Immunohistochemical and molecular pathologic subclassification of thyroid tumor with prominent hyalinizing trabecular pattern

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Immunohistochemical and molecular pathologic subclassification of thyroid tumor with prominent hyalinizing trabecular pattern

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Sarah Lee

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ABSTRACT

Immunohistochemical and molecular pathologic subclassification of thyroid tumor with prominent hyalinizing trabecular pattern

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The purpose of this study was to evaluate the immunohistochemical and molecular pathologic characteristics of thyroid tumors with a prominent hyalinizing trabecular pattern (TTHTP). The immunohistochemical stains for TTF-1, thyroglobulin, CD56, cytokeratin (CK) 19, galectin-3, and Ki-67 were performed on 16 cases of TTHTP, and genetic analysis for $BRAF^{V600E}$ point mutation were studied on 12 of 16 cases. All TTHTPs were positive for TTF-1 and thyroglobulin, and nine cases expressed CD56 and Ki-67. Out of these nine cases, seven satisfied the strict criteria of Carney, and four cases were positive for CK19 or/and galectin-3 and negative for Ki-67

and CD56. The remaining three cases had no Ki-67, CD56, CK19 or galectin-3 expression. $BRAF^{V600E}$ mutation was detected in only one of 12 cases, showing immunohistochemical characteristics of PTC type. Eleven of 12 cases lacked $BRAF^{V600E}$ mutation.

All TTHTPs meeting the criteria of Carney were hyalinizing trabecular tumors (HTT), and TTHTPs which did not satisfy the criteria of Carney were subclassified according to the immunohistochemical results into HTT type [Ki-67 (+) and CD56 (+)], PTC type [CK19 or galectin-3 (+)/Ki-67 (-) and CD56 (-)], or null type [Ki-67 (-), CD56 (-), CK19 (-) and galectin-3 (-)]. TTHTPs with typical histological features or with typical immunohistochemical manifestations can be categorized as HTT, and the remaining TTHTPs should be categorized as PTC or null type. Moreover, the absence of $BRAF^{V600E}$ mutation of TTHTP is valuable for the diagnosis of HTT.

Key words: hyalinizing trabecular tumor, immunohistochemistry, thyroid, BRAF

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I. INTRODUCTION

Since hyalinizing trabeculular tumors (HTT) were first reported in 1987[1], a large amount of literature on HTT has been published[2-5]. However, the biology and behavior of these types of tumors have not been understood until recently. Terms such as hyalinizing trabecular adenoma, hyalinizing trabecular carcinoma, and hyalinizing trabeculular tumor have all been used to describe these tumors[6]. Based on results of our study, HTT is benign tumor. A large scale study with more than 100 HTTs did not show invasive features, recurrence, or metastasis except in one case[2]. Genetic mutations such as B-raf, and N-raf mutations were not observed in HTT[7, 8], and the CK19, galectin-3, and p63 expressions typical of papillary thyroid carcinoma (PTC) were not detected[4, 5]. In contrast, the view that HTT is a variant of PTC was based on

the following evidence. The nuclear features of HTT are very similar to those of PTC[1], and RET/PTC rearrangement was identified in HTT[3, 9]. In addition, galectin-3 and CK 19 could be expressed in HTT[5, 10]. Although not typical, some HTTs show vascular invasion, capsular invasion and metastasis, possibly due to biologic variability[11-15]. In surgical pathology, thyroid tumors with a hyalinizing trabecular pattern are occasionally present. In some cases, thyroid tumors such as PTC and follicular neoplasm display hyalinizing trabecular architecture, resulting in diagnostic issues.

The purpose of this study is to investigate immunohistochemical and molecular pathologic characteristics of thyroid tumor with prominent hyalinizing trabecular pattern (TTHTP) and to correlate immunohistochemical and molecular pathologic results with clinicopathologic features of TTHTP.

