

CD56 and High Molecular Weight Cytokeratin as Diagnostic Markers of Papillary Thyroid Carcinoma

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Background: The incidence of papillary thyroid carcinoma (PTC) has been increasing recently and a precise diagnosis is essential for optimal treatment. Ancillary immunohistochemical stains are important for diagnosing some difficult cases. **Methods:** The diagnostic value of CD56, high molecular weight cytokeratin (HMCK), galectin-3 (GAL3), and cytokeratin 19 (CK19) were evaluated to distinguish PTC from other benign thyroid lesions (BTL). We studied 23 cases of papillary thyroid overt carcinomas, 57 papillary thyroid microcarcinomas, five follicular adenomas, five cases of Hashimoto's thyroiditis, and 12 nodular hyperplasias. **Results:** The statistical analysis showed significantly different expressions of CD56, HMCK, GAL3, and CK19 in PTC vs other BTL. The diagnostic specificity of HMCK and CD56 (90.9% and 72.7%, respectively) was higher than that of GAL3 and CK19 (50.0% and 36.4%, respectively). However, the sensitivity of HMCK and CD56 detection (92.5% and 95.0%, respectively) was lower than that of GAL3 and CK19 (98.8% and 100.0%, respectively). The combined use of CD56, HMCK, GAL3, and CK19 showed 87.5% sensitivity, 100.0% specificity, and 100.0% positive predictive value in differentiating PTC from other BTL. **Conclusions:** Although the differential diagnosis of thyroid follicular lesions are based on histological and cytomorphological criteria, CD56 and HMCK might be useful markers for diagnosing PTC.

Key Words: CD56; High molecular weight cytokeratin; Thyroid papillary carcinoma

Carcinoma of the thyroid is currently the most common endocrine malignancy in Korea. An obvious increase in the incidence of papillary thyroid carcinoma (PTC) has been reported in recent decades. PTC constitute about 90-95% of the reported thyroid cancers in Korea.¹

This is largely due to advances in medical surveillance of impalpable nodules, which allows for increased detection of occult thyroid cancers, rather than a true increase in the number of thyroid cancers.² The diagnosis of PTC is based on architectural features combined with nuclear clearing, overlapping, grooves, and pseudo-inclusions. Accurately distinguishing the follicular variant of PTC from cellular adenomatous nodules may be challenging in the absence of papillary architecture.³

Less commonly, papillary hyperplastic nodules may be difficult to distinguish from PTC.³ Several reports have used ancillary studies, particularly immunohistochemistry and molecular techniques, in an attempt to solve problematic cases. Although some of these techniques are useful, they should be used cautiously as none of the ancillary studies seem to be consistent nor 100% reliable.⁴ Hence, none of these markers has solved the di-

agnostic controversy.

CD56 is a neural cell adhesion molecule (NCAM) that mediates homotypic and heterotypic cell-cell adhesion through a homophilic binding mechanism. CD56 is normally expressed in the thyroid gland. Loss of CD56 expression has been noted in papillary carcinoma and such loss can serve as a specific and sensitive marker of PTC.^{2,4-8} High molecular weight cytokeratin (HMCK) expression increases significantly in patients with PTC and helpful for distinguishing PTC from other benign and malignant thyroid nodules.⁹⁻¹³ Galectin-3 (GAL3) is a member of a growing family of β -galactoside-binding animal lectins, which is involved in regulating cell-cell and cell-matrix interactions, cell growth, neoplastic transformation, and apoptosis. GAL3 is a well known marker to distinguish benign and malignant thyroid nodules.^{2,13,14} However, reports have casted doubt on the reliability of GAL3 as a thyroid malignancy marker.¹⁵⁻¹⁸

Cytokeratin 19 (CK19) is a type I intermediate filament protein and the smallest known keratin. CK19 is useful in the diagnosis of papillary carcinoma, where it shows diffuse and strong cytoplasmic staining.^{2,3,6,11-13}

We compared and evaluated the diagnostic value of CD56, HMCK, GAL3, and CK19 immunohistochemical stains separately or in combination in distinguishing PTC from other benign thyroid lesions (BTL).

MATERIALS AND METHODS

Study approval was obtained from the Institutional Review Board at Kangnam Sacred Heart Hospital of Hallym University Medical Center. In total, 102 patients who underwent thyroid surgery from June 2009 to July 2010 (including four cases of follicular adenoma in 2003) at Kangnam Sacred Heart Hospital of Hallym University Medical Center were selected for this study.

