

CD56, HBME-1 and cytokeratin 19 expressions in papillary thyroid carcinoma and nodular thyroid lesions

Senay Erdogan-Durmus, Deniz Ozcan¹, Enver Yarikkaya¹, Ali Kurt, Aynur Arslan²

Department of Pathology, Erzurum Region Training and Research Hospital, Erzurum, ¹Department of Pathology, Okmeydani Training and Research Hospital, ²Department of Internal Medicine, İstinye State Hospital, İstanbul, Turkey

Background: Carcinomas of the thyroid follicular epithelium are the most common cancers of the endocrine system. In the diagnosis of thyroid nodules and tumors, the gold standard is histological evaluation. In cases which have morphological overlap, immunohistochemistry is needed for differential diagnosis. The purpose of this study is to investigate the expressions of CD56, HBME-1, cytokeratin 19 (CK19) antibodies in papillary thyroid carcinoma (PTC) and thyroid nodular lesions and their contributions to differential diagnosis. **Materials and Methods:** In this study, 47 PTCs (26 follicular variant, 21 classic type) and 26 benign thyroid lesions (15 nodular hyperplasia, 10 follicular adenomas, 1 Hurtle cell adenoma) were analyzed retrospectively. HBME-1, CK19, and CD56 antibodies were performed with immunohistochemical methods. The results were evaluated statistically. **Results:** +3 staining with HBME-1 and CK19 was observed in 72.3% and 83% of patients with PTC. In 95.7% of PTC cases, loss of CD56 expressions in various degrees was identified. A statistically significant difference was detected in HBME-1, CK19, and CD56 expressions between PTCs and benign lesions ($P < 0.001$). **Conclusion:** In our study, positive staining of HBME-1, CK19, and loosing expression of CD56 that supports malignancy was found and concluded that CD56 is a helpful antibody for the differential diagnosis of benign and malignant lesions and may increase the diagnostic accuracy when used with HBME-1 and CK19.

Key words: CD56, HBME-1, immunohistochemistry, papillary thyroid carcinoma

How to cite this article: Erdogan-Durmus S, Ozcan D, Yarikkaya E, Kurt A, Arslan A. CD56, HBME-1 and cytokeratin 19 expressions in papillary thyroid carcinoma and nodular thyroid lesions. J Res Med Sci 2016;21:49.

INTRODUCTION

Thyroid nodules are quite common in society. The prevalence of palpable thyroid nodules is 4–7% in adult populations.^[1] Thyroid neoplasms are the most common types of the endocrine system cancer and 1% of all cancers. Papillary thyroid carcinoma (PTC) constitutes about 80% of thyroid neoplasms.^[2] At present, histopathologic evaluation using hematoxylin and eosin staining is the “gold standard” for the diagnosis of thyroid nodules and tumors. However, morphological overlap especially between follicular lesions and follicular variant papillary thyroid carcinoma (FVPTC) is common. In such cases, diagnosing is often impossible

only on the basis of morphological features.^[3] In the differentiation of thyroid lesions, cytokeratin 19 (CK19) and mesothelioma antibody (HBME-1: Mesothelioma ab-1) expressions were examined in many studies and significant results were obtained.^[4-6] Similarly, there were studies showing that loss of CD56 expression in malignant thyroid lesions.^[3,5-7] CD56 is a neural cell adhesion molecule that is expressed in natural killer cells, activated T-lymphocytes, and neural and muscle tissue.^[8,9] Studies reported that CD56 expressed in normal thyrocytes, benign or malignant follicular lesions but not in PTC and had quite high sensitivity and specificity in differentiating PTC other follicular thyroid lesions.^[10,11]

In this study, we investigated the role of CD56, HBME-1, and CK19 in discriminating the PTC from

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Access this article online

Quick Response Code:



Website:

www.jmsjournal.net

DOI:

10.4103/1735-1995.183986

Address for correspondence: Dr. Şenay Erdogan-Durmus, Department of Pathology, Erzurum Region Training and Research Hospital, Erzurum, Turkey. E-mail: senayerdgn@gmail.com

Received: 17-01-2016; **Revised:** 14-03-2016; **Accepted:** 06-04-2016

other nodular lesions of the thyroid. Although there were similar studies on this subject, only a few studies were performed in Turkey. We aimed to support the literature with our results and to make a contribution to the routine practice.