II. MATERIALS AND METHODS

1. Patient selection and histologic review

A retrospective review was performed on all patients who presented with a thyroid tumor with a hyalinizing trabecular pattern and who had undergone surgery at Severance Hospital or Gangnam Severance Hospital between January 2000 and December 2008. The study was approved by the Institutional Review Board of Yonsei University Severance Hospital. The criterion of TTHTP in this study was defined as a thyroid tumor showing a more than 90% hyalinizing and/or trabecular pattern without definite papillary

or follicular architecture. Twenty cases of thyroid tumors with a hyalinizing trabecular pattern were collected. Sixteen of which were included in this study. The other four cases were reclassified into papillary carcinoma (two cases) and follicular adenoma (two cases). We evaluated the histology of the 16 cases of TTHTP according to the criteria of Carney et al. (1): (a) good circumscription or encapsulation; (b) overwhelming trabecular architecture; (c) trabeculae composed of spindled to plump thyrocytes, two- to four-cells thick; (d) thyrocytes with enlarged nuclei with prominent grooving and numerous intranuclear pseudoinclusions; (e) delicate to hyalinized stroma; and (f) no identifiable conventional or follicular variant of PTC. Based on histological examinations, all 16 cases satisfied Carney's criteria and were diagnosed as HTT.

The clinicopathologic features such as age, gender, tumor size, tumor location, associated thyroid tumor or disease, and tumor recurrence or metastasis were collected from patient charts.

2. Immunohistochemistry

The antibodies used for immunohistochemistry are shown in Table 1. All immunostainings were performed using 5-μm-thick, formalin-fixed, paraffin-embedded tissue sections obtained with a microtome, transferred into adhesive slides, and dried at 62°C for 30 min. After incubation with primary antibodies, immunodetection was performed with biotinylated anti-mouse

immunoglobulin, followed by peroxidase-labeled streptavidin using a labeled streptavidin biotin kit with 3,3′-diaminobenzidine chromogen as a substrate. The primary antibody incubation step was omitted in the negative control. Slides were counterstained with Harris hematoxylin. Positive controls for each antibody were used as appropriate.

Table 1. Clones, dilutions, and sources of antibodies used

Antibody	Clone	Dilution	Source
CK19	RCK108	1:100	DAKO, Glostrup, Denmark
Galectin-3	9C4	1:200	Novocastra, UK
CD56	123C3	1:150	Zymed, CA, USA
Ki-67	MIB-1	1:150	DAKO, Glostrup, Denmark
TTF-1	8G7G3/1	1:100	DAKO, Glostrup, Denmark
Thyroglobulin	Polyclonal	1:1000	DAKO, Glostrup, Denmark

Abbreviations: CK19, cytokeratin 19; *TTF-1,* thyroid transcription factor 1

3. Interpretation of immunohistochemical staining

All immunohistochemical markers were assessed under light microscopy. Scoring of immunostained slides was conducted according to the percentage of tumor cells exhibiting cytoplasmic (galectin-3, cytokeratin 19, and CD56), and membrane (Ki-67) staining. The IHC stain results were considered positive when more than 10% of the tumor cells were stained.

4. Detection of $BRAF^{V600E}$ gene mutation

Genomic DNA were extracted in 12 of 17 cases using QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions from 5-μm-thick, formalin-fixed, paraffin-embedded tissue sections. Exon 15 BRAF was amplified by polymerase chain reaction (PCR) by detection PCR kit (Seegene, Seoul, Korea). The used PCR primers for amplifying were as follows:

Exon 15-forward, 5'-TCATAATGCTTGCTCTGATAGGA-3';

Exon 15-reverse, 5'-GGCCAAAAATTTAATCAGTGGA-3'.

PCR products were electrophoresed by microchip electrophoresis system using MCE-202 MultiNA (Shimadzu biotech, Kyoto, Japan) and sequenced. Direct sequencing for $BRAF^{V600E}$ mutations was performed by ABI PRISM DNA sequencer (Applied Biosystems, Foster City, CA, USA).