All cases had hematoxylin and eosin (H&E) stained and paraffin blocks for immunohistochemical staining available for review. The H&E slides were reviewed by two authors independently and the diagnosis was agreed upon using well-established histopathological criteria. We followed the same histological criteria as those proposed by Chan,⁴ for the diagnosis of PTC as applied to diagnose PTC which are divided into major and minor features. The major features include: 1) nuclei are ovoid rather than round; 2) nuclei are crowded, often manifesting as a lack of polarization in the cells that line the follicle; 3) nuclei show a clear or pale chromatin pattern; 4) psammoma bodies are found. If one of the four features was lacking, four or more of the following features may occur: 1) presence of abortive papillae; 2) predominantly elongated or irregularly shaped follicles; 3) dark-staining colloid; 4) presence of rare nuclear pseudoinclusions; or 5) multinucleated histiocytes in follicle lumens. Adenomas were defined as completely encapsulated follicular tumors with homogeneous architecture and morphology, lacking nuclear features of PTC, and without capsular and vascular invasion.⁴ We independently reviewed the H&E-stained sections and interpreted immunohistochemical staining results. A consensus regarding controversial cases was reached at a multi-headed microscope.

Immunohistochemistry was performed on 4 µm-thick sec-

tions using a standard technique (streptavidin-biotin-peroxidase technique) with appropriate positive and negative controls. The primary antibodies used were CD56, HMCK, GAL3, and CK19 (Table 1). GAL3 expression was both cytoplasmic and/or nuclear. CD56, HMCK, and CK19 were membranous with or without cytoplasmic staining.

Multiple microscopic fields were examined, and the findings were expressed semi-quantitatively according to the estimated percentage of positive tumor cells: 0, staining of <10% of the cells; 1, staining in 10-33% of the cells; 2, staining in 33-66% of the cells; 3, staining in >66% of the cells. A score of 0 was considered negative, and scores of 1-3 were considered positive.

Statistical analysis

The statistical analysis was performed with SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA). Fisher's exact test was used to compare frequencies between the groups. The sensitivity, specificity, and accuracy of the markers and their combination for diagnosing of PTC were compared. *p*-values < 0.05 were considered significant.

RESULTS

The selected cases consisted of 80 with PTC (including 23 papillary thyroid overt carcinomas [POC] and 57 papillary thyroid microcarcinomas [PMC]) and 22 BTL (including five follicular adenomas [FA], five cases of Hashimoto's thyroiditis [HT], and 12 nodular hyperplasias [NH]). Among the 23 POC, one case of solid variant, one case of PTC with an exuberant nodular fasciitis-like stroma, two cases of encapsulated follicular variant and two cases of follicular variant were found. The other 17 POC cases were classic type and all 57 PMC were of the classic type.

CD56, HMCK, GAL3, and CK19 expression is shown in Table 2 and a comparison of the results between groups is presented in Table 3.

CD56 expression was negative in 76 of 80 PTC cases (Fig. 1C). CD56 expression was also negative in 21 of 23 in POC

Table 1. Properties of the primary antibodies

| Antibody | Clone | Supplier | Source | Dilution | Antigen retrieval |
|----------|--------------|------------|-------------------|----------|-------------------|
| CD56 | NCL-CD56-1B6 | Novocastra | Mouse, monoclonal | 1 : 300 | 20 min, BOND™ ERS |
| HMCK | 34βE12 | Dako | Mouse, monoclonal | 1 : 5 | 20 min, BOND™ ERS |
| GAL3 | 9C4 | Novocastra | Mouse, monoclonal | 1 : 400 | 20 min, BOND™ ERS |
| CK19 | b170 | Novocastra | Mouse, monoclonal | 1 : 100 | 20 min, BOND™ ERS |

ERS, Epitope Retrieval Solution; HMCK, high molecular weight cytokeratin; GAL3, galectin-3; CK19, cytokeratin 19.