MATERIALS AND METHODS

The material of this case-control retrospective study included 73 specimens of surgically removed, formalin-fixed, and paraffin-embedded thyroid lesions that were received at the Pathology Department of Okmeydani Training and Research Hospital, İstanbul, from January 2009 to January 2013. Parameters were obtained from the pathology reports such as age, gender, tumor size, multicentric disease, subtypes, extrathyroidal spreading, and lymph node metastasis.

Our 73 selected thyroid lesions included:

- 47 PTC cases
- 26 cases of nodular thyroid lesions.

Forty-seven PTC cases were further classified into 21 cases of classic PTCs and 26 cases of FVPTCs. Twenty-six cases of nodular thyroid lesions included 15 cases of nodular hyperplasia (NH), 10 cases of follicular adenoma (FA), and one case of Hurtle cell adenoma. Cases were randomly selected from the database of the hospital. Follicular carcinomas (FCs) and consultation cases were excluded from the study.

Immunohistochemistry

All 73 samples (47 PTC, 26 nodular thyroid lesions) were subjected to immunohistochemical staining with HBME-1 (Clone: HBME-1, Thermo Scientific®), CK19 (Clone: A53-B/A2.26 Thermo Scientific®), and CD56 (clone: 123C3.D5 Thermo Scientific®) antibodies. The paraffin-embedded tissue sections were deparaffinized by one-night incubation in the oven at 56°C and waiting in xylene. Tissue sections were rehydrated through absolute alcohol. Antigen retrieval in citrate buffer was used after the sections were treated in a microwave 3 times for 5 min, and the sections were then left to cool for 20 min. Respectively, sections were incubated in tris-buffered saline (TBS) 10 min, 3% hydrogen peroxide 20 min, TBS 10 min. Primary antibodies for HBME-1, CK19, and CD56 were applied to sections and incubated for 30 min. This was followed by the secondary biotin-conjugated antibody (Biotinylated Goat antiserum) for 20 min and finally, the peroxidase-conjugated streptavidin for another 20 min. 3-amino-9-ethylcarbazole chromogen was added for 25–35 min and then counterstained with Harris hematoxylin followed by dehydration, clearing, and mounting.

Interpretation of immunohistochemical staining of CD56, HBME-1, and cytokeratin 19

The results of immunohistochemical staining were evaluated by two independent observers semiquantitatively. For all three antibodies, percentage and severity of staining were assessed. HBME-1 and CK19 expressions were scored as follows: 0, staining in <5% of the cells; 1, staining in 5–30% of the cells; 2, staining in 31–69% of the cells; 3, staining in >70% of the cells. CD56 expression was scored as follows: 0, staining in <10% of the cells; 1, staining in 11–25% of the cells; 2, staining in 26–50% of the cells; 3, staining in >50% of the cells.

Statistical analysis

Data were analyzed using the SPSS program version 21 (IBM®). Descriptive statistics for the evaluation of results have been shown in the form of mean; the nominal variables have been shown as the number of cases and percentage (%). Compliance normal distribution of numerical values was analyzed by the Shapiro-Wilk test. Unfit for normal distribution values was given in the form of median (minimum–maximum). Comparison of qualitative variables between groups was carried out using the Chi-square test. Kruskal-Wallis test was used for assessing the percentage and severity of staining in comparing with lesions sizes. A $P=0.05$ was chosen as the level of significance.

RESULTS

Forty-seven of 73 cases (64, 4%) were PTC, and 26 of 73 cases (35, 6%) were benign nodular thyroid lesions. The ages of the patients were between 21 and 77 years, and the arithmetic mean of age 48.2 for PTC and 50.8 for benign lesions. About 83.6% of the patients ($n = 61$) were female and 16.4% of the patients ($n = 12$) were male. In benign and malignant groups, female gender was higher, but there was no significant difference between the two groups in terms of gender.

About 46.8% of PTC cases had multicentric tumors, and 63.8% of PTC cases the tumor was encapsulated. Capsule invasion, thyroid capsule invasion, and lymph node metastasis were observed in 31.9%, 19.1%, and 4.3% of cases, respectively. In PTC subtypes, the rate of capsular invasions was 23.8% in classical type and 38.4% in follicular variant.