III. RESULTS

1. Clinicopathologic features of TTHTP

Table 2 shows the clinicopathologic features of the 16 cases of TTHTP. The mean patient age was 50 years (range; 22-69 years), and 13 (81%) patients were female. The mean tumor size was 1.9 cm (range; 0.5-6.0 cm). In nine cases, the tumor was located in the left thyroid lobe, and in seven cases the

Table 2. Clinicopathologic and immunuhistochemical features of thyroid tumor with prominent hyalinizing trabecular pattern

Case No.	Age (years)	Sex	Tumor size (cm)	Tumor side	Thyroid disease	Other thyroid tumor	Pathologic features not satisfied with Carney's criteria	CD56	CK19	Galectin-3	Ki-67	Immunophenotype
1	55	Female	1.6	Left	Goiter		Rare hyalinized stroma	-	-	-	-	Null type
2	48	Female	2.0	Left			None	+	-	-	+	HTT type
3	65	Female	2.2	Right			Not prominent nuclear groove and pseudoinclusion	+	-	+	+	HTT type
4	50	Female	1.5	Right	Lymphocytic thyroiditis, goiter		None	+	-	+	+	HTT type
5	41	Male	6	Left		PTC (Rt)	Rare hyalinized stroma	-	+	-	-	PTC type
6	22	Female	0.8	Left	Goiter		Rare hyalinized stroma	-	-	-	-	Null type
7	48	Female	1.0	Right		PTC (Lt)	None	+	-	-	+	HTT type
8	50	Male	4.0	Left			Vascular invasion in peritumoral area	-	-	-	-	Null type
9	50	Female	1.0	Right		PTC (Rt & Lt)	Not prominent nuclear groove and pseudoinclusion	-	-	+	-	PTC type

10	40	Male	5.0	Left		PTC (Rt)	Rare hyalinized stroma	-	+	+	-	PTC type
11	45	Female	0.5	Left			Rare hyalinized stroma	+	-	-	+	HTT type
12	54	Female	0.5	Right		PTC (Rt)	None	+	-	-	+	HTT type
13	69	Female	1.5	Right	Goiter	PTC (Rt & Lt)	Rare hyalinized stroma	-	+	+	-	PTC type
14	50	Female	0.8	Left	Lymphocytic thyroiditis, goiter	PTC (Lt)	None	+	-	-	+	HTT type
15	55	Female	0.5	Right	Goiter	PTC (Rt & Lt)	None	+	-	+	+	HTT type
16	43	Female	0.7	Left			None	+	-	+	+	HTT type

Abbreviations: *HTT*, hyalinizing trabecular tumor, *PTC* papillary thyroid carcinoma, *Rt* Right, *Lt* Left.

tumor was located in the right thyroid. In six cases, an adenomatous goiter was present, and two cases were lymphocytic thyroiditis. In eight cases, PTC was synchronously identified, two of which presented with ipsilateral PTC, three with contralateral PTC, and three with bilateral PTC. Seven of 16 cases satisfied the strict criteria of Carney, and the remaining nine cases presented with an extra histologic feature. Among these nine cases, six had rare hyalinized stroma (Figure 1B), two revealed no prominent nuclear groove and pseudoinclusion (Figure 1C), and one case indicated vascular invasion (Figure 1D).

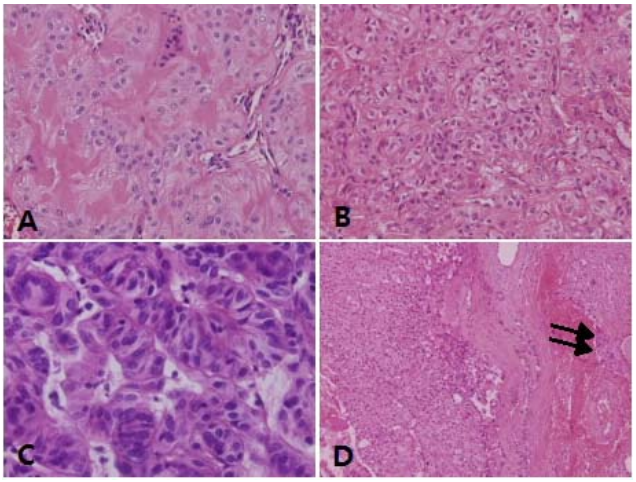


Figure 1. Histologic features not consistent with Carney's criteria of HTT. The typical HTT shows hyalinized stroma, trabecular cell arrangement, prominent nuclear groove and pseudoinclusion (A, X200, H&E). The tumor shows non-prominent hyalinized stroma (B, X200, H&E). Tumor cells do not demonstrate a prominent nuclear groove or pseudoinclusion (C, X200, H&E). The tumor shows vascular invasion in the peritumoral area (arrow, D, X40, H&E).