Table 2. The results of immunohistochemical staining for CD56, high molecular weight cytokeratin (HMCK), galectin-3 (GAL3), and cytokeratin 19 (CK19) in various thyroid lesions

| Antibody | Diagnosis | Immunohistochemical expression | | | | Subtotal |
|----------|-----------|--------------------------------|----------|-----------|------------|------------|
| | | 0 | 1 | 2 | 3 | |
| CD56 | POC | 21 (91.3) | 0 (0.0) | 2 (8.7) | 0 (0.0) | 2 (8.7) |
| | PMC | 55 (96.5) | 2 (3.5) | 0 (0.0) | 0 (0.0) | 2 (3.5) |
| | FA | 0 (0.0) | 3 (60.0) | 0 (0.0) | 2 (40.0) | 5 (100.0) |
| | NH | 5 (41.7) | 4 (33.3) | 3 (25.0) | 0 (0.0) | 7 (58.3) |
| | HT | 1 (20.0) | 2 (40.0) | 1 (20.0) | 1 (20.0) | 4 (80.0) |
| HMCK | POC | 4 (17.4) | 1 (4.4) | 6 (26.1) | 12 (52.2) | 19 (82.6) |
| | PMC | 2 (3.5) | 6 (10.5) | 10 (17.5) | 39 (68.4) | 55 (96.5) |
| | FA | 5 (100.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | NH | 10 (83.3) | 1 (8.3) | 0 (0.0) | 1 (8.3) | 2 (16.7) |
| | HT | 5 (100.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| GAL3 | POC | 1 (4.4) | 0 (0.0) | 0 (0.0) | 22 (95.7) | 22 (95.7) |
| | PMC | 0 (0.0) | 0 (0.0) | 1 (1.8) | 56 (98.3) | 57 (100.0) |
| | FA | 5 (100) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | NH | 6 (50.0) | 2 (16.7) | 3 (25.0) | 1 (8.3) | 6 (50.0) |
| | HT | 0 (0.0) | 2 (40.0) | 3 (60.0) | 0 (0.0) | 5 (100.0) |
| CK19 | POC | 0 (0.0) | 0 (0.0) | 1 (4.4) | 22 (95.7) | 23 (100.0) |
| | PMC | 0 (0.0) | 0 (0.0) | 0 (0.0) | 57 (100.0) | 57 (100.0) |
| | FA | 1 (20.0) | 4 (80.0) | 0 (0.0) | 0 (0.0) | 4 (80.0) |
| | NH | 7 (58.3) | 1 (8.3) | 4 (33.3) | 0 (0.0) | 5 (41.7) |
| | HT | 0 (0.0) | 2 (40.0) | 2 (40.0) | 1 (20.0) | 5 (100.0) |

Values are presented as number (%).

0, stained in less than 10% of the cells; 1, stained in 10% to 1/3; 2, stained in more than 1/3 to 2/3; 3, stained in more than 2/3; POC, papillary thyroid overt carcinoma; PMC, papillary thyroid microcarcinoma; FA, follicular adenoma; NH, nodular hyperplasia; HT, Hashimoto's thyroiditis.

cases (91.3%) and 55 of 57 PMC cases (96.5%). The four cases showing positive CD56 expression were one case of POC with exuberant nodular fasciitis-like stroma, one case of classic type POC and two cases of PMC. The two cases of encapsulated follicular variant and the two cases of follicular variant were negative for CD56 expression. No statistical difference was observed between the POC and PMC ($p=0.5745$). CD56 was also negative in five of 12 NH cases (41.7%) and one of five HT cases (20.0%).

All five FA cases showed positive findings for CD56. CD56 protein expression was diffuse and strong in NH, FA and HT (Figs. 1D, 2B, D). Using Fisher's exact test, CD56 distinguished PTC from FA, NH, and HT (Table 3) with statistical significance. CD56 was 95.0% sensitive and 72.7% specific for distinguishing PTC from other BTL (Table 4).

HMCK expression was positive in 74 of 80 PTC cases (Fig. 1A), 19 of 23 POC cases (82.6%) and 55 of 57 PMC cases (96.5%). Six cases showing negative HMCK expression were one case of encapsulated follicular variant of POC, one case of follicular variant of POC, two cases of classic type POC, and two cases of PMC. No significant difference was observed between the POC and PMC cases ($p=0.0537$). HMCK was also positive in two of 12 NH cases (16.7%). All five FA cases and

all HT cases were negative for HMCK (Figs. 1B, 2A, C). HMCK was also able to distinguish PTC from FA, NH, and HT (Table 3) to a statistically significant degree. The sensitivity and specificity of HMCK were 92.5% and 90.9%, respectively (Table 4). The specificity was higher than that of CD56, whereas the sensitivity was lower than that of CD56.

