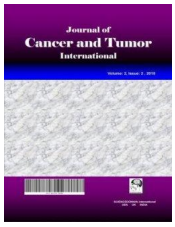

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Role of Immunohistochemistry in Diagnosis of Papillary Thyroid Carcinoma: The Use of Ck19, CD56, P63 and CD117

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Objective: Papillary thyroid carcinoma (PTC) is the most frequent histologic type of all thyroid malignancies. The presence of characteristic nuclear changes focally in a thyroid lesion may cause diagnostic dilemma. Immunohistochemistry may be helpful in the diagnosis of PTC yet not conclusive. The aim of this study is to test the applicability immunohistochemical markers; CK19, P63, CD56 and CD117 in distinguishing PTC from other follicular thyroid.
Methods: Fifty nine cases of unequivocal diagnosis were selected to be rolled in our study; 24 papillary carcinoma cases and 35 cases representing other follicular thyroid lesions. Immunohistological studies include CK19, P63, CD56 and CD117. Subsequent statistical analysis of immunohistochemical data in relation to diagnosis was performed.
Results: The diagnosis of PTC was significantly associated with Strong diffuse Ck19 expression, P63 expression and negative CD56 in relation to studied non PTC follicular thyroid lesions. On the other hand, CD117 was negative in most of the studied thyroid lesions with no significant difference between PTC and other lesions. CK19 was the most sensitive marker (91.2%) and P63 was the most specific one (87.5%), with better specificity in combining markers. Expression of CK19 and lost CD56 provided 97.1% sensitivity and 91.2% diagnostic accuracy in differentiating PTC from other studied lesions.

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Conclusions: Immunohistochemical markers, Ck19, P63 and CD56 are helpful in diagnosis of PTC and their combination can further improve diagnostic accuracy. CD117 is of no value in the diagnosis of studied cases.

Keywords: Papillary thyroid carcinoma; CK19; P63; CD56; CD117.

1. INTRODUCTION

Thyroid carcinoma is the most common malignancy of the endocrine system. Papillary thyroid carcinoma (PTC) is the most frequent histologic type, comprising 70% to 85% of all thyroid malignancies [1,2].

Up till today the gold standard for diagnosis of thyroid lesions particularly PTC is histopathology [3]. Characteristic nuclear changes are necessary for the diagnosis of papillary thyroid carcinoma (PTC), however when present focally they cause diagnostic dilemma in distinguishing it from other thyroid lesions [4].

Although these cases are minority of cases, labeling patients with cancer and their over management is unacceptable, even though it protects the pathologists from facing an under diagnosed PTC with future metastasis [5].

Some of the ancillary studies as immunohistochemistry and molecular techniques may be helpful, but none of them is conclusive.

Hence the diagnosis of PTC in some cases still subjective with Inter observer variation between expert thyroid pathologists that varies between benignity and malignancy on the same case [5].

Cytokeratin 19 (CK19) is a type I intermediate filament protein and is the smallest known keratin, found in a variety of simple or glandular epithelia of the gastroenteropancreatic and hepatobiliary tracts, both normal and their neoplastic counterparts [6]. In the thyroid gland, normal follicular epithelium usually has shown no detectable CK19 expression. Many studies reported a strong and diffuse staining pattern of CK19 in PTC, hence could be added as part of a panel of immunomarkers in the diagnosis of PTC [7].

P63, a member of p53 family nuclear transcription factor that is located on 3q27, having a major role in regulating the epithelial proliferation and differentiation processes [8]. It is consistently expressed in basal, squamous and myoepithelial cells such as in basal cells of the prostate acini and ducts, myoepithelial cells of the breast and squamous cell carcinoma. Studies on the involvement of P63 protein in thyroid tumor processes are few and have different results [9].

CD56 is a neural cell adhesion molecule, so its expression may affect the migration of tumor cells. CD56 is expressed in NK cells, activated T cells, large granular lymphocytes, specific endocrine, and brain tissue normally, and can also be expressed in follicular cells of the normal thyroid gland [10]. Several studies have shown that loss of CD56 expression correlates with poor prognosis and metastatic potentials in some malignant tumors [3].

CD117 (c-KIT) is a type III receptor tyrosine kinase. Aberrations in CD117 expression and signaling have been well characterized in several tumors, including gastrointestinal stromal tumors (GISTs). However, few studies have investigated CD117 in the thyroid gland or in thyroid malignancies with controversial results [11].