One patient (case 8) who presented to the hospital due to bone pain was diagnosed with bone metastasis upon radiologic examination. A curettage of the bone tumor was performed, and the pathologic diagnosis was metastatic tumor with a prominent hyalinizing trabecular architecture and nuclear inclusion. To detect the primary tumor location, immunohistochemical stains for TTF-1, thyroglobulin, chromogranin A, and synaptophysin were performed. Since TTF-1 and thyroglobulin were expressed, the thyroid gland was identified as the primary tumor site, a thyroid tumor was located and thyroidectomy performed. The histologic features of the thyroid and bone tumors were very similar in appearance, both illustrating a prominent hyalinizing trabecular architecture and characteristic nuclear features such as nuclear grooves and pseudoinclusions. Pathologic examination concluded that the primary thyroid tumor showed vascular invasion (Figure 1D). The patient was diagnosed with a malignant thyroid epithelial tumor with a prominent hyalinizing trabecular pattern.

2. Immunohistochemical features of TTHTP

Table 2 presents the immunohistochemical features of TTHTP. The immunohistochemical stains for TTF-1 and thyroglobulin were reactive in all cases, and nine cases presented with simultaneous CD56 and Ki67 immunostain positivity, with Ki-67 expressed in the cell membranes of all positive cases. Three (19%) cases were positive for CK19, the expression

patterns of which were focal and weak. Eight (50%) cases showed moderately intense expression of galectin-3. According to the results of these immunohistochemical stains, the TTHTPs were classified into three subtypes as follows: nine cases of HTT type [Ki-67 (+) and CD56 (+)], four cases of PTC type [CK19 or galectin-3 (+)/Ki-67 (-) and CD56 (-)], and three cases of null type [Ki-67 (-), CD56 (-), CK19 (-) and galectin-3 (-)] (Figure 2).