The median of lesion sizes in benign group was 2 cm (min-max: 0.4–5.5 cm), and the median of lesion sizes in PTC cases was 1.5 cm (min-max: 0.2–5 cm). There was no significant difference in comparing with lesions' sizes with the percentage and severity of staining for HBME-1, CK19, and CD56.

In PTC cases, +3 staining percentages for HBME-1, CK19, and CD56 were 72.3%, 83%, and 4.3%, respectively.

Assessment of CD56 staining in the 47 PTC cases showed negative CD56 expression in 32 cases (68.1%), and 43 cases had varying degrees of loss in CD56 expression (95.7%) [Figures 1 and 2]. All of the benign cases showed positive staining with CD56. About 80.8% of these cases had +3 staining [Table 1 and Figures 3, 4]. Between benign and malignant groups, there found a significant difference for percentages of HBME-1, CK19, and CD56 staining with Chi-square test ($P < 0.001$). The percentages of HBME-1, CK19, and CD56 staining for subtypes of lesions are shown in Table 2.

DISCUSSION

The most important method for determining the biological behavior of thyroid nodules is routine pathological

examination. However, follicular and papillary structures can be seen in both benign and malignant lesions. Furthermore, some nuclear properties of papillary carcinoma can be seen in benign lesions. All these lead to serious differences at the evaluation and different diagnoses for the same lesion between pathologists.^[2] The diagnostic concordance rates were found high in papillary and anaplastic carcinomas but low in FC. These facts indicate the need for further diagnostic immunohistochemical markers in the differential diagnosis of thyroid tumors (TTs) and many studies have been made.^[2,7,12-14]

Nasr *et al.* have worked a lot of immunohistochemical markers in 51 PTC and 57 benign thyroid lesions. They have found HBME-1 staining in 96% of the malignant group and staining was not observed in 93% of benign lesions.^[13] Similarly, in our

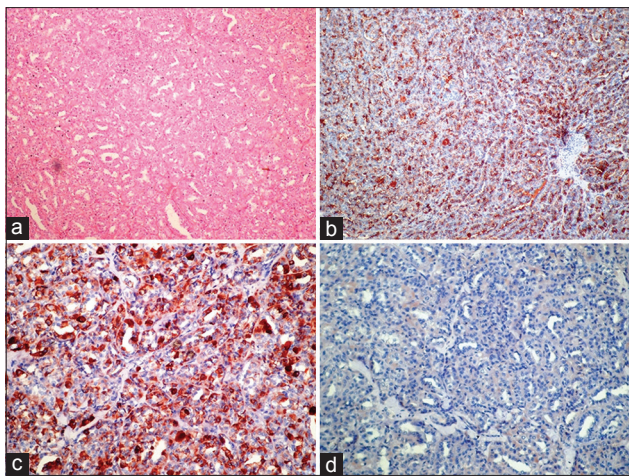


Figure 1: (a) A case of follicular variant papillary thyroid carcinoma composed largely of irregularly shaped small- to medium-sized follicles with nuclear features of papillary thyroid carcinoma. There are no papillary structures. In the same case, positive membranous staining with HBME-1 (b), positive staining with cytokeratin 19 (c), and no staining with CD56 (d) (a: H and E×100; b: HBME-1×100; c: CK19×200; d: CD56×100)

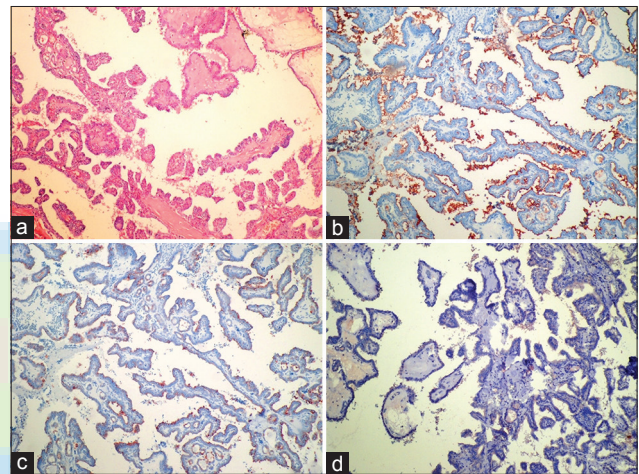


Figure 2: (a) A case of classic papillary thyroid carcinoma. There are branching papillary structures, fibrovascular cores, polygonal-shaped neoplastic cells with eosinophilic cytoplasm, and overlapping. In the same case, positive membranous staining in luminal side with HBME-1 (b), positive staining with cytokeratin 19 (c), and no staining with CD56 (d) (a: H and E×100; b: HBME-1 ×100; c: CK19×100; d: CD56×100)

