ULTRA SONO GRAPHY

Hyalinizing trabecular tumor of the thyroid: diagnosis of a rare tumor using ultrasonography, cytology, and intraoperative frozen sections

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ORIGINAL ARTICLE

http://dx.doi.org/10.14366/usg.15054
pISSN: 2288-5919 • eISSN: 2288-5943
Ultrasonography 2016;35:131-139

Received: September 16, 2015
Revised: November 4, 2015
Accepted: November 8, 2015

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Purpose: The goal of this study was to evaluate the clinicopathological and imaging features of thyroid nodules surgically diagnosed as hyaline trabecular tumor (HTT), and to assess the role of cytology and frozen sections (FS) in the diagnosis of HTT.

Methods: This study included 21 thyroid nodules in 21 patients treated from August 2005 to March 2015 (mean age, 53.3 years) who were either diagnosed as HTT or had HTT suggested as a possible diagnosis based on cytology, FS, or the final pathology report. Patients' medical records were retrospectively reviewed for cytopathologic results and outcomes during the course of follow-up. Sonograms were reviewed and categorized.

Results: Twelve nodules from 12 patients were surgically confirmed as HTT. Ultrasonography (US)-guided fine needle aspiration (FNA) was performed on 11 nodules, of which six (54.5%) were papillary thyroid carcinoma (PTC) or suspicious for PTC and three (27.3%) were HTT or suspicious for HTT. Intraoperative FS suggested the possibility of HTT in seven nodules, of which four (57.1%) were confirmed as HTT. US-FNA suggested the diagnosis of HTT in 10 nodules, of which three (30.0%) were confirmed as HTT. Common US features of the 12 pathologically confirmed cases of HTT were hypoechogenicity or marked hypoechogenicity (83.4%), absence of calcifications (91.7%), parallel shape (100.0%), presence of vascularity (75.0%), and probable benignity (58.3%).

Conclusion: HTT should be included in the differential diagnosis of solid tumors with hypoechogenicity or marked hypoechogenicity and otherwise benign US features that have been diagnosed as PTC through cytology.

Keywords: Thyroid gland; Thyroid nodule; Ultrasonography; Biopsy, fine-needle; Frozen sections

How to cite this article:
Jang H, Park CK, Son EJ, Kim EK, Kwak JY, Moon HJ, et al. Hyalinizing trabecular tumor of the thyroid: diagnosis of a rare tumor using ultrasonography, cytology, and intraoperative frozen sections. Ultrasonography. 2016 Apr;35(2):131-139.

Introduction

Hyalinizing trabecular tumor (HTT) of the thyroid gland is a rare neoplasm of follicular cell origin that was initially described by Carney et al. [1] This rare form of tumor is commonly circumscribed or encapsulated, consisting of polygonal and spindle cells arranged in a trabecular pattern and separated by hyalinized stroma [2]. Microscopically, this neoplasm shows hyaline contents and nuclei with frequent grooves and intranuclear inclusions, mimicking the presence of amyloid in medullary thyroid carcinoma (MTC) or the nuclear features of papillary thyroid carcinoma (PTC), potentially leading to misdiagnosis of this benign tumor as malignant based on preoperative fine needle aspiration (FNA) cytology [3–6]. HTT is generally accepted to be a benign tumor [7], in which the majority of tumors do not present with aggressive behavior such as capsular/vascular invasion, local recurrences, or distant metastases.

Considering its benign features, efforts have been made to identify ways of differentiating this benign tumor from other thyroid malignancies, since the preoperative diagnosis can influence the extent of surgery. Several studies have evaluated the role of preoperative ultrasonography (US)-guided FNA results [3–6] and frozen sections (FS) [8] in predicting the diagnosis of HTT, and for the most part have found difficulties in the accurate preoperative diagnosis of HTT by cytology or FS. Moreover, since most studies have focused on preoperative US-FNA cytology or the intraoperative FS results of thyroid nodules ultimately diagnosed as HTT, little is known about the final outcome of thyroid nodules for which HTT was suggested as a possible diagnosis on cytology or FS.

The purpose of this paper was to address this gap by evaluating the clinicopathological and imaging features of thyroid nodules surgically diagnosed as HTT, as well as the role of cytology and FS in the diagnosis of HTT.

Materials and Methods

This retrospective study was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea. Neither patient approval nor informed consent was required for the review of medical records, cytopathologic specimens, and sonograms.

Patients

The medical record database of our institution was searched for patients treated from August 2005 to March 2015, for whom HTT was suggested as a possible diagnosis either in cytologic reports from US-FNA or in pathology reports including FS results from surgery. A total of 21 thyroid nodules from 21 patients satisfied these inclusion criteria and were included in this study, with 10 cytology reports, seven FS reports, and 12 final surgical pathology reports. The mean age of the patients was 53.3 years (range, 31 to 80 years). The mean size of the thyroid nodules was 17.7 mm (range, 3 to 41 mm). Of the 21 patients, three (14.3%) were men and 15 (85.7%) were women.

