopathology and an analysis of the clinical symptoms, the present study described a patient with HTT.

Case report

A 31-year-old female patient, during a routine health checkup at the Affiliated Hospital of Shandong Second Medical University (Weifang, China), in January 2022, was found to have a thyroid mass on the right side. The patient did not undergo any treatment for this condition until she presented to the Affiliated Hospital of Shandong Second Medical University in June 2023. The patient had no symptoms upon the second admission for treatment. The trachea of the patient was centrally located and not deviated. A palpable mass ~2x2 cm in size was present on the right side of the thyroid, with a firm texture, clear borders and no tenderness. The mass moved up and down with swallowing. The left side of the thyroid was normal and the lymph nodes in the neck were not enlarged. Ultrasound examination revealed a hypoechoic nodule that was 2.2x2.0x1.5 cm in dimension on the right side of the thyroid (Fig. 1), which, using the thyroid imaging reporting and data system (TIRADS), was classed as TIRADS 3 (10). Solitary cystic thyroid nodules with a maximum diameter of 3 mm were observed on the left side of the thyroid (TIRADS 2), no similar cystic nodules in the right lobe of the thyroid were observed. The patient had no previous history of thyroid disease, and a routine blood test (including white and red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration) showed no abnormalities. The following day, the patient underwent the total removal of the right lobe of the thyroid under general anesthesia. A lymph node resection was not carried out because: i) HTT is not classified as a malignant tumor and therefore lymph node dissection is not routinely performed (11); ii) the preoperative ultrasound did not reveal any abnormal enlarged lymph nodes; iii) the patient is 31 years old and relatively young, and there was a preference for maintaining quality of life; and iv) upon reviewing the literature, the majority of patients were treated with only complete resection

Correspondence to: Dr Lu Guo, Department of Oncology, Affiliated Hospital of Shandong Second Medical University, 2428 Yuhe Road, Weifang, Shandong 261042, P.R. China
E-mail: glu2001@163.com

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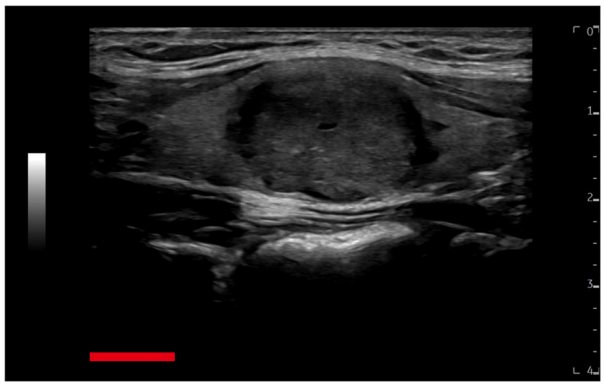

Figure 1. Ultrasound image. An ultrasound of the right thyroid lobe revealed a solid, well-defined hypoechoic nodule (scale bar, 1 cm).

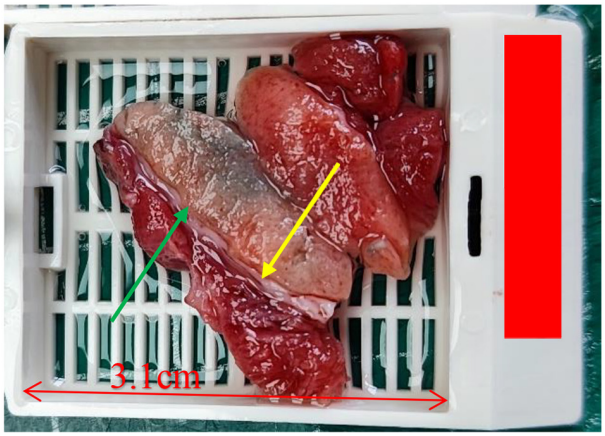

Figure 2. Macroscopic tumor image. An image of the surgically removed right lobe of the thyroid with the tumor indicated by a green arrow and the tumor capsule indicated by a yellow arrow.