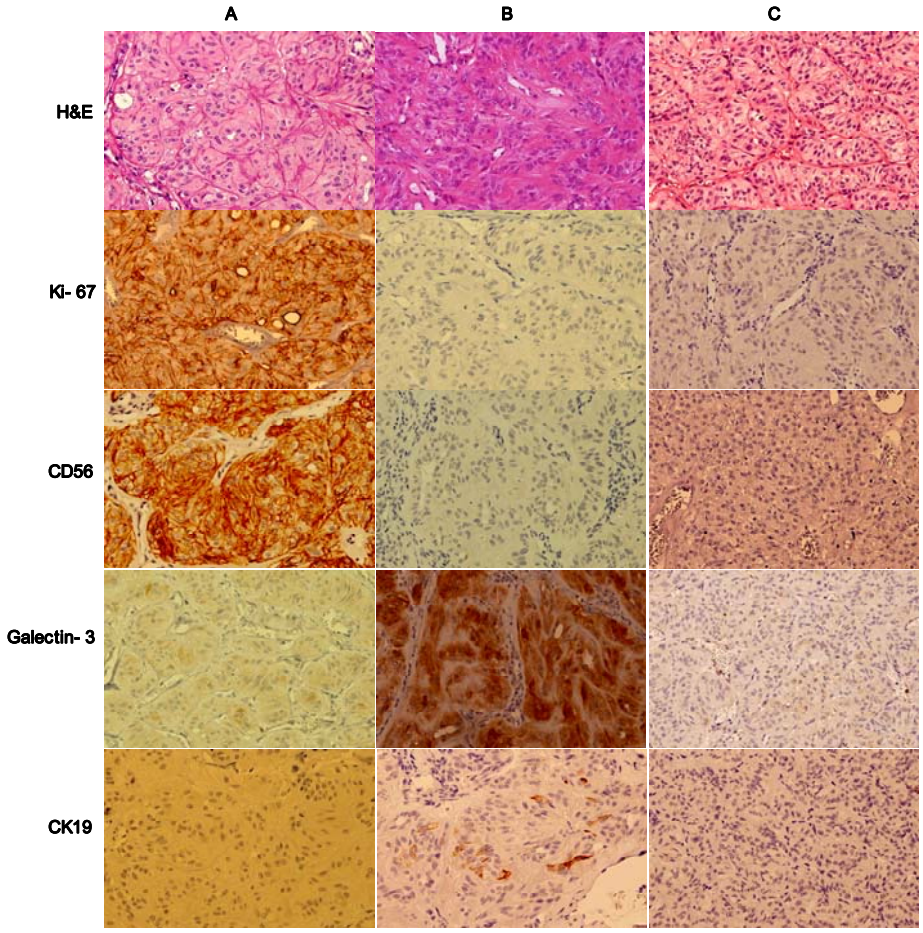


Figure 2. Immunohistochemical classification of TTHTP. The first type shows Ki-67 membranous staining and CD56 expression but no CK19 expression. Galectin-3 was negative or weakly positive in this type (A). The second type demonstrates galectin-3 or/and CK19 expression but no Ki-67 membranous staining or CD56 expression (B). The third type is negative for Ki-67, CD56, galectin-3 and CK19 (C).

3. $BRAF^{V600E}$ mutation analysis in TTHTP

$BRAF^{V600E}$ mutation was detected in one (case 13) of 12 cases in PCR, showing immunohistochemical stain results of PTC type. Nine of 12 cases lacked the $BRAF^{V600E}$ gene mutation, including 3 of null type, 4 of HTT type and 2 of PTC type by immunohistochemical subclassification. (Figure 3) Direct sequence demonstrated a heterozygous $BRAF^{V600E}$ mutation in one case (case 13). (Figure 4)

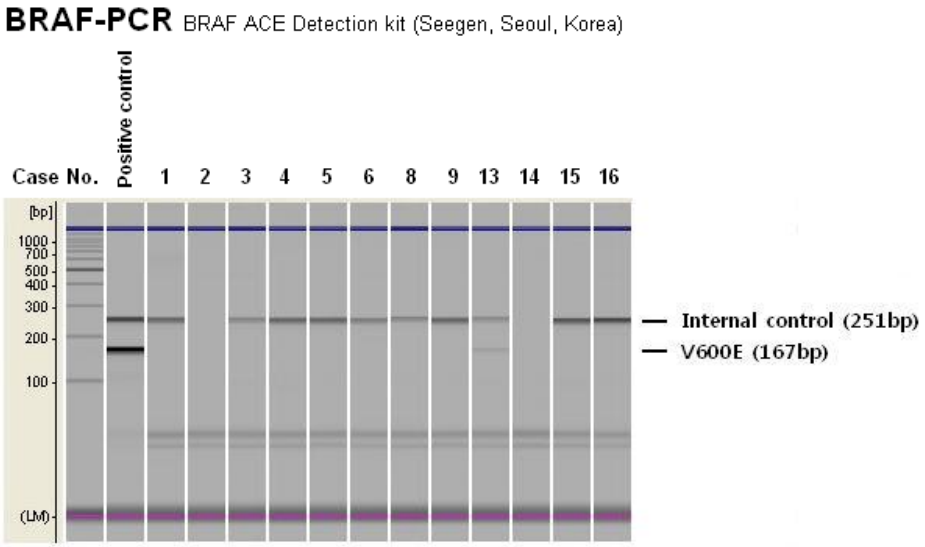
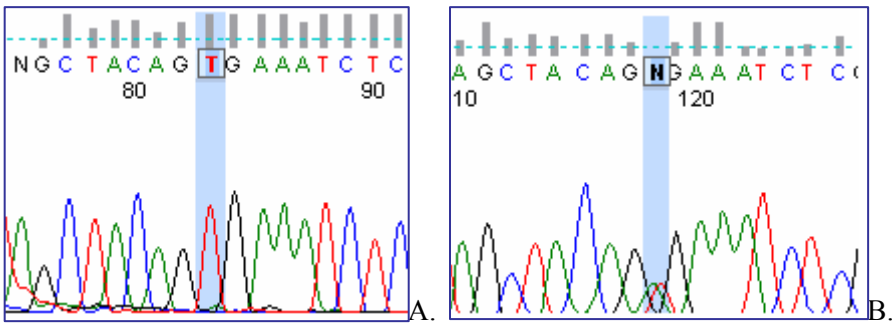


Figure 3. BRAF-PCR. $BRAF^{V600E}$ mutation was detected in one (case 13) of 12 cases.