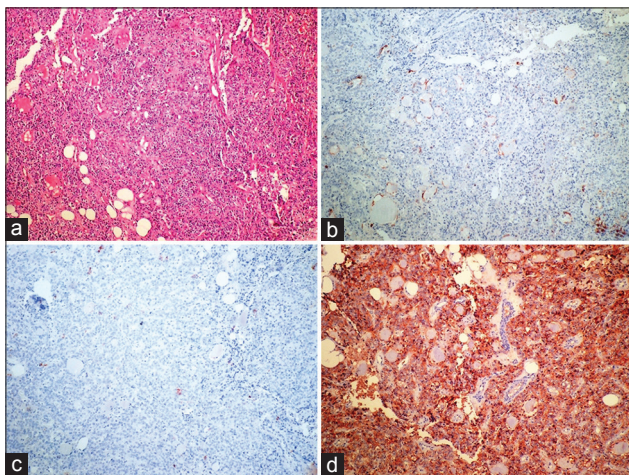


Figure 3: (a) A case of follicular adenomas. There are so many follicles with various sizes and some of them have colloid in lumen. In the same case, weak and focal staining with HBME-1 (b), no staining with cytokeratin 19 (c), and strong staining with CD56 (d) (a: H and E×100; b: HBME-1 ×100; c: CK19×100; d: CD56×100)

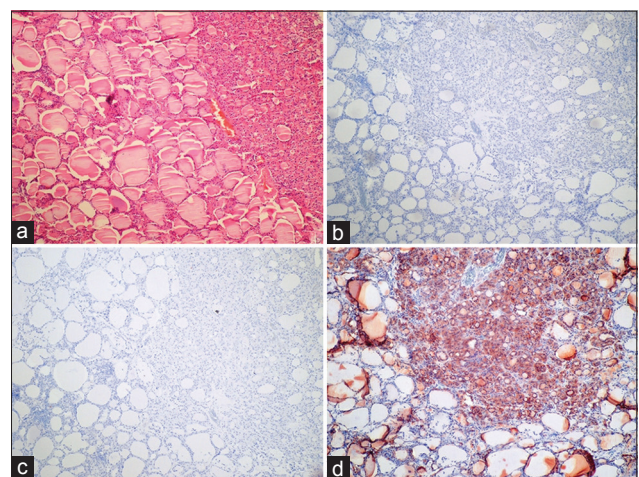


Figure 4: (a) A case of nodular hyperplasia. There are multiple variably size nodules (one of them was shown). In the same case, no staining with HBME-1 (b) and cytokeratin 19 (c) and strong staining with CD56 (d) (a: H and E×100; b: HBME-1 ×100; c: CK19×100; d: CD56×100)

Table 1: Staining prevalences of HBME-1, cytokeratin 19, and CD56 in papillary thyroid carcinoma and benign groups

	0 (%)	+1 (%)	+2 (%)	+3 (%)	Total (%)	P value in Chi-square test
HBME-1						
PTC	10.6	12.8	4.3	72.3	100	<0.001
Benign	92.3	0	3.8	3.8	100	
Total	39.7	8.2	4.1	47.9	100	
CK19						
PTC	2.1	10.6	4.3	83.0	100	<0.001
Benign	65.4	23.1	0	11.5	100	
Total	24.7	15.1	2.7	57.5	100	
CD56						
PTC	68.5	23.4	4.3	4.3	100	<0.001
Benign	0	7.7	11.5	80.8	100	
Total	43.8	17.8	6.8	31.5	100	

PTC = Papillary thyroid carcinoma; CK19 = Cytokeratin 19

Table 2: Staining prevalences of HBME-1, cytokeratin 19, and CD56 in subtypes of papillary thyroid carcinoma and benign lesions