GAL3 expression was noted in 79 of 80 PTC cases (98.75%) and was diffuse, strong, and positive in more than 66% of tumor cells. GAL3 expression was negative only in one case of encapsulated follicular variant of POC. No significant difference was observed between the POC and PMC cases ($p=0.2875$). It was also positive in all five HT cases and 6 of the 12 NH cases, although less strong and diffuse than in the PTC cases (Fig. 3A). All five FA were negative for GAL3. GAL3 distinguished PTC from FA and NH to a statistically significant degree, but could not distinguish PTC from HT (Table 3). The sensitivity and specificity of GAL3 were 98.75% and 50.00%, respectively (Table 4). The sensitivity was higher than that of CD56 and HMCK, but the specificity was much lower than that of CD56 and HMCK.

CK19 was positive in all PTC and more than 66% of tumor cells were strongly and diffusely positive. CK19 was also positive in four of five cases of FA (80%), five of 12 cases of NH

Table 3. The results of statistical analyses for immunohistochemical expression

| Antibody expression | Diagnosis | Positive | Negative | Total | Comparing | p-value |
|---------------------|-----------|----------|----------|-------|---------------|---------|
| CD56 expression | POC | 2 | 21 | 23 | With PMC | 0.5745 |
| | PMC | 2 | 55 | 57 | | |
| | PTC | 4 | 76 | 80 | With FA+NH+HT | <0.0001 |
| | FA | 5 | 0 | 5 | With PTC | <0.0001 |
| | NH | 7 | 5 | 12 | With PTC | <0.0001 |
| HMCK expression | HT | 4 | 1 | 5 | With PTC | 0.0002 |
| | POC | 19 | 4 | 23 | With PMC | 0.0537 |
| | PMC | 55 | 2 | 57 | | |
| | PTC | 74 | 6 | 80 | With FA+NH+HT | <0.0001 |
| | FA | 0 | 5 | 5 | With PTC | <0.0001 |
| GAL3 expression | NH | 2 | 10 | 12 | With PTC | <0.0001 |
| | HT | 0 | 5 | 5 | With PTC | <0.0001 |
| | POC | 22 | 1 | 23 | With PMC | 0.2875 |
| | PMC | 57 | 0 | 57 | | |
| | PTC | 79 | 1 | 80 | With FA+NH+HT | <0.0001 |
| CK19 expression | FA | 0 | 5 | 5 | With PTC | <0.0001 |
| | NH | 6 | 6 | 12 | With PTC | <0.0001 |
| | HT | 5 | 0 | 5 | With PTC | 1.0000 |
| | POC | 23 | 0 | 23 | With PMC | - |
| | PMC | 57 | 0 | 57 | | |
| | PTC | 80 | 0 | 80 | With FA+NH+HT | <0.0001 |
| | FA | 4 | 1 | 5 | With PTC | 0.0588 |
| | NH | 5 | 7 | 12 | With PTC | <0.0001 |
| | HT | 5 | 0 | 5 | With PTC | - |

POC, papillary thyroid overt carcinoma; PMC, papillary thyroid microcarcinoma; PTC, papillary thyroid carcinoma; FA, follicular adenoma; NH, nodular hyperplasia; HT, Hashimoto's thyroiditis; HMCK, high molecular weight cytokeratin; GAL3, galectin-3; CK19, cytokeratin 19.

(41.7%) and all five cases of HT (100%), although less strong and diffuse than that of PTC (Fig. 3B).

CK19 was able to distinguish PTC from some of the FA, NH, and HT, however it could not distinguish all cases of FA and HT (Table 3). The sensitivity and specificity of CK19 were 100% and 36.36%, respectively (Table 4).

With the combination of three markers [CD56(-), GAL3(+), and CK19(+)], 75 of 80 PTC cases showed positive finding (93.8%) and only two of 22 other benign lesions were positive. With the combination of four markers [CD56(-), GAL(+), CK19(+), and HMCK(+)], 70 of 80 PTC cases and none of 22 other benign lesions were positive (Table 5). Thus, with the combination of four markers [CD56(-), GAL(+), CK19(+), and HMCK(+)], the specificity and positive predictive value were 100% each, but sensitivity was 87.5% (Table 4).