We evaluated the diagnostic value of proteins expressions using antibodies against CK 19, P63, CD56 and CD117 in PTC and other follicular thyroid lesions, and follicular thyroid neoplasms, provided that the right morphological features are fulfilled.

2. MATERIALS AND METHODS

In this study, a total of 188 previously diagnosed archival formalin fixed- paraffin embedded blocks with thyroid lesions were initially revised; the cases were collected from pathology lab archive in our institute during the period from January 2015 to January 2016. Study was based on cross sectional analysis dealing with archival slides and paraffin blocks, not related to patient's privacy, impairment or treatment. The study complied ethics principles of the 1964 declaration of Helsinki and all subsequent revisions and Good Clinical Practice (GCP) guidelines, approved by the Institutional Research Board (IRB), Faculty of Medicine, Mansoura University.
Fifty nine cases of unequivocal diagnosis were selected to be rolled in our study; 24 papillary

carcinoma cases including 6 follicular variant, 7 follicular carcinoma, 7 follicular adenoma including 2 Hürthle cell adenoma, 7 hyperplastic nodules, 7 thyroiditis (4 lymphocytic and 3 Hashimoto) and 7 colloid goiter.

2.1 Histopathology

The formalin fixed paraffin embedded blocks were retrieved and sections of 4 µm thickness have been cut from formalin fixed paraffin embedded blocks for H&E, other sections were prepared on charged slides for immhistochemistry. Cases were reviewed by two pathologists. Examination of three tumor slides from each specimen was done on an Olympus CX51 light microscope. Pictures were obtained by a PC-driven digital camera (Olympus E-620) using the computer software (Cell*, Olympus Soft Imaging Solution GmbH).

For the diagnosis of PTC, we followed the same histological criteria applied to the diagnosis of PTC as those proposed by Chan 2002, 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 lack of polarization in the cells that line a follicle; 3. Nuclei show a clear or pale chromatin pattern; 4. Psammoma bodies are found. If one of the 4 features is lacking, 4 or more of the following subsidiary 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 the lumens of follicles [12].

Adenomas were defined as completely encapsulated follicular or Hürthle cell tumors with homogeneous architecture and morphology, lacking nuclear features of PTC and without capsular and vascular invasion while follicular carcinoma showed previous features together with capsular and vascular invasion [13].

2.2 Immunohistochemistry

The primary antibodies used were CK-19 (M0888, Clone RCK108; Dako, Carpinteria, CA, USA, dilution 1:100), P63 (M7247, Clone 4A4; Dako, Carpinteria, CA, USA, dilution 1:100), CD-56 (M7304, Clone 123c3; Dako, Carpinteria, CA, USA, dilution 1:250) and CD 117 (clone YR145, prediluted; Cell Marque, Rocklin, Calif). Detection kit used high sensitive kit (Dako Cytomation envision +dual link system peroxidase code K4061) using DAB as chromagen. Antigen retrieval obtained by pretreatment with 1 ml mol EDETA (at PH 8.0) for 20 minutes in microwave. Proper positive controls were prepared for each antibody; skin for CK19and P63, tonsil for CD56, GIST and tumor infiltrating mast cells (internal control) for CD117. Negative control was prepared without addition of primary antibody.

2.3 Imunnohistochemical Analysis

Evaluation of the immunohistochemical staining was performed by light microscopy using a 10× objective lens with the selective use of a 20–40× objective lens for confirmation. Cytoplasmic and membranous staining for CK 19, CD56, CD 117 and nuclear staining for p63 were accepted as positive in the tumor cells. For the three antibodies, >10% staining in the tumor was accepted as positive while a value <10%was negative [5,14,15].

2.4 Statistical Analysis

The $\chi 2$ test and Fisher's exact test were used for comparing the expressions of the applied immunohistochemical markers in papillary thyroid carcinomas and the other thyroid lesions. The statistical analysis was performed using statistical package for social science (SPSS) program version 20, and results with the *p*-value of <0.05 were considered statistically significant.

3. RESULTS

The expression of Ck19, P63, CD56 and CD117 in the studied 59 thyroid lesion was summarized in Table 1.