US and US-FNA Procedures

Real-time US was performed using a 7- to 15-MHz linear array transducer (HDI5000, Philips Medical Systems, Bothell, WA, USA), an 8- to 15-MHz linear array transducer (Acuson Sequoia, Siemens Medical Solutions, Mountain View, CA, USA), or a 5- to 12-MHz linear array transducer (*i*U22, Philips Medical Systems). Compound imaging was obtained in all images from a HDI5000 or *i*U22 machine.

US and subsequent US-FNA was performed by one of 26 radiologists (four faculty members and 22 fellows) with 1 to 15 years of experience in thyroid imaging. US-FNA was performed on thyroid nodules showing suspicious US features or on the largest mass when none of the multiple thyroid nodules observed showed any suspicious US features.

Sonograms of the thyroid nodules were retrospectively reviewed by one radiologist (J.H.Y.) with 7 years of experience in thyroid imaging. The US features were described according to the following categories: internal components, margin, echogenicity, calcifications, shape, and vascularity [9]. The internal components were further classified into solid, mainly solid (>50% solid content), and mainly cystic (<50% solid content). The margins were classified as circumscribed or non-circumscribed (i.e., microlobulated or irregular margins). Echogenicity was classified as hyperechoic or isoechoic (nodules showing hyperechogenicity to isoechogenicity when compared to the surrounding thyroid parenchyma), hypoechoic (nodules showing hypoechogenicity compared to the surrounding thyroid parenchyma), and markedly hypoechogenic (nodules showing hypoechogenicity compared to the adjacent strap muscle). The presence of calcifications was assessed as no calcifications; microcalcifications or mixed calcifications; and macrocalcifications, including eggshell calcifications. Shape was classified as parallel or non-parallel (larger in the anteroposterior dimension than the transverse dimension, 'taller than wide'). Vascularity was evaluated on Doppler sonograms, and was classified as no vascularity, defined as the absence of Doppler signals at the periphery or within the thyroid nodule; peripheral vascularity, defined as the presence of Doppler signals at the periphery of the nodule; and intranodular vascularity, defined as the presence of Doppler signals within the thyroid nodule with or without the presence of vascular flow at the periphery of the nodule.

Marked hypoechogenicity, non-circumscribed margins, micro-

calcifications or mixed calcifications, and non-parallel shape were considered to be US features indicative of malignancy, based on criteria that have been presented in the literature [9]. The final assessment of the thyroid nodules was probably benign when none of the suspicious US features described above were present, and suspicious for malignancy when one or more of the suspicious US features were present.

US-FNA was performed at least twice from each thyroid nodule using a 23-gauge needle attached to a 2-mL disposable syringe without an aspirator. Local anesthesia was not routinely applied. The aspirated material was expelled on glass slides and immediately placed in 95% ethanol for Papanicolaou staining. The remaining material in the syringe was rinsed in saline for cell block processing. Cytopathologists were not present during the procedures, and additional staining was performed on a case-by-case basis at the cytopathologists' request. One of the seven cytopathologists specializing in thyroid pathology interpreted the cytology slides. Until December 2009, cytology reports at our institution were divided into the following five categories [10]: (1) malignancy, specimen showing abundant cells with unequivocal cytologic features of malignancy; (2) suspicious for malignancy, specimen exhibiting cytological atypia, but insufficient cellularity to make a definitive diagnosis of malignancy; (3) indeterminate (including follicular neoplasm or Hürthle cell neoplasms), specimen showing cytological findings of monotonous cellular population and scanty colloid, lacking papillary carcinoma features; (4) benign, including colloid nodules, nodular hyperplasia, lymphocytic thyroiditis, Graves' disease, and postpartum thyroiditis; and (5) inadequate, specimen showing fewer than six groupings of well-preserved thyroid cells, each consisting of fewer than 10 cells per group [11]. After December 2009, cytology reports

Table 1. Clinical features of the 12 patients surgically diagnosed with hyalinizing trabecular tumor (HTT)

Case No.	Sex	Age (yr)	Size (mm)	Symptom	Multiplicity	US assessment	FNA	FS	Operation	IHC on surgery	Associated findings	Follow-up (mo)
1	F	53	25	Palpable mass	Solitary	Probably benign	Suspicious for PTC	HTT	Subtotal	Ki-67 (+) CK19 (–)	None	72
2	F	49	10	Negative	Solitary	Probably benign	PTC	NA	Subtotal	Ki-67 (+) CK19 (–)	Lymphocytic thyroiditis Adenomatous hyperplasia	10
3	F	70	41	Negative	Multiple[a]	Probably benign	PTC vs. HTT	Defer, HTT vs. PTC	Hemitotal	Ki-67 (+)	None	22
4	F	44	8	Negative	Solitary	Probably benign	Suspicious for PTC	NA	Hemitotal	NA	None	13
5	F	52	21	Negative	Solitary	Probably benign	Follicular neoplasm	Follicular adenoma	Hemitotal	Ki-67 (–)	None	18
6	F	53	5	Hypothyroidism	Solitary	Probably benign	AUS/FLUS	NA	Hemitotal	Ki-67 (+)	Lymphocytic thyroiditis Adenomatous hyperplasia	21
7	F	52	11	Negative	Multiple[a]	Suspicious malignant	PTC vs. HTT[b]	HTT	Hemitotal	Ki-67 (+) CK19 (–)	None	31
8[c]	F	68	3	Negative	Multiple[c] PTC, left	Suspicious malignant	NA	NA	Total	Ki-67 (–)	Adenomatous hyperplasia	17
9	M	52	9	Negative	Multiple[a]	Suspicious malignant	PTC	NA	Total	Ki-67 (+) CK19 (–)	Lymphocytic thyroiditis	NA
10	F	49	15	Negative	Multiple[a]	Probably benign	PTC	NA	Total	NA	Lymphocytic thyroiditis	NA
11	F	62	3	Negative	Multiple	Suspicious malignant	HTT	Defer, HTT vs. PTC	Hemitotal	NA	None	55.9
12	F	56	10	Negative	Solitary	Probably benign	Suspicious for PTC	PTC vs. MTC	Total	Ki-67 (+)	None	NA