But the sensitivity and specificity were 93.8% and 90.9%, respectively, to distinguish PTC from other BTL with the combination of three markers [CD56(-), GAL3(+), and CK19(+)]. When PTC were divided into two groups: 1) POC, > 1 cm in

Table 4. The sensitivity, specificity, positive and negative predictable values, and accuracy for distinguishing papillary thyroid carcinoma from other benign thyroid lesions

| Markers | SEN | SPEC | PPV | NPV | Accuracy |
|--|--------|--------|--------|--------|----------|
| CD56(-) | 95.00 | 72.73 | 92.68 | 80.00 | 90.20 |
| GAL3(+) | 98.75 | 50.00 | 87.78 | 91.69 | 88.24 |
| CK19(+) | 100.00 | 36.36 | 85.11 | 100.00 | 86.27 |
| HMCK(+) | 92.50 | 90.91 | 97.37 | 76.92 | 92.16 |
| CD56(-), GAL3(+), and CK19(+) | 93.75 | 90.91 | 97.40 | 80.00 | 93.14 |
| CD56(-), GAL3(+), CK19(+), and HMCK(+) | 87.50 | 100.00 | 100.00 | 68.75 | 90.20 |

Values are presented as percentage.

SEN, sensitivity; SPEC, specificity; PPV, positive predictive value; NPV, negative predictive value; GAL3, galectin-3; CK19, cytokeratin 19; HMCK, high molecular weight cytokeratin.

Table 5. The positive and negative number of cases using three markers together and four markers together

| | Positive | Negative | Total |
|--|----------|----------|-------|
| CD56(-), GAL3(+), and CK19(+) | | | |
| PTC | 75 | 5 | 80 |
| BTL | 2 | 20 | 22 |
| Total | 77 | 25 | 102 |
| CD56(-), GAL3(+), CK19(+), and HMCK(+) | | | |
| PTC | 70 | 10 | 80 |
| BTL | 0 | 22 | 22 |
| Total | 70 | 32 | 102 |

GAL3, galectin-3; CK19, cytokeratin 19; PTC, papillary thyroid carcinoma; BTL, benign thyroid lesions; HMCK, high molecular weight cytokeratin.

size, and 2) PMC, ≤ 1 cm in size, no significant difference was observed in the expression of these four markers (Table 3).

DISCUSSION

CD56 is a homophilic binding glycoprotein of the Ig-superfamily and its antibody targets an NCAM isoform that is expressed normally in natural killer cells, activated T cells, large granular lymphocytes, and specific endocrine, and brain tissues.^{2,4,6} NCAM is a multi-valent adhesion molecule that mediates homotypic and heterotypic cell-cell adhesion through a homophilic binding mechanism.⁷ Reduced CD56 expression has been implicated in tumor progression of patients with cancer. CD56 is present on follicular cells of the normal thyroid,^{5,8} but its expression is markedly reduced by malignant transformation as previously reported in cases of follicular carcinoma, anaplastic carcinoma, and papillary carcinoma.^{2,4,6-8,19} Recently, several studies about the usefulness of CD56 for distinguishing thyroid lesions, particularly PTC from other lesions, have been report-