A. B.

Figure 4. BRAF^{V600E} mutation detection by direct sequence. Sequence chromatograms of exon 15. A. Wild type sequence of 11 cases. B. Heterozygous transition of T→A in case 13.

IV. DISCUSSION

This study identified and evaluated the immunohistochemical features and clinicopathologic implications of 16 cases of TTHTP. Thyroid tumors can often present with hyalinizing trabecular architecture similar to HTT, including cellular adenomatoid nodules, follicular neoplasms, and follicular variants of papillary carcinoma[4]. Therefore, diagnostic criteria for HTT must be applied strictly, and only 16 of 20 cases of thyroid tumor with a hyalinizing trabecular pattern from the surgical pathology files were included in this study. When a patient presents with specific features other than HTT, even if they are partial, it is more appropriate to diagnose a thyroid tumor. The tumors which satisfied all of the Carney criteria were HTT and were reactive to both CD56 and Ki67.In addition, there were cases that did not met all histologic criteria of Carney but could have be diagnosed as HTT due to the

membranous expression of Ki-67and positivity for CD56. The subjective histologic features which did not satisfy Carney's criteria in this study were "hyalinized stroma" and "prominent nuclear groove and pseudoinclusion". In cases where confirmative diagnosis of HTT was difficult due to these subjective histologic parameters, specific immunohistochemical stains, such as Ki67 and CD56 helped diagnose HTT. The seven cases that satisfied all of Carney's criteria were positive for CD56 and Ki-67 expressions, and the two cases in which not all of Carney's criteria was met, showed membranous expression of Ki-67. In a previous study, Ki-67 was determined to be a very sensitive and specific marker for HTT due to its membranous expression in every HTT case and the lack of expression in PTC[14]. However, such an unusual expression is observed only when MIB-1 clonal antibody is used and incubated at room temperature, not 37℃ in automated immunostainer[15]. One explanation about membranous expression in only MIB-1 clonal antibody is cross-reactivity to an epitope expressed on cell membrane by peculiar neoplastic phenotype[15], whereas other explanation is the artifact phenomenon[16]. Absence of membranous staining pattern at 37℃ is explained by temperature-induced modification of the antigen spatial conformation In addition, Ki-67 is occasionally not expressed in specimen for cytologic examination[17] and may be irreproducible and vulnerable to changes in staining conditions. CD56 is expressed in normal thyroid follicular cells, proliferative follicular cells, and follicular neoplasms but not in PTCs,

including follicular variants[18]. The evaluation of CD56 expression in HTT has rarely been established. This study illustrated that HTT has reactivity with CD56 and Ki-67. Of the nine cases of confirmed HTT according to histologic features and immunoprofiles for CD56 and Ki-67, five had positive expression of galectin-3, in concordance with a previous study reporting an intermediately intense galectin-3 expression rate of 86.2% in HTT[10]. All five cases in our study with positive expression of galectin-3 showed weak to moderate staining intensity.

Four of the 16 cases of TTHTP in this study demonstrated CK19 or/and galectin-3 positivity and Ki-67 and CD56 negativity. In support of the belief that HTT frequently accompanies PTC[1], eight cases of TTHTP in this study were concurrent with PTC. Of these eight cases, four (50.0%) showed positive expression for CK19 and/or galectin-3, which are well-known to be expressed in PTC, and negative expression of CD56, which is also negative in PTC. Whether TTHTP with expression for CK19 and/or galectin-3, but no expression for CD56 and Ki-67 can be diagnosed as PTC with prominent hyalinizing trabecular architecture is uncertain but possible because all 4 cases of this type of TTHTP were associated with synchronous PTC in this study and in general PTC can have various architectures[4]. Three cases of TTHTP were negative for Ki-67, CD56, CK19 and galectin-3. Since this type of TTHTP is positive for thyroglobin and TTF-1, it may be considered ‘thyroid epithelial tumor with a prominent hyalinizing trabucular pattern,’ and the

possibility of its being a subtype of follicular neoplasm cannot be completely eliminated. One of three cases of null type had bone metastasis such as follicular carcinoma. Therefore, this type of TTHTP should be fully evaluated for follicular neoplasm, specifically for capsular and vascular invasion.