US, ultrasonography; FNA, fine needle aspiration; FS, frozen section; IHC, immunohistochemical staining; F, female; PTC, papillary thyroid carcinoma; CK19, cytokeratin 19; NA, not applicable; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; M, male; MTC, medullary thyroid carcinoma.
[a]Probably benign nodules on US. [b]Diagnosed by gun biopsy. [c]Incidentally detected HTT after surgery for PTC in the contralateral lobe.

from US-FNA of thyroid nodules were based on the six categories of the Bethesda System for Reporting Thyroid Cytopathology [12]. During both periods, if HTT was considered in the diagnosis, this was mentioned in the cytological reports, along with the five or six categories that indicated the level of suspicion for malignancy.

Intraoperative FS

Tissue samples from the resected thyroid nodule and/or the adjacent thyroid parenchyma were obtained and processed for FS analysis. Frozen tissue samples were cut and stained for histological analysis, and the surgical team in the operating room was notified of the results. FS results were classified into benign (including HTT), malignant, and deferred diagnosis.

Results

During the study period, 12 thyroid nodules in 12 patients were confirmed as HTT in the final pathology report. The clinical and cytopathologic features of the 12 patients who were diagnosed with HTT upon surgery are summarized in Table 1. One patient with HTT presented with a palpable mass, while the other 11 patients were asymptomatic, with incidentally detected thyroid masses on neck US imaging that was performed for a range of reasons. The mean age of the patients with HTT was 55.0 years (range, 44 to 70 years). Only one of the 12 patients (8.3%) was a man, while the remaining 11 (91.7%) were women. The mean size of the 12 nodules were 13.4 mm (range, 3 to 41 mm). Six of the 12 patients with HTT had solitary lesions, while the others had multiple coexisting nodules.

Eleven of the 12 patients underwent US-FNA before surgery, and three underwent FNA twice. One patient underwent total thyroidectomy with the diagnosis of PTC in the left thyroid gland and was incidentally diagnosed with HTT in the right lobe. The cytopathologic results were PTC in three patients, suspicious for PTC in three patients, atypia of undetermined significance or follicular lesion of undetermined significance in one patient, follicular neoplasm in one patient, HTT or PTC in two patients, and suggestive of HTT in one patient. Among the six patients diagnosed with PTC or suspicious PTC based on FNA cytology, five patients were assessed as probably benign on US. Six of the 12 patients underwent FS during surgery, with the following intraoperative FS results: HTT in two patients, follicular adenoma in one patient, PTC or medullary carcinoma in one patient, and deferred in in two patients. Ki-67 staining results were available for nine patients who underwent additional immunohistochemical staining (IHC), of whom seven (77.8%) had positive Ki-67 results (Fig. 1). Nine patients underwent follow-up US (mean follow-up period, 25.5 months; range, 10 to 72 months), and none had radiologic features suggesting tumor recurrence during follow-up.

US Features of the 12 Thyroid Nodules Diagnosed as HTT

The US features of the 12 nodules diagnosed as HTT are presented in Table 2. All 12 nodules had a solid composition. Common US features were hypoechogenicity or marked hypoechogenicity (83.4%), the absence of calcifications (91.7%), a parallel shape (100.0%), and the presence of vascularity (75.0%). None of the patients had any pathologic cervical lymph nodes seen on US. Seven (58.3%) of the 12 thyroid nodules were assessed as probably benign in the final assessment (Figs. 1, 2).