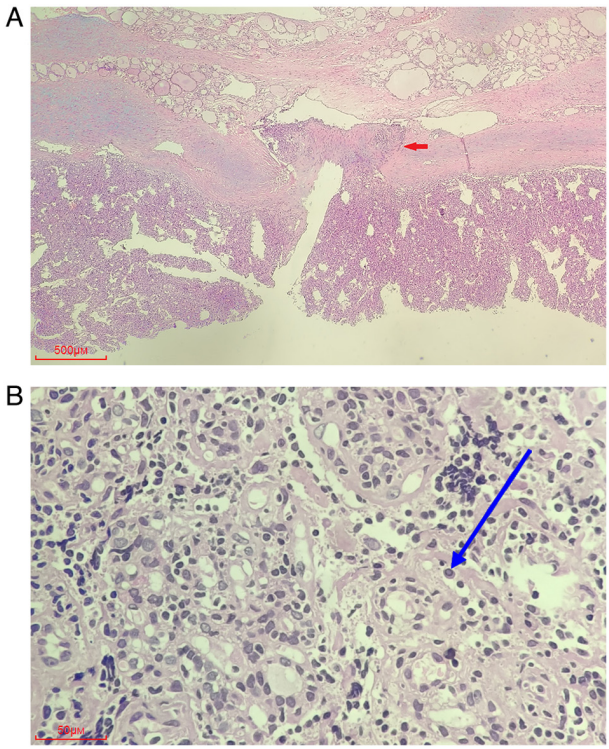

Figure 3. Hematoxylin and eosin staining of the tumor. (A) Tumor cells infiltrated the capsule (red arrow). Magnification, x20; scale bar, 500 μm. (B) Histological presentation of the hyalinizing trabecular tumor revealed an intranuclear pseudoinclusion (blue arrow) with extracellular hyalinization. Magnification, x200; scale bar, 50 μm.

of the tumor followed by surveillance (2,12,13). Therefore, lymph node biopsy was not performed during surgery.

Macroscopic examination revealed a piece of grayish-red tissue measuring 4.0x3.0x2.5 cm, with a visible grayish-yellow to grayish-brown nodule measuring 2.1x2.0x1.8 cm on the cut surface (Fig. 2).

Hematoxylin and eosin (H&E) staining and immunohistochemical staining were carried out and examined using an Olympus BX53 light microscope. The tumor specimens were fixed in 10% neutral formalin at room temperature for ~48 h, then embedded in paraffin and cut into 4-μm slices. H&E staining was performed at room temperature, with hematoxylin staining for 5 min, followed by eosin staining for 2 min. Immunohistochemical staining was performed using the following pre-diluted primary antibodies (ready-to-use) provided by Guangzhou LBP Medical Science and Technology Co., Ltd.: anti-thyroglobulin (TG, cat. no. IM138), anti-cytokeratin 19 (CK19, cat. no. IM378), anti-thyroid transcription factor 1 (TTF-1, cat. no. IM301), anti-calcitonin (CT, cat. no. IM382), anti-galectin-3 (cat. no. IR365), anti-chromogranin A (CgA, cat. no. IM053), anti-CD34 (cat. no. IM034), anti-podoplanin (D2-40, cat. no. IM070), and anti-Ki-67 (cat. no. IR098). For immunohistochemical staining, paraffin blocks were sectioned at a thickness of 3 μm. These sections were then deparaffinized in an alcohol gradient (xylene, 100% ethanol, 95% ethanol, 75% ethanol, ethanol-free water) and subjected to high-temperature (97˚C) antigen retrieval for 21 min using EnVision FLEX Target Retrieval Solution (pH=9.0; cat. no. DM828; Agilent Technologies, Inc.). After cooling to room temperature, the sections were rinsed with Tris-buffered saline solution (cat. no. DM831, Agilent Technologies, Inc.). The primary antibodies were incubated at room temperature for 25 min. After rinsing with Tris-buffered saline solution, the sections were treated with a peroxidase blocking reagent (ready-to-use, cat. no. SM801, Agilent Technologies, Inc.) for 15 min at room temperature, followed by the application of the secondary antibody (ready-to-use, Dako EnVision FLEX/HRP detection reagent, cat. no. SM802, Agilent Technologies, Inc.) and incubated in the dark at room temperature for 20 min. After rinsing, the sections were developed using EnVision FLEX DAB (cat. no. DM827, Agilent Technologies, Inc.), observed under a microscope, and the development time was controlled. Subsequently, the sections were counterstained with hematoxylin and coverslipped.