Figure 5 presents a diagnostic flow chart of TTHTP. When histologic features of the thyroid tumor with prominent hyalinizing and/or trabecular feature were completely consistent with the criteria of Carney, it can be diagnosed as HTT, and when TTHTP did not completely satisfy the strict criteria of Carney, immunohistochemistry for Ki-67 and CD56 was performed. Although there is possibility of controversy, TTHTP can be diagnosed as HTT if it presents with membranous expression of Ki-67 and positive expression of CD56. If the tumor is negative for Ki-67 and CD56, then immunohistochemical staining of CK19 and galectin-3 is performed. The tumor can be diagnosed as PTC if it is positive for CK19 and/or galectin-3, although there is possibility of controversy, and if not, the diagnosis of either benign thyroid epithelial tumor with a hyalinizing trabecular pattern or a malignant thyroid epithelial tumor with a hyalinizing trabecular pattern can be reached after meticulous search for capsular or vascular invasion.

A generalized conclusion cannot be reached due to the relatively small number of cases, attributed to the strict selection criteria of TTHTP. A previous study reported that only four of 18 cases of thyroid tumor with

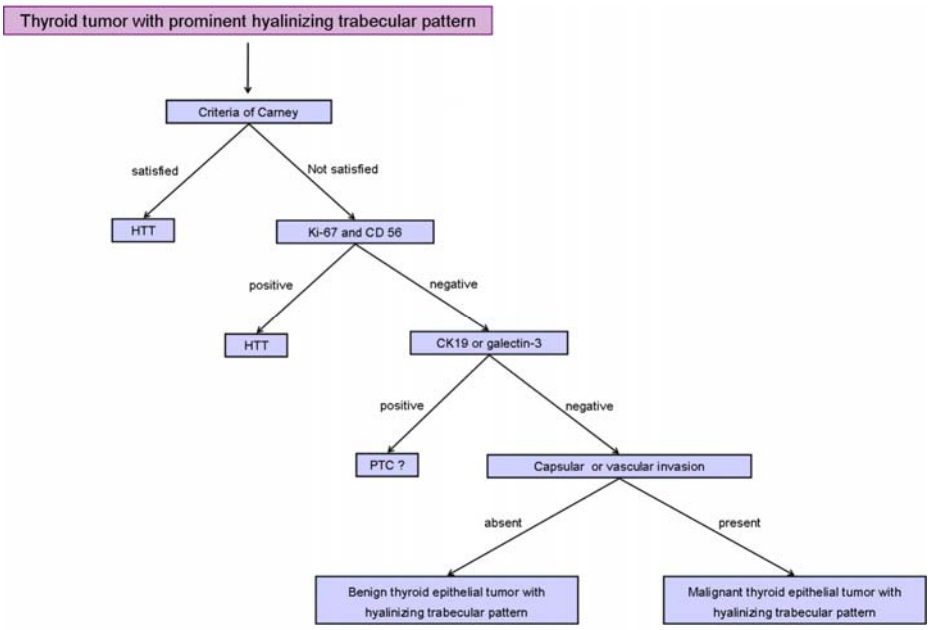


Figure 5. The proposed diagnostic flow chart of TTHTP.

Abbreviations: TTHTP, thyroid tumors with a prominent hyalinizing trabecular pattern; *HTT,* hyalinizing trabecular tumor; *CK19,* cytokeratin 19; *PTC,* papillary thyroid carcinoma.

prominent sclerosis or hyalinization and trabecular architecture were consistent with HTT when the criteria of Carney were applied[4]. The four cases were all negative for HBME-1, CK19, and p63. Previous studies on immunohistochemical staining profiles of HTT have presented with immunophenotypic heterogenicity in HTT. High-molecular weight cytokeratin, a marker of PTC, was positive in about 30% of the cases[19]. In addition, thyroperoxidase, a marker of follicular neoplasm, was positive in about 25% of the cases[19], and some provided positive expressions of neuroendocrine markers[20]. The study concluded that a thyroid tumor with histologic features of HTT can have various immunohistochemical profiles. Our study is the first to classify TTHTP with similar histologic features to HTT according to immunohistochemical staining profiles.