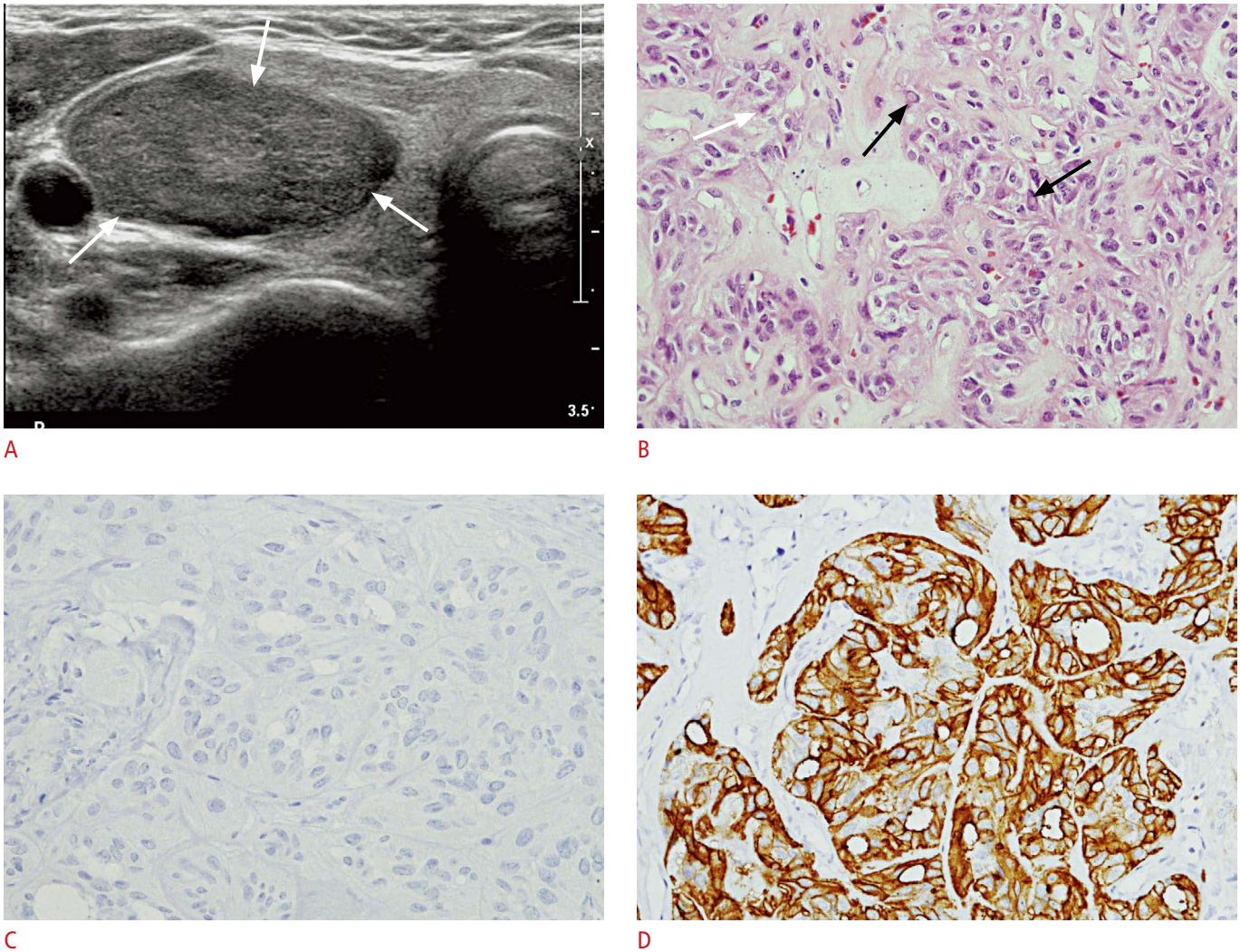
Table 2. Ultrasonography (US) features of the 12 patients surgically diagnosed with hyalinizing trabecular tumor

US features	No. (%)
Composition	
Solid	12 (100)
Mainly solid	0
Mainly cystic	0
Margin	
Circumscribed	7 (58.3)
Not circumscribed	5 (41.7)
Echogenicity	
Hyperechoic to isoechoic	2 (16.6)
Hypoechoic	5 (41.7)
Markedly hypoechoic	5 (41.7)
Calcifications	
None	11 (91.7)
Macro- or eggshell	1 (8.3)
Micro- or mixed	0
Shape	
Parallel	12 (100)
Not parallel	0
Vascularity	
None	3 (25.0)
Peripheral	5 (41.7)
Central	1 (8.3)
Both	3 (25.0)
Cervical lymph nodes on US	
Absent	12 (100)
Present	0
Final assessment	
Probably benign	7 (58.3)
Suspicious for malignancy	5 (41.7)

Table 3. Clinical features of seven thyroid nodules with the possibility of hyalinizing trabecular tumor (HTT) suggested on intraoperative frozen section (FS) analysis