	0 (%)	+1 (%)	+2 (%)	+3 (%)	Total
HBME-1					
FVPTC** (n=26)	11.5	15.4	3.8	69.2	100
Classic PTC* (n=21)	9.5	9.5	4.8	76.2	100
Total	10.6	12.8	4.3	72.3	100
NH*** (n=15)	86.6	0	6.7	6.7	100
FA**** (n=10)	100	0	0	0	100
HCA***** (n=1)	100	0	0	0	100
Total	92.3	0	3.8	3.85	100
CK19					
FVPTC (n=26)	0	15.4	3.8	80.8	100
Classic PTC (n=21)	4.8	4.8	4.8	85.7	100
Total	2.1	10.6	4.3	83.0	100
NH (15)	86.6	13.4	0	0	100
FA (n=10)	30	40	0	30	100
HCA (n=1)	100	0	0	0	100
Total	65.4	23.1	0	11.5	100
CD56					
FVPTC (n=26)	65.4	23.1	7.7	3.8	100
Classic PTC (n=21)	71.4	23.8	0	4.8	100
Total	68.1	23.4	7.7	3.1	100
NH (n=15)	0	13.3	6.7	80	100
FA (n=10)	0	0	20	80	100
HCA (n=1)	0	0	0	100	100
Total	0	7.7	11.5	80.8	100

*PTC = Papillary thyroid carcinoma; **FVPTC = Follicular variant papillary thyroid carcinoma; ***NH = Nodular hyperplasia; ****FA = Follicular adenoma; *****HCA = Hurtle cell adenoma; CK19 = Cytokeratin 19

study, 72.3% of PTC group had diffuse and strong staining with HBME-1, and the staining was not observed in 92.3% of benign lesions. There is a significant difference between PTC group and benign group for the HBME-1 staining ($P < 0.01$).

In a study which examined the expressions of HBME-1, CK19, and galectin in papillary hyperplasias and papillary

carcinomas, they found that all three markers showed diffuse positive staining in papillary carcinomas. In contrast, positive staining has been seen in benign lesions with CK19 and galectin. HBME-1 was found more specific than other two markers.^[14] In another study, HBME-1, CK19, and galectin-3 antibodies were performed in 393 benign thyroid lesions and 65 malignant thyroid lesions. Specificity rates for HBME-1, CK19, and galectin-3 were determined 99.7%, 97.7%, and 99.2%, respectively.^[15]

In the current study, in PTC group, the percentage of staining for HBME-1 and CK19 was 72.3% and 83.3%, respectively. The loss of CD56 expression was observed in 95.7% of malignant lesions. In benign lesions, staining prevalence of HBME-1, CK19, and CD56 was 7.7%, 23.1%, and 100%, respectively. According to these findings, the most specific marker was CD56 and the least specific marker was CK19 for distinguishing benign and malignant lesions. HBME-1 was found more specific than CK19 for PTC.

Saleh *et al.* worked galectin-3, HBME-1, CK19, and Ret oncoprotein immunohistochemically in 98 benign thyroid nodules (52 hyperplastic nodules, 46 follicular or HHA) and 54 malignant TTs (22 FC, 20 classic PTC, and 12 FVPTC). They found strong staining with CK19 in 85% of classic PTC and 83.3% of FVPTC cases. About 31.6% of benign nodules showed staining with CK19 in different prevalence and severity. In the same study, staining percentage of HBME-1 in classic PTC and FVPTC was 90% and 91.7%, respectively.^[16] Similar results were obtained in our study for staining percentage of HBME-1 and CK19 at FVPTC and classic PTC.

In a study, the expression of CD56 in PTC has investigated with the immunohistochemistry and polymerase chain reaction (PCR) methods. CD56 staining was not seen in 18 out of 61 PTC cases and focal weak staining was observed in 43 cases. In all PTC cases, absence or decrease in expression of CD56 was observed with PCR. CD56 expression was seen in FA and normal thyroid tissue.^[17] Similarly, in our study, CD56 staining was not seen in 32 out of 47 PTC cases, focal weak staining in 13 cases, and strong staining in 2 cases. In all benign lesions, there was positive CD56 staining with different rates (+3, +2, +1).

Park *et al.* have worked CD56, galectin-3, and CK19 immunohistochemically in thyroid carcinomas and benign thyroid nodules. There was no staining with CD56 in 92.5% of PTC cases. They found strong staining (3+) only in one case. Staining percentages of CD56 for FA and NH cases were 93.3% and 90.5%, respectively. For this study, the most specific marker was CD56 in comparison with CK19 and galectin-3.^[11] In our study, strong staining (3+) with CD56 was seen only in two cases (4.3%). Staining percentages of CD56 for benign lesions (FA and NH) were 100%. Similar

to the literature, CD56 was the most specific marker at distinction between benign and malignant lesions.