Genetically, previous studies have shown the transition of thymine→adenine at nucleotide 1799 (V600E) in exon 15 of BRAF gene is another character of PTC. In contrast, the lack of $BRAF^{V600E}$ mutations in the HTT were repeatedly reported. In this study, one of 12 TTHTP was detected $BRAF^{V600E}$ mutation and it had immunophenotype of PTC. Six cases with HTT type of immunostain pattern were included the analysis of $BRAF^{V600E}$ gene mutation, and none of them were detected $BRAF^{V600E}$ mutation. These features of molecular analysis support the previously reported view that HTT is not a variant of PTC.

V. CONCLUSION

We conclude that TTHTPs with typical histological features or with typical immunohistochemical manifestations can be categorized as HTT, and the remaining TTHTPs should be categorized as PTC or null type. Moreover, the absence of $BRAF^{V600E}$ mutation of TTHTP is valuable for the diagnosis of HTT. Further studies are necessary to evaluate the clinical and pathological implication of null type TTHTPs.

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ABSTRACT(IN KOREAN)

현저한 유리질 소주형 형태를 보이는 갑상샘 종양의 면역조직화학 및 분자병리학적 아형 분류

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본 연구에서는 현저한 유리질 소주형 형태를 보이는 갑상샘 종양(thyroid tumors with a prominent hyalinizing trabecular pattern, 이하 TTHTP)의 면역 조직 화학적 분자병리학적 특성을 알아보고자 하였다. 16개의 TTHTP 증례에 대하여 TTF-1, thyroglobulin, CD56, cytokeratin(CK) 19, galectin-3, Ki-67 면역조직화학 염색을 시행하였고, 그 중 12개의 증례에서 BRAF 유전자 돌연변이 검사를 시행하였다. 모든 TTHTP 증례에서 TTF-1과 thyroglobulin이 양성소견을 보였고, 9개의 증례에서 CD56과 Ki-67이 발현되었다. 이 9개의 증례 중에서, 7 증례는 Carney's criteria를 엄격한 기준에서 만족시켰고, 4 증례에서 CK19 및 galectin-3에 양성, Ki-67과 CD56에 음성의 결과를 얻었다. 나머지 3 증례에서는 Ki-67, CD56, CK19, galectin-3가 모두 발현되지

않았다. BRAF 유전자 돌연변이는 12개의 증례 중에서 PTC형의 면역조직화학 특성을 보였던 1개의 증례에서만 발견되었다. 검사를 시행한 12개의 증례 중 11개의 증례에서는 돌연변이가 나타나지 않았다.

TTHTP 중에서 Carney's criteria에 합당한 병변은 유리질 소주형 종양(hyalinizing trabecular tumor, 이하 HTT)으로 분류할 수 있고, Carney's criteria를 만족시키지 못하는 TTHTP는 면역조직화학 염색 결과에 따라 HTT형 [Ki-67 (+), CD56 (+)], 갑상선 유두암(papillary thyroid carcinoma, 이하 PTC)형 [CK19 또는 galectin-3 (+)/Ki-67 (-), CD56 (-)], 또는 무효형 [Ki-67 (-), CD56 (-), CK19 (-), galectin-3 (-)]으로 분류할 수 있다. 조직학적으로 전형적인 HTT의 형태를 보이거나, 전형적 면역조직화학 특성을 보이는 TTHTP는 HTT로 분류가 가능하고, 그 외의 TTHTP는 PTC형 또는 무효형의 범주에 넣어야 한다. 또한, TTHTP 중 BRAF 유전자 돌연변이 검사가 음성이면 HTT를 진단하는데에 도움을 얻을 수 있다.

핵심되는 말: 유리질 소주형 종양, 면역조직화학, 갑상샘, BRAF