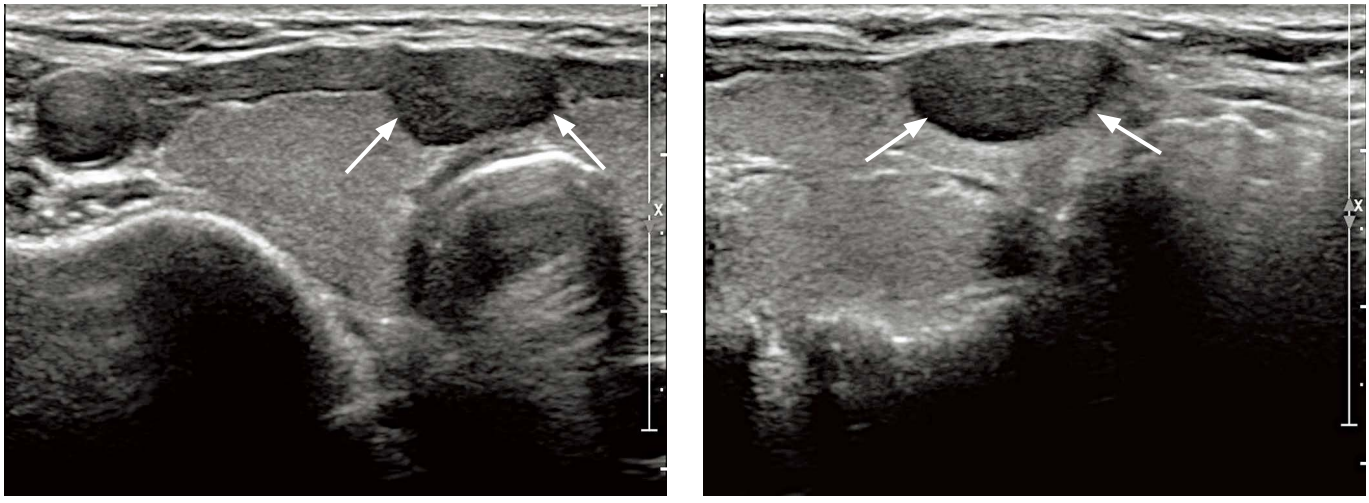
Case No.	Sex	Age (yr)	Size (mm)	FNA	FS	Pathology
1	F	53	25	r/o PTC	HTT	HTT
2	F	52	11	HTT vs. PTC	HTT	HTT
3	F	62	3	HTT	r/o HTT	HTT
4	F	51	37	Benign	Defer, HTT vs. FN	FA
5	F	70	41	HTT vs. PTC	Defer, HTT vs. PTC	HTT
6	F	54	29	HTT	Defer, HTT vs. PTC	FC, MI
7	M	59	39	AUS/FLUS	Defer[a)]	Poorly differentiated carcinoma

FNA, fine needle aspiration; F, female; r/o, rule out; PTC, papillary thyroid carcinoma; FN, follicular neoplasm; FA, follicular adenoma; FC, follicular carcinoma; MI, minimally invasive; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; M, male.
[a)]Hyalinizing trabecular tumor, medullary carcinoma, papillary carcinoma (less likely), and poorly differentiated carcinoma (less likely) were included in the differential diagnosis.