In a study that examined the expressions of CD56 and claudin-1 in thyroid lesions, CD56 positive staining was detected in 89.4% of nodular lesions with follicular pattern. Staining percentage for FA was 91.7% while it was 87.5% for hyperplastic nodules. CD56 staining was not observed 82.8% of PTC cases. Staining observed in 5 patients was reported to be focal staining and poor (score 2 skor1 and staining). In five cases which observed positive staining with CD56, staining was focal weak. Weak staining with CD56 was seen in 3 out of 16 FVPTC cases and 2 out of 13 classic PTC cases.^[3] In our study, results were similar to the literature. CD56 staining percentages were 100% in benign cases. Strong staining with CD56 (3+) was seen in 80% of FA and NHs. CD56 staining was not observed in 68.1% of PTC cases. Strong CD56 staining (3+) was seen in one out of 26 FVPTC cases and one out of 21 classic PTC cases. A statistically significant difference was found between the benign and malignant groups among the staining characteristics ($P < 0.001$).

In another study, evaluation of CD56 staining in the 73 PTC cases showed negative CD56 expression in 49 cases (65.7%). In 20 (27.3%) cases, CD56 expression was cytoplasmic (not membranous) and considered negative. On the other hand, expression of CD56 in nonpapillary carcinoma lesions such as FC and FA was positive (membranous) in 70 cases out of 73 cases (95.8%).^[18] Our results were similar to the current study. However, in our study, we did not see any cytoplasmic staining for CD56. We thought that it was about clone of antibody.

Nechifor-Boila *et al.* evaluated CD56 in 11 PTC cases and 31 TTs of uncertain malignant potential (TTs-UMP). Nine of 11 PTC cases (5/6 classic PTC and 4/5 FVPTC) were negative for CD56. Nineteen of 31 TTs-UMP cases (61.3%) showed positive staining with CD56.^[19] In a study which researched CD56, e-cadherin, HBME-1, galectin-3, and CK19 expressions in PTCs, benign thyroid lesions such as FA, NH, and well-differentiated tumors of uncertain malignant potential (WDT-UMPs), CD56 negativity was observed in 92 (91.1%) of 101 PTCs, 5 (8.3%) of 60 benign lesions, and 13 (65%) of 20 WDT-UMPs. These researchers suggested that the double and triple panels of the CD56 negative marker with HBME-1 and/or galectin-3 positive markers might very useful for differential diagnosis of PTC cases.^[20] Similar to the literature, in our study, 43 (95.7%) of 47 PTC cases showed loss of CD56 expression in varying degrees.

CONCLUSION

In our study, we found that positive staining of HBME-1, CK19, and loosing expression of CD56 support malignancy.

However, in benign lesions such as FA and NH, we observed strong CD56 staining by immunohistochemically. In the majority of PTC cases, CD56 was negative or there was a loss of expression in various degrees. Eventually, we suggested that CD56 is a helpful antibody for the differential diagnosis of benign and malignant thyroid lesions and may increase the diagnostic accuracy when used with HBME-1 and CK19.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors have no conflicts of interest.