In the right thyroid lobe, the tumor was surrounded by a fibrous capsule, but the capsule was invaded by tumor cells. Tumor cells were arranged in trabeculae-like structures. Stromal hyaline material was observed between the trabeculae, and nuclear grooves and nuclear pseudoinclusions were observed in the nucleus (Fig. 3). The immunohistochemical staining results demonstrated that the tumor cells were positive for TG, CK19 and TTF-1 and focally positive for galectin-3 (Fig. S1A-D). The hotspots (areas that exhibit the highest

density of Ki-67 staining) in the tumor revealed a positive rate of 5% for Ki-67, but the staining was negative for CT and CgA (Fig. S1E and F). These results were consistent with HTT. The immunohistochemistry results for CD34 and D2-40 did not reveal the presence of tumor cells within the blood vessels or lymphatic vessels (Fig. S1G and H). Furthermore, based on the absence of red blood cells within the 'spaces', it was considered that the vessel-like dilated spaces were not actual blood vessels but rather thyroid follicles. Close follow-up of the patient was recommended.

The patient has recovered post operation. Thyroid function tests at the 1-month postsurgical follow-up indicated no abnormalities. At the 3-month follow-up, a thyroid ultrasound examination also revealed no issues. A thyroid ultrasound and thyroid function test 7-months after the surgery of the patient indicated no abnormalities (Fig. S2).

Discussion

In 1987, the study by Carney *et al* (1) provided a detailed report on the tumor histopathology of 11 patients with HTT, which was then named hyalinizing trabecular adenoma. The 2004 classification by the World Health Organization (WHO) provides a distinct category for this type of tumor, designating it as HTT and classifying it as having a low malignant potential (2). The 2017 WHO Classification of Tumors of Endocrine Organs also uses this categorization (7). However, studies suggest that HTT is a benign tumor (3,14,15), despite a small number of reports describing cases of HTT with capsular invasion and distant metastasis (15-17). The study by Sambade *et al* (18) reports a case with HTT with minimal capsular invasion, as well as another case with metastasis to a regional lymph node. Additionally, the study by Molberg and Albores-Saavedra (17) details 3 cases in which the tumors reveal capsular and/or vascular invasion, classifying these as minimally invasive carcinomas. However, a number of studies suggest that this may be due to the misdiagnosis of papillary thyroid carcinoma (PTC) as HTT (3,19). In the present case, the tumor cells invaded the capsule (albeit without capsular penetration). Therefore, we hypothesize that it is inappropriate to classify HTT as a benign tumor, as this may mislead clinicians regarding the malignant potential of HTT. The present report provided new evidence of the invasive capability of HTT.

HTT is more common in women compared with men, although this is debated (4). With a mean onset age of 47 years, it does not typically present with noticeable clinical symptoms (20). The etiology of HTT is not established. However, the study by Casey *et al* (6) reveals rearranged during transfection gene/PTC mutations in a subset of HTTs, suggesting that HTT is a form of PTC.