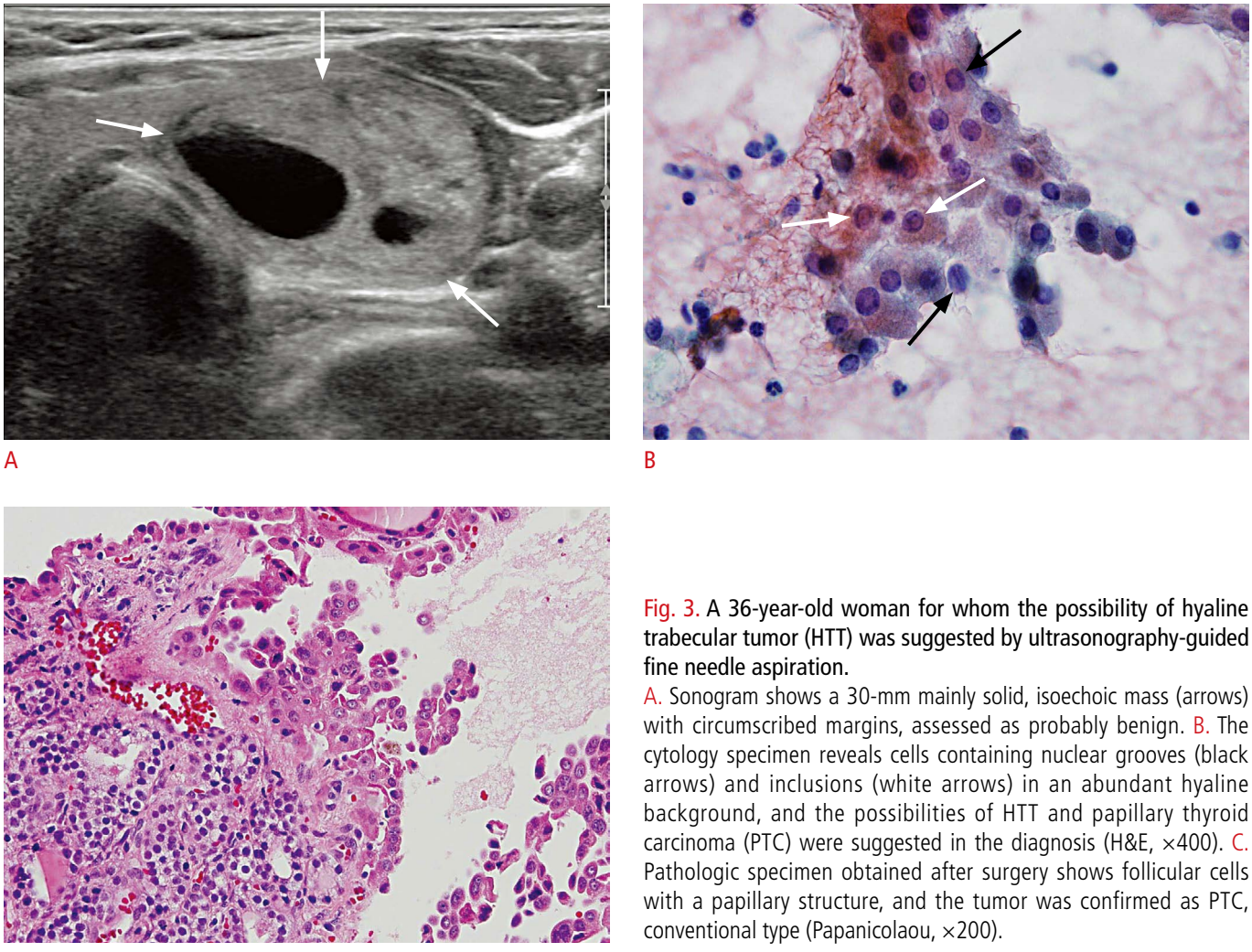
A B C D

Fig. 1. A 70-year-old woman was surgically diagnosed with hyaline trabecular tumor (HTT).
A. Ultrasonography (US) reveals a 40-mm hypoechoic solid mass (arrows) with relatively benign US features that was assessed as probably benign. B. Microscopy shows cells containing nuclear grooves (white arrow) and inclusions (black arrows; H&E, ×200). C, D. Immunohistochemical staining for cytokeratin 19 is negative (cytokeratin 19, ×200) (C), but membrane expression for Ki-67 is found (Ki-67, ×200) (D), confirming the diagnosis of HTT.



A B

Fig. 2. A 49-year-old woman was surgically diagnosed with hyaline trabecular tumor.
Ultrasonography (A, transverse; B, longitudinal) shows a 15-mm solid nodule (arrows) with marked hypoechogenicity, circumscribed margins, parallel shape, and no calcifications. The final assessment of this nodule was probably benign.



A B C

Fig. 3. A 36-year-old woman for whom the possibility of hyaline trabecular tumor (HTT) was suggested by ultrasonography-guided fine needle aspiration.
A. Sonogram shows a 30-mm mainly solid, isoechoic mass (arrows) with circumscribed margins, assessed as probably benign. B. The cytology specimen reveals cells containing nuclear grooves (black arrows) and inclusions (white arrows) in an abundant hyaline background, and the possibilities of HTT and papillary thyroid carcinoma (PTC) were suggested in the diagnosis (H&E, ×400). C. Pathologic specimen obtained after surgery shows follicular cells with a papillary structure, and the tumor was confirmed as PTC, conventional type (Papanicolaou, ×200).

Table 4. Clinical features of the 10 thyroid nodules with the possibility of hyalinizing trabecular tumor (HTT) suggested on ultrasonography-guided fine needle aspiration (FNA)

Case No.	Sex	Age (yr)	Size (mm)	FNA	FS	Pathology	IHC on surgery
1	F	62	3	Suggestive of HTT	Defer HTT vs. PTC	HTT	–
2	F	54	29	Suggestive of HTT	HTT, most likely, DDx of PTC	FC, MI	CK19 (–)
3	F	31	13	PTC vs. HTT	Defer, follicular neoplasm	FA	–
4	F	33	27	Consistent with PTC Cannot rule out HTT	FVPTC	FVPTC	–
5	F	73	7	Suspicious for PTC Cannot rule out HTT	PTC	Papillary microcarcinoma showing oncocytic cytoplasm, follicular subtype	–
6	M	42	20	Consistent with PTC Cannot rule out HTT	NA	PTC, conventional	–
7	F	80	9	HTT vs. unusual variant of thyroid tumor	NA	FVPTC	–
8	F	36	30	Suspicious for PTC Cannot rule out HTT	Oncocytic follicular neoplasm	PTC, conventional	–
9	F	70	41	Consistent with PTC Cannot rule out HTT	Defer, HTT vs. PTC	HTT	Ki-67 (+)
10	F	52	11	PTC, solid variant PTC, follicular variant HTT	HTT	HTT	Ki-67 (+) CK19 (–)

FS, frozen section; IHC, immunohistochemical staining; F, female; PTC, papillary thyroid carcinoma; DDx, differential diagnosis; FC, follicular carcinoma; MI, minimally invasive; CK19, cytokeratin 19; FA, follicular adenoma; FVPTC, follicular variant of papillary thyroid carcinoma; NA, not applicable.

Outcomes of Intraoperative FS and US-FNA Cytology Suggesting HTT

Intraoperative FS results suggested the possibility of HTT in seven thyroid nodules in seven patients, of which four were confirmed as HTT, one was follicular adenoma, one was minimally invasive follicular carcinoma, and one was poorly differentiated carcinoma (Table 3).