Strong diffuse Ck19 immunohistochemical staining was encountered in 87.5% of papillary thyroid carcinoma (PTC) including 5 follicular variants (FVPTC). However, the remaining 3 PTC cases showed Ck19 immunoreactivity of moderate intensity in less than 10% of tumor cells hence considered negative. Non papillary thyroid (non PTC) lesions including follicular neoplasms, hyperplastic nodule, thyroiditis and goiter showed weak to moderate CK19 expression in 10% - 30% of cells in 8 cases (22.86%) (Fig. 1), with statistically significant difference *P< .001* (Table 2). Regarding Ck 19 expression in PTC versus follicular neoplasms and hyperplastic nodules in the study, statistically significant differences were detected (*P< .001, P= .002* respectively) (Table 2).

Table 1. Expression of the markers in studied thyroid lesions

IHC marker		Papillary carcinoma	Follicular carcinoma	Follicular adenoma	Hyperplastic nodule	Thyroiditis	Goiter	P value
CK19	(+)ve	21(87.5%)	1(14.29%)	2(28.57%)	2(28.57%)	2(28.57%)	1(14.29%)	.000*
	(-)ve	3(12.5%)	6(85.71%)	5(71.43%)	5(71.43%)	5(71.43%)	6(85.71%)	
P63	(+)ve	13(54.17%)	2(28.57%)	1(14.29%)	1(14.29%)	0	0	.012*
	(-)ve	11(45.83%)	5(71.43%)	6(85.71%)	6(85.71%)	7(100%)	7(100%)	
CD56	(+)ve	4(16.67%)	5(71.43%)	5(71.43%)	6(85.71%)	6(85.71%)	7(100%)	.000*
	(-)ve	20(83.33%)	2(28.57%)	2(28.57%)	1(14.29%)	1(14.29%)	0	
CD117	(+)ve	1(4.17%)	2(28.57%)	1(14.29%)	0	0	1(14.29%)	.294
	(-)ve	23(95.83%)	5(71.43%)	6(85.71%)	7(100%)	7(100%)	6(85.71%)	

Table 2. Differential expression of the markers between PTC and other thyroid lesions

IHC marker		Papillary carcinoma (PTC)	▪Non papillary thyroid lesions	Follicular neoplasm	Hyperplastic nodule	P value
CK19	(+)ve	21(87.5%)	8(22.86%)	3(21.43%)	2(28.57%)	[a].000*
	(-)ve	3(12.5%)	27(77.14%)	11(78.57%)	5(71.43%)	[b].000* [c].002*
P63	(+)ve	13(54.17%)	4(11.43%)	3(21.43%)	1(14.29%)	[a].000*
	(-)ve	11(45.83%)	31(88.57%)	11(78.57%)	6(85.71%)	[b].049* [c].062
CD56	(+)ve	4(16.67%)	29(82.86%)	10(71.43%)	6(85.71%)	[a].000*
	(-)ve	20(83.33%)	6(17.14%)	4(28.57%)	1(14.29%)	[b].001* [c].001*
CD117	(+)ve	1(4.17%)	4(11.43%)	3(21.43%)	0	[a].325
	(-)ve	23(95.83%)	31(88.57%)	11(78.57%)	7(100%)	[b].094 [c].338

▪ Non papillary thyroid lesions include follicular neoplasms, hyperplastic nodule, thyroiditis and goiter

*a PTC vs Non papillary thyroid lesions; b PTC vs follicular neoplasms; c PTC vs hyperplastic nodule; * P ≤ 0.05*

As demonstrated in Table 1 and 2, P63 was expressed in 54.17% of papillary carcinoma cases including 2 follicular variants (FVPTC) while expressed in 3 follicular neoplasms, one hyperplastic nodule and non of the thyroiditis or goiter cases (Fig. 2), with statistically significant difference. When comparing papillary thyroid carcinoma with other studied cases, the expression of p63 was significantly higher in papillary thyroid carcinoma than the other thyroid lesions *p< .001*, follicular neoplasms *P= .049* and nodular hyperplasia *P= .062* (Table 2).

Reversely, CD56 immunostaining was negative in most of PTC cases with weak focal expression in only 4 cases of PTC (16.67%) including 3 follicular variants (FVPTC). On the other hand, CD56 expression was strong in 10 cases of follicular neoplasm, most of non neoplastic lesions (Fig. 3) with statistically significant difference. CD56 expression was significantly higher in non PTC lesions as compared to PTC cases *P< .001*. Comparing papillary thyroid carcinoma with other studied cases, CD56 was significantly lower in papillary thyroid carcinoma than the other thyroid lesions *p< .001*, follicular neoplasms P=0.001 and nodular hyperplasia *P= .001*(Table 1, 2).