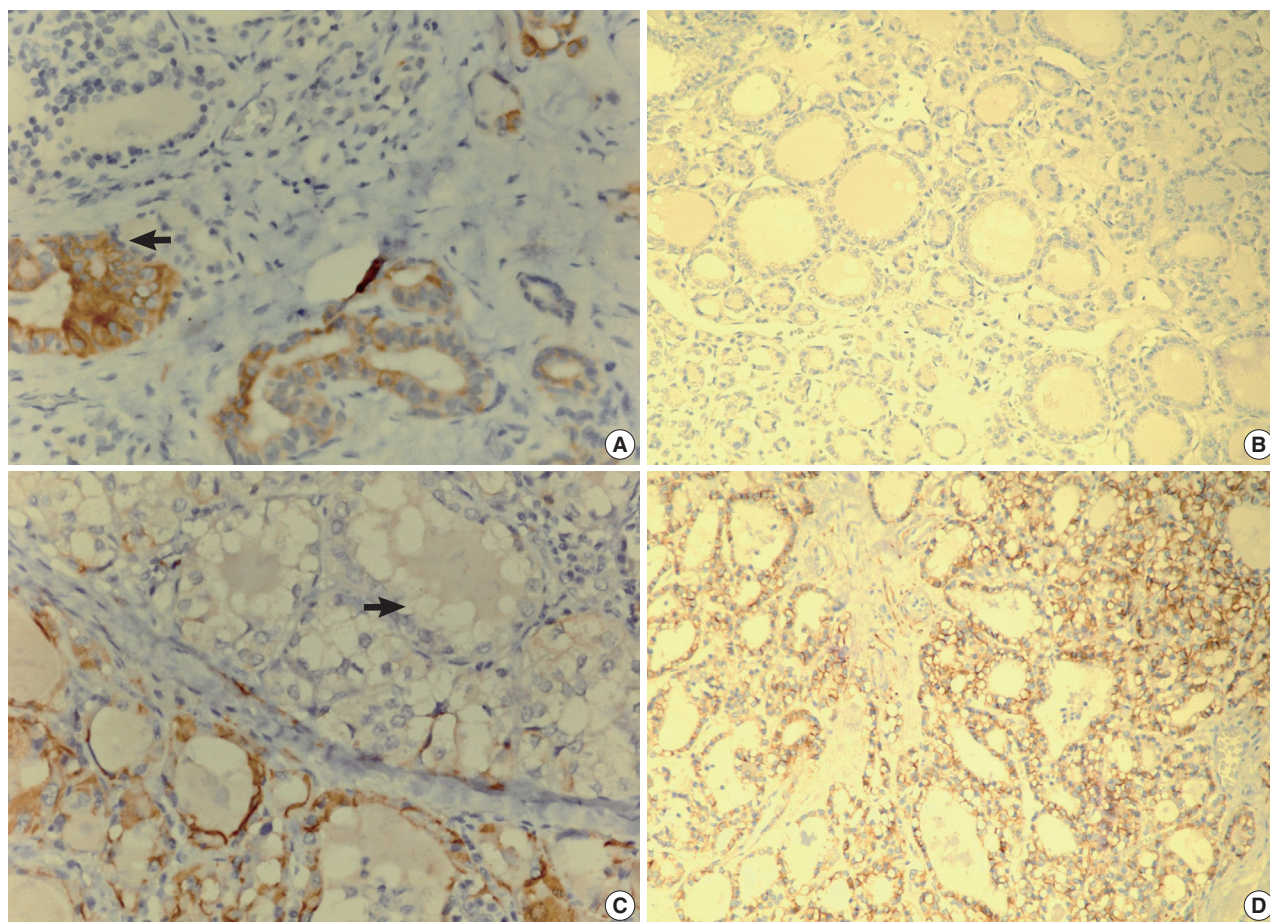


Fig. 1. Immunohistochemical features showing strong patchy to diffuse positive findings (arrow) in papillary thyroid microcarcinomas (A), negative finding in follicular adenomas (FA) (B) of high molecular weight cytokeratin, negative finding (arrow) in papillary thyroid overt carcinomas (C) contrasting positivity of the peripheral non-tumorous tissue and positive finding in FA (D) for CD56.

ed.^{2,4,6,7} Scarpino *et al.*⁷ studied CD56 expression in tissue sections of 61 PTC cases and 14 cases of lymph node metastasis by PTC using immunohistochemical staining. That study revealed negative CD56 findings in 18 primary tumors and CD56 was expressed in <5% of tumor cells in the remaining 43 cases. Similar results were obtained when CD56 expression was evaluated at the RNA level.⁷

A recent study by El Demellawy *et al.*⁶ used 175 cases of neoplastic and non-neoplastic thyroid lesions. That study included 75 carcinomas (72 papillary, two follicular, and one Hürthle cell), 35 adenomas (32 follicular and three Hürthle cell), and 65 non-neoplastic thyroid lesions (25 NH, five thyrotoxic hyperplasia, 19 lymphocytic thyroiditis, and six HT). They qualified the case as CD56 “positive (+)” when a positive membranous expression with or without cytoplasmic staining in 10% or more of neoplastic cells was present. Their results showed CD56 positivity in all lesions and tumors except for PTC in all cases

(100%).

In our study, even though we used the same scale (10% cut-off for recording negative CD56 expression) to interpret positive staining, four cases of PTC showed positive findings for CD56 (one case of POC with exuberant nodular fasciitis-like stroma, one case of classic type POC and two cases of PMC). Thus, we think that CD56 is not a 100% sensitive or specific marker for PTC. A recent study by Park *et al.*² also showed positive CD56 expression in five of 62 PTC cases. Only four cases of a PTC follicular variant were included in this study, and all showed negative CD56 expression. No significant difference was observed in CD56 expression between POC and PMC.