Table 4 summarizes the clinical course of the 10 thyroid nodules with the possibility of HTT suggested on US-FNA. The mean age of the patients was 53.3 years (range, 31 to 80 years) and the mean size of the thyroid nodules was 19 mm (range, 3 to 41 mm). Nine of the 10 patients were women. The diagnosis of HTT was strongly suggested in two nodules (20.0%) on cytology, while both HTT and PTC were included in the differential diagnosis of eight nodules (80.0%). Of the two nodules with cytology results strongly suggestive of HTT, one was diagnosed as HTT during surgery, and one as minimally invasive follicular carcinoma. Of the remaining eight nodules with the possibility of both HTT and PTC suggested on US-FNA, two were confirmed as HTT, three as PTC (Fig. 3), two as follicular variant of PTC, and one as follicular adenoma.

Discussion

Surgical intervention is necessary when a thyroid malignancy such as PTC or MTC is suggested by FNA cytology. Unfortunately, the cytologic features of HTT resemble those of PTC, with nuclei that have frequent intranuclear inclusions and grooves, and MTC, containing abundant hyaline material in stains of the tumor [3–6]. Due to these overlapping features, the differential diagnosis of HTT from PTC or MTC based on FNA cytology alone is very challenging [3,4]. Moreover, the correct diagnosis of HTT is made more difficult by its rarity; therefore, most surgically proven cases of HTT are misdiagnosed as PTC in FNA cytology. Several studies have retrospectively reviewed the preoperative cytologic results of surgically proven HTT, and the presence of cytological features suggestive of HTT have been reported in 58%–100% of cases classified as PTC or suspicious for PTC [2,7,8,13]. In contrast, the same studies reported that the diagnosis of HTT was suggested in preoperative US-FNA in approximately 0%–20% of cases [2,7,8,13], which demonstrates the low accuracy of cytology in the diagnosis of HTT. The results of our study are similar to previous findings; among the eleven patients who underwent US-FNA, 54.5% (6/11) were misdiagnosed as PTC, while approximately 27% (3/11) had findings that were interpreted as HTT or possible HTT (2/11).

HTT is a benign tumor that can be adequately treated with thyroid lobectomy alone. However, the misdiagnosis of HTT as PTC or MTC on FNA cytology can lead to overtreatment with total or subtotal thyroidectomy. Therefore, studies have attempted to identify ways of effectively differentiating HTT from PTC or other thyroid malignancies, especially using imaging features [2,13]. Common US features of the 12 nodules confirmed as HTT in our study were hypoechogenicity or marked hypoechogenicity, the absence of calcifications, a parallel shape, and the presence of vascularity. A final assessment of probably benign was made for 58.3% of the 12 HTT nodules, consistent with the results of prior studies in that the majority of HTT cases showed benign features on US [2,13]. In addition, our study included a single case of HTT showing macrocalcifications on US, which is quite rare; only one study has previously reported a case of HTT showing calcifications [14]. Lee et al. [2] concluded that HTT should be included in the list of nodules showing discordant US-cytology results, and that HTT should be suspected in thyroid nodules diagnosed as PTC on cytology but with benign US features. In addition, a relatively high proportion (41.7%) of the 12 HTT nodules seen in our study had markedly hypoechogenic features compared to the echogenicity of the adjacent strap muscle, and all 12 HTT nodules had a solid tumor composition. Similarly high rates of marked hypoechogenicity were reported by Choi et al. [13], with marked hypoechogenicity seen in 29.2% of the HTT nodules. This finding may be useful in differentiating HTT from the follicular variant of PTC, which can also show relatively benign US features together with the cytologic features of PTC [2,13]. Based on our results, HTT should be included in the differential diagnosis of solid thyroid tumors showing marked hypoechogenicity with otherwise benign US features and cytological results indicative of PTC.

With the increased awareness of HTT, attempts to predict the diagnosis of HTT based on intraoperative FS have been reported. Sung et al. [8] reviewed nine patients diagnosed with HTT and found that none of the patients diagnosed as HTT based on FS were ultimately diagnosed with other thyroid malignancies such as PTC, MTC, or metastatic cancer. In our study, however, the possibility of HTT was suggested in intraoperative FS results in seven thyroid nodules in seven patients, of which only four were confirmed as HTT. The pathologist correctly diagnosed HTT on FS in three cases that were finally confirmed as HTT, but the diagnosis was deferred in the remaining four cases (57.1%). The final diagnosis of the four nodules with deferred results on FS was as follows: HTT in one, follicular adenoma in one, minimally invasive follicular carcinoma in one, and poorly differentiated carcinoma in one. As Sung et al. [8] suggested, intraoperative FS may play an additional role in preventing total thyroidectomy by predicting HTT, but it has its limitations, since approximately 57.1% of the thyroid nodules with intraoperative FS suggesting the possibility of HTT had a deferred diagnosis, which may only lead to confusion and the delayed treatment of malignant tumors.