CD117 was focally expressed in one case of FVPTC, 2 follicular carcinoma, one follicular adenoma and one goiter (Fig. 4). CD117 did not significantly differ between either the studied groups (Table 1, 2).

The sensitivity and specificity of Ck19, P63 and CD56 in the diagnosis of PTC among non PTC thyroid lesions are shown in Table 3. Positive Ck19 showed the highest sensitivity (87.5%) with high specificity, while P63 showed the highest specificity (88.6%) yet with low sensitivity (54.2%). Negative CD56 showed high sensitivity and specificity. The combination of the three markers raised the specificity to 97.1% although the sensitivity decreased. A better test accuracy (91.2%) was obtained by combination of Ck19 expression/CD56 loss with high sensitivity and specificity.

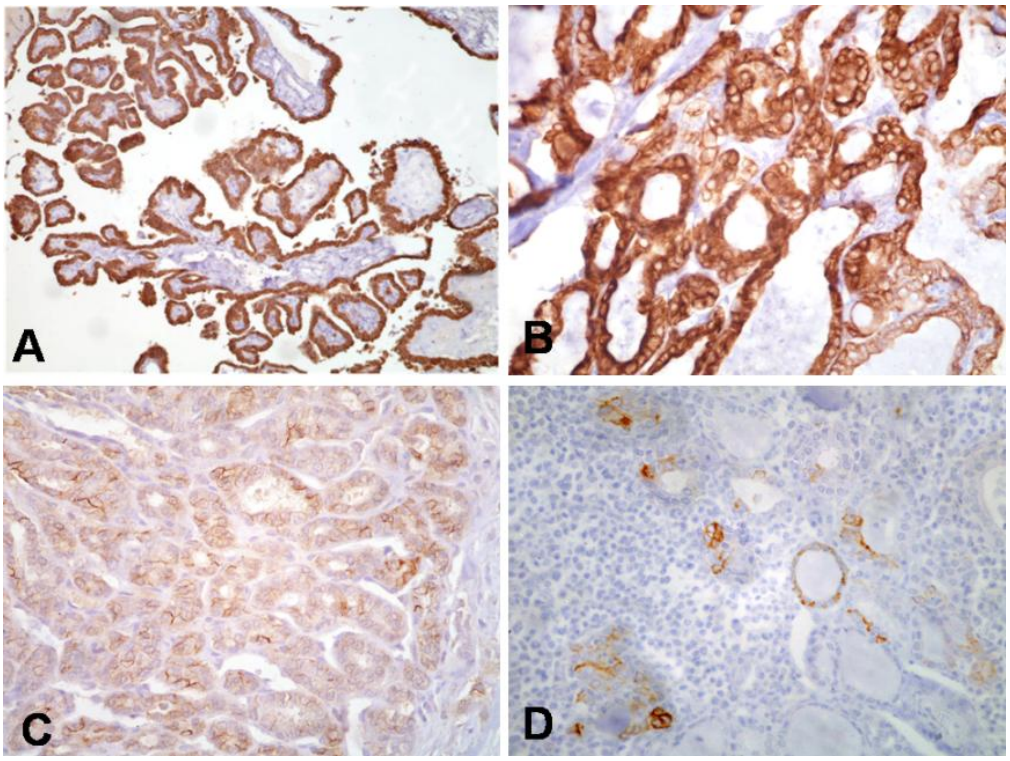

Fig. 1. Ck19 expression (DAB immunoperoxidase). (A) Diffuse strong membranous and cytoplasmic expression in PTC (X100). (B) Diffuse strong membranous and cytoplasmic expression in FV PTC (X400). (C) Mild to moderate expression in a case of follicular adenoma (X400). (D) Moderate focal expression in a case of lymphocytic thyroiditis (X400)