HMCK expression increases significantly in PTC and is helpful to distinguish PTC from other benign and malignant thyroid nodules.⁹⁻¹³ In our study, 74 of 80 PTC cases showed positive findings. The six cases that were negative for HMCK expression included one case of encapsulated follicular variant of

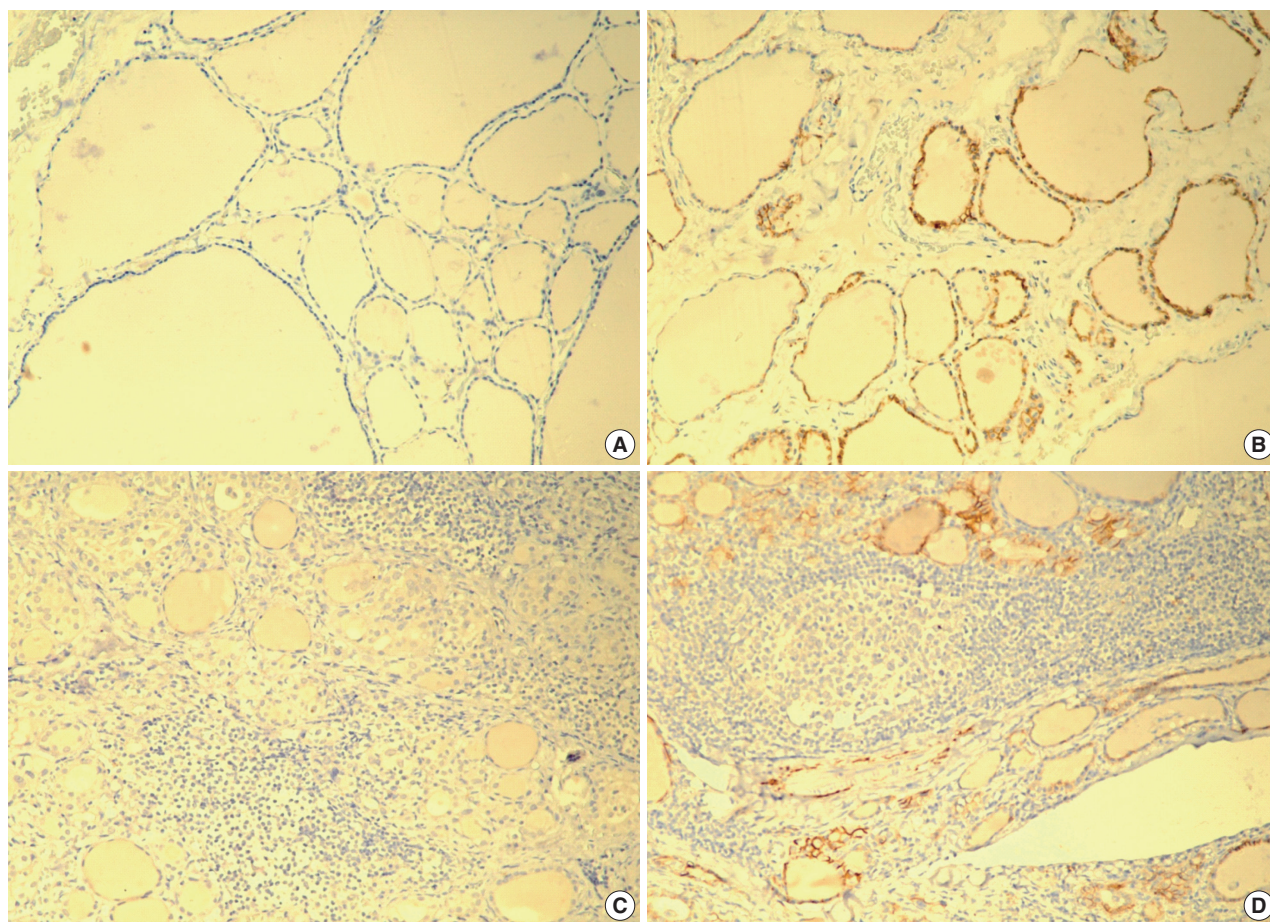


Fig. 2. Negative finding for high molecular weight cytokeratin immunohistochemical stain (A, C) and positive finding for CD56 immunohistochemical stain (B, D) in Hashimoto's thyroiditis and nodular hyperplasia.