Most studies have focused on the preoperative US-FNA cytology results of thyroid nodules finally diagnosed as HTT. To the best of our knowledge, this is the first report to present the outcomes of thyroid nodules for which HTT was suggested as a possible diagnosis on US-FNA cytology. In our study, the possibility of HTT was suggested on US-FNA cytology for 10 nodules, of which only three cases were eventually confirmed as HTT. These results confirm the previously identified difficulties in predicting HTT with US-FNA cytology, and also reflect the poor diagnostic performance of US-FNA cytology, since only 30.0% of nodules considered suspicious for HTT were confirmed as HTT on surgery. In addition, recent studies have shown that IHC, such as Ki-67 (MIB-1) and cytokeratin 19, is capable of differentiating HTT from PTC [7,15,16]. In our study, approximately 77.8% of the HTT nodules that underwent IHC were positive for Ki-67, consistent with prior studies. Furthermore, as Casey et al. [17] reported that Ki-67 may be applied to FNA cytology smears for the diagnosis of HTT, we may anticipate future improvement in preoperative diagnosis using cytology.

This study has several limitations. First, this was a retrospective study. Second, one radiologist retrospectively reviewed the US features of the 21 thyroid nodules included in this study, in order to minimize interobserver variability that may occur among different radiologists and affect the results. Third, seven cytopathologists were involved in the cytopathologic interpretation, including US-FNA cytology and intraoperative FS, and interobserver variability among the readers was not analyzed. Finally, due to the rarity of this specific pathologic diagnosis, a limited number of cases was included in this study.

In conclusion, US-FNA cytology and intraoperative FS has limited value in the preoperative diagnosis of HTT. HTT should be considered in the differential diagnosis of solid tumors with hypoechogenicity or marked hypoechogenicity with otherwise benign US features that are diagnosed as PTC on cytology.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This study was supported in part by the Research Fund of the Korean Society of Ultrasound in Medicine.

References

1. Carney JA, Ryan J, Goellner JR. Hyalinizing trabecular adenoma of the thyroid gland. Am J Surg Pathol 1987;11:583-591.
2. Lee S, Han BK, Ko EY, Oh YL, Choe JH, Shin JH. The ultrasonography features of hyalinizing trabecular tumor of the thyroid are more consistent with its benign behavior than cytology or frozen section readings. Thyroid 2011;21:253-259.
3. Bondeson L, Bondeson AG. Clue helping to distinguish hyalinizing trabecular adenoma from carcinoma of the thyroid in fine-needle aspirates. Diagn Cytopathol 1994;10:25-29.
4. Akin MR, Nguyen GK. Fine-needle aspiration biopsy cytology of hyalinizing trabecular adenomas of the thyroid. Diagn Cytopathol 1999;20:90-94.
5. Evenson A, Mowschenson P, Wang H, Connolly J, Mendrinos S, Parangi S, et al. Hyalinizing trabecular adenoma: an uncommon thyroid tumor frequently misdiagnosed as papillary or medullary thyroid carcinoma. Am J Surg 2007;193:707-712.
6. Kuma S, Hirokawa M, Miyauchi A, Kakudo K, Katayama S. Cytologic features of hyalinizing trabecular adenoma of the thyroid. Acta Cytol 2003;47:399-404.
7. Carney JA, Hirokawa M, Lloyd RV, Papotti M, Sebo TJ. Hyalinizing trabecular tumors of the thyroid gland are almost all benign. Am J Surg Pathol 2008;32:1877-1889.
8. Sung SY, Shen HY, Hsieh CB, Duh QY, Su TF, Chan DC, et al. Hyalinizing trabecular tumor of thyroid: does frozen section prevent unnecessarily aggressive operation? Six new cases and a literature review. J Chin Med Assoc 2014;77:573-577.
9. Kim EK, Park CS, Chung WY, Oh KK, Kim DI, Lee JT, et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. AJR Am J Roentgenol 2002;178:687-691.
10. Kwak JY, Kim EK, Kim HJ, Kim MJ, Son EJ, Moon HJ. How to combine ultrasound and cytological information in decision making about thyroid nodules. Eur Radiol 2009;19:1923-1931.
11. Yoon JH, Moon HJ, Kim EK, Kwak JY. Inadequate cytology in thyroid nodules: should we repeat aspiration or follow-up? Ann Surg Oncol 2011;18:1282-1289.
12. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2009;19:1159-1165.
13. Choi WJ, Baek JH, Ha EJ, Choi YJ, Hong MJ, Song DE, et al. The ultrasonography features of hyalinizing trabecular tumor of the thyroid gland and the role of fine needle aspiration cytology and core needle biopsy in its diagnosis. Acta Radiol 2015;56:1113-1118.
14. Gupta S, Modi S, Gupta V, Marwah N. Hyalinizing trabecular tumor of the thyroid gland. J Cytol 2010;27:63-65.
15. Hirokawa M, Carney JA. Cell membrane and cytoplasmic staining for MIB-1 in hyalinizing trabecular adenoma of the thyroid gland. Am J Surg Pathol 2000;24:575-578.
16. Hirokawa M, Carney JA, Ohtsuki Y. Hyalinizing trabecular adenoma and papillary carcinoma of the thyroid gland express different cytokeratin patterns. Am J Surg Pathol 2000;24:877-881.
17. Casey MB, Sebo TJ, Carney JA. Hyalinizing trabecular adenoma of the thyroid gland identification through MIB-1 staining of fine-needle aspiration biopsy smears. Am J Clin Pathol 2004;122:506-510.