In the diagnostic process for nearly all thyroid nodules, the initial course of action typically involves conducting an ultrasound examination followed by a fine-needle aspiration (FNA) biopsy (4). The main ultrasound finding that indicates HTT is the presence of a single, clearly defined, oval or round, solid hypoechoic nodule without microcalcifications and with peri- or intranodular vascularity (8,13); however, these diagnostic features are not specific for HTT. Furthermore, upon FNA, both HTTs and PTCs can demonstrate hypercellularity, psammoma bodies and cellular atypia, including cytoplasmic invaginations, nuclear grooves and nuclear pseudoinclusions, contributing to the diagnostic complexity (9,16). Therefore, additional diagnostic methods are needed for the diagnosis of HTT. Commonly used methods include histopathological and molecular diagnoses (3).

On gross examination, HTT is usually well circumscribed or encapsulated, and its colors usually vary from yellow to tan. By contrast, PTC is typically white and lacks a capsule (18).

Under the microscope, the histological features of HTT originating from follicular cells include a trabecular arrangement of the tumor cells, transparency between trabecular cells and an acidophilic cytoplasm. The tumor cells typically have a decreased nuclear-to-cytoplasmic ratio compared with normal cells, often with nuclear grooves and pseudoinclusions (3,4,21). Furthermore, HTT often coexists with lymphocytic thyroiditis and/or multinodular goiter in the surrounding tumor tissue (3,21). An important immunohistochemical antibody used to differentiate between HTT and PTC is mindbomb homolog-1 (MIB-1; a monoclonal antibody of Ki-67), which can be used to detect Ki-67 on the cell membrane of HTT cells (8). Additionally, the hyaline material of HTT stains positive with periodic acid-Schiff staining (21).

Molecular testing of FNA biopsy samples can notably increase accuracy of preoperative FNA diagnoses. This prevents the misdiagnosis and over-treatment of patients, the additional and unnecessary surgical risks, decreased quality of life, and unwarranted healthcare expenses (22). One commonly used molecular test for HTT, is a test for paired-box gene 8 (PAX8)-GLI-similar 3 (GLIS3) rearrangement, which is present in 93% of HTT cases (22) and, to the best of our knowledge, is not found in PTC. The PAX8-GLIS3 rearrangement can lead to the overexpression of GLIS, which upregulates the production of various collagens and transparent matrices, including type IV collagen. This leads to the morphological features of HTT, which is characterized by the deposition of hyalinized material (7,23). Additionally, HTT lacks the BRAF V600E mutation (13) that is frequently observed in PTC (24). Furthermore, there is not an upregulation of microRNA in HTT, further distinguishing it from PTC (25).

In practical pathological work, considering the rarity of HTT compared with PTC and medullary carcinomas, which are more common, pathologists may not be inclined to diagnose HTT without further examination (such as using immunohistochemistry and molecular testing); therefore, HTT requires a differential diagnosis. Previous studies (9,21,26) also highlight the importance of differentiating HTT from papillary and medullary carcinomas. Although histopathology of PTC is similar to HTT, MIB-1 is positively expressed on the cell membrane in HTT but not in PTC (21). Therefore, MIB-1 helps to distinguish between HTT and PTC. Medullary thyroid carcinoma originates from the parafollicular cells of the thyroid, generally with inconspicuous nucleoli and a lack of mitotic figures. Immunohistochemical staining of medullary thyroid carcinoma indicates a positive expression of CgA and CT and a negative expression of TG, whereas HTT reveals opposite results (27). The purpose of differential diagnosis is to ensure that the possibility of HTT is not overlooked during the diagnostic process.

In conclusion, although diagnosing HTT is challenging, combining immunohistochemistry and molecular diagnoses

may improve the diagnostic accuracy. Although there is controversy regarding the benign or malignant nature of HTT, the present case provided evidence of its aggressive behavior. The close follow-up of a patient may be necessary to accurately assess their condition and guide the subsequent treatments.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LZ and LG designed and conceived the study and revised the manuscript. LZ, QM and ZS performed the research and analyzed the data. LZ wrote the manuscript. LZ and ZS confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the present case study to be published.

Competing interests

The authors declare that they have no competing interests.

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