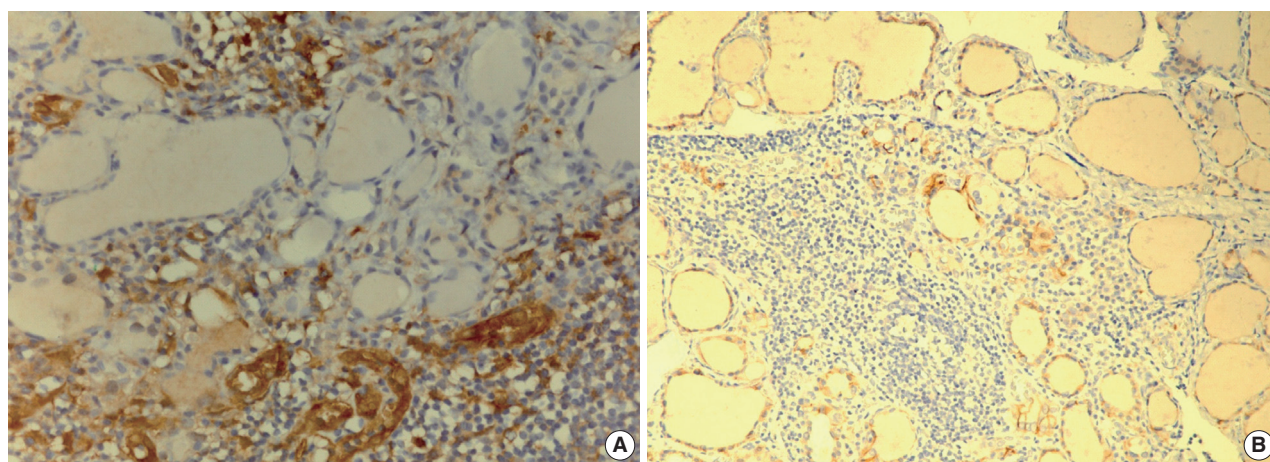


Fig. 3. Immunohistochemical stains showing the positivity of galectin-3 and cytokeratin 19 in Hashimoto's thyroiditis (A, B).

POC, one case of follicular variant of POC, two cases of classic type of POC and two cases of PMC. No positive case was noted in five cases of FA and five cases of HT. Two of 12 cases of NH

cases were positive. HMCK disclosed the highest specificity (90.9%) to distinguish PTC from BTL among the four immunohistochemical markers that we used and also a relatively high

sensitivity (92.5%), although it was the lowest among the markers that we used. Four cases of follicular variant PTC showed low HMCK expression (two cases were negative, one case was 1+, and one case was weak 2+).

No significant difference in HMCK expression was observed between POC and PMC.

GAL3 is a well known marker to distinguish between benign and malignant thyroid nodules.^{2,13,14} However, some studies have doubted the reliability of GAL3 as a marker of thyroid malignancy.¹⁵⁻¹⁸ In this study, only one case of POC (encapsulated follicular variant of POC) showed a negative finding. So the sensitivity for distinguishing PTC from BTL was very high (98.8%). But all five cases of HT revealed GAL3 positivity. So, GAL3 may not provide support for distinguishing PTC from HT in difficult cases of HT. Six of 12 NH cases showed positive GAL3 findings. Thus, it remains difficult to distinguish PTC from NH showing papillary features using GAL3. No significant difference in GAL3 expression was observed between POC and PMC.

CK19 is useful for diagnosing papillary carcinoma, which it shows diffuse and strong cytoplasmic staining.^{2,3,6,11-13} All 80 of our PTC cases including four cases of follicular variant showed strong and diffuse CK19 immunoreactivity. However, our HT, FA, and NH cases showed CK19 immunoreactivity of 100%, 80.0%, and 41.7%, respectively. Although the sensitivity of CK19 for distinguishing PTC from BTL was 100%, the specificity (36.4%) was the lowest among those markers tested.

No significant difference in CK19 expression was observed between POC and PMC.

The sensitivity and specificity were 93.8% and 90.9%, to distinguish PTC from other BTL, using a combination of three markers [CD56(-), GAL3(+), and CK19(+)]. With the combination of four markers [CD56(-), GAL(+), CK19(+), and HMCK(+)], the specificity or positive predictive value was 100%, respectively although sensitivity was only 87.5% (Table 4).

In this study, because only four cases of the PTC follicular variant were included, precise analysis about the difference in immunohistochemical stains between the PTC follicular variant and classic type PTC could not be performed.

Further studies including a larger number of PTC follicular variants may indicate the usefulness of these markers to distinguish follicular proliferative lesions from PTC follicular variants.

In conclusion, CD56 was valuable as a negative diagnostic marker for distinguishing PTC from BTL and HMCK was very specific marker for PTC, where as GAL3 and CK19 were very sensitive markers for PTC. Although the differential diagnoses

of thyroid follicular lesions are based on histological and cytomorphological criteria, CD56 and HMCK might be useful markers for diagnosing PTC.

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