AUTHORS' CONTRIBUTIONS

All authors contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

REFERENCES

- Dobrinja C, Trevisan G, Liguori G, Romano A, Zanconati F. Sensitivity evaluation of fine-needle aspiration cytology in thyroid lesions. *Diagn Cytopathol* 2009;37:230-5.
- DeLellis RA, Williams ED. Tumours of the thyroid and parathyroid. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C, editors. *WHO Classification of Tumors, Pathology and Genetics of Tumours of Endocrine Organs*. 3rd ed. Lyon, France: IARC Press; 2004. p. 49-133.
- Abd El Atti RM, Shash LS. Potential diagnostic utility of CD56 and claudin-1 in papillary thyroid carcinoma and solitary follicular thyroid nodules. *J Egypt Natl Canc Inst* 2012;24:175-84.
- Prasad ML, Pellegata NS, Huang Y, Nagaraja HN, de la Chapelle A, Kloos RT. Galectin-3, fibronectin-1, CITED-1, HBME1 and cytokeratin-19 immunohistochemistry is useful for the differential diagnosis of thyroid tumors. *Mod Pathol* 2005;18:48-57.
- Papotti M, Rodriguez J, De Pampa R, Bartolazzi A, Rosai J. Galectin-3 and HBME-1 expression in well-differentiated thyroid tumors with follicular architecture of uncertain malignant potential. *Mod Pathol* 2005;18:541-6.
- Ozolins A, Narbutis Z, Strumfa I, Volanska G, Stepanovs K, Gardovskis J. Immunohistochemical expression of HBME-1, E-cadherin, and CD56 in the differential diagnosis of thyroid nodules. *Medicina (Kaunas)* 2012;48:507-14.
- Shin MK, Kim JW, Ju YS. CD56 and high molecular weight cytokeratin as diagnostic markers of papillary thyroid carcinoma. *Korean J Pathol* 2011;45:477-84.
- Migita K, Eguchi K, Kawakami A, Ida H, Fukuda T, Kurata A, *et al.* Detection of Leu-19 (CD56) antigen on human thyroid epithelial cells by an immunohistochemical method. *Immunology* 1991;72:246-9.
- Lanier LL, Testi R, Bindl J, Phillips JH. Identity of Leu-19 (CD56) leukocyte differentiation antigen and neural cell adhesion molecule. *J Exp Med* 1989;169:2233-8.
- El Demellawy D, Nasr A, Alowami S. Application of CD56, P63 and CK19 immunohistochemistry in the diagnosis of papillary carcinoma of the thyroid. *Diagn Pathol* 2008;3:5.
- Park WY, Jeong SM, Lee JH, Kang HJ, Sin DH, Choi KU, *et al.* Diagnostic value of decreased expression of CD56 protein in

- papillary carcinoma of thyroid gland. *Basic Appl Pathol* 2009;2:63-8.
12. Zeromski J, Dworacki G, Jenek J, Niemir Z, Jezewska E, Jenek R, *et al.* Protein and mRNA expression of CD56/N-CAM on follicular epithelial cells of the human thyroid. *Int J Immunopathol Pharmacol* 1999;12:23-30.
 13. Nasr MR, Mukhopadhyay S, Zhang S, Katzenstein AL. Immunohistochemical markers in diagnosis of papillary thyroid carcinoma: Utility of HBME1 combined with CK19 immunostaining. *Mod Pathol* 2006;19:1631-7.
 14. Casey MB, Lohse CM, Lloyd RV. Distinction between papillary thyroid hyperplasia and papillary thyroid carcinoma by immunohistochemical staining for cytokeratin 19, galectin-3, and HBME-1. *Endocr Pathol* 2003;14:55-60.
 15. Barut F, Onak Kandemir N, Bektas S, Bahadir B, Keser S, Ozdamar SO. Universal markers of thyroid malignancies: Galectin-3, HBME-1, and cytokeratin-19. *Endocr Pathol* 2010;21:80-9.
 16. Saleh HA, Jin B, Barnwell J, Alzohaili O. Utility of immunohistochemical markers in differentiating benign from malignant follicular-derived thyroid nodules. *Diagn Pathol* 2010;5:9.
 17. Scarpino S, Di Napoli A, Melotti F, Talerico C, Cancrini A, Ruco L. Papillary carcinoma of the thyroid: Low expression of NCAM (CD56) is associated with downregulation of VEGF-D production by tumour cells. *J Pathol* 2007;212:411-9.
 18. Mokhtari M, Eftekhari M, Tahririan R. Absent CD56 expression in papillary thyroid carcinoma: A finding of potential diagnostic value in problematic cases of thyroid pathology. *J Res Med Sci* 2013;18:1046-50.
 19. Nechifor-Boila A, Catana R, Loghin A, Radu TG, Borda A. Diagnostic value of HBME-1, CD56, Galectin-3 and Cytokeratin-19 in papillary thyroid carcinomas and thyroid tumors of uncertain malignant potential. *Rom J Morphol Embryol* 2014;55:49-56.
 20. Ceyran AB, Şenol S, Şimşek BC, Sağıroğlu J, Aydın A. Role of cd56 and e-cadherin expression in the differential diagnosis of papillary thyroid carcinoma and suspected follicular-patterned lesions of the thyroid: The prognostic importance of e-cadherin. *Int J Clin Exp Pathol* 2015;8:3670-80.