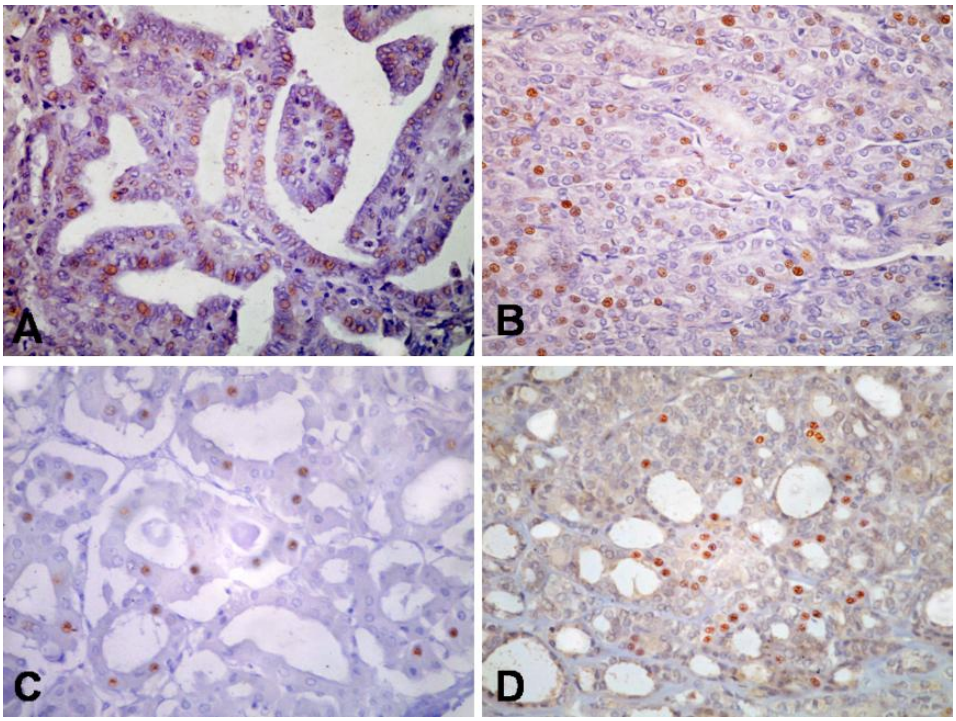

Fig. 2. NuclearP63 expression (DAB immunoperoxidase X 400). (A)In PTC (B) In FV PTC (C) In a case of follicular adenoma, Hürthle cell type (D) In hyperplastic nodule (X400)

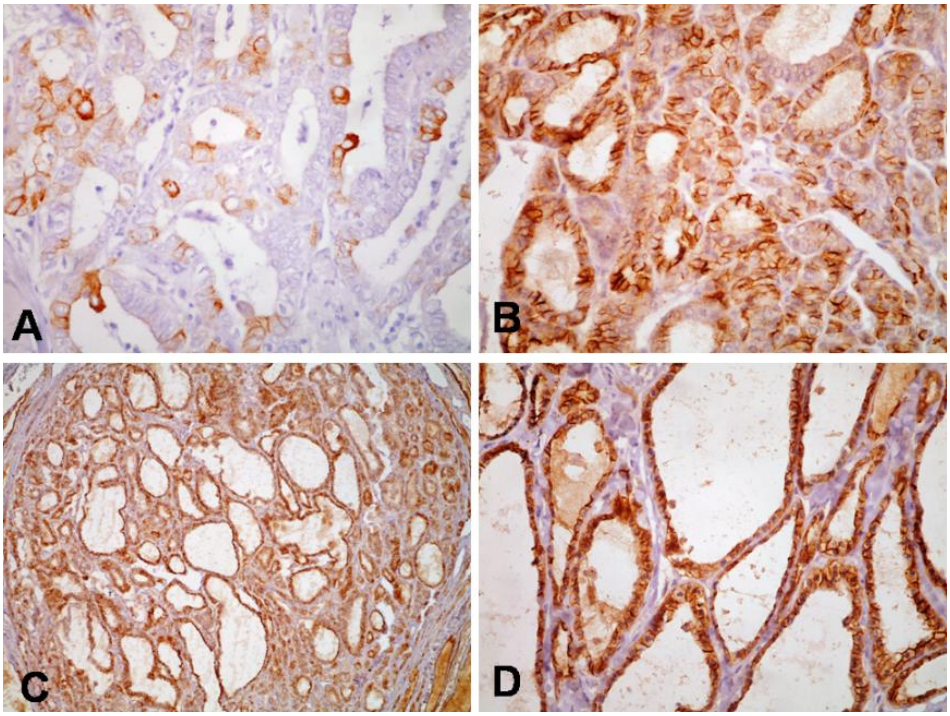

Fig. 3. CD56 expression (DAB immunoperoxidase). (A) Moderate focal membranous and cytoplasmic expression in PTC (X400). (B) Diffuse strong membranous and cytoplasmic expression in follicular carcinoma (X400). (C) strong expression in hyperplastic nodule (X100). (D) Strong expression in colloid goiter (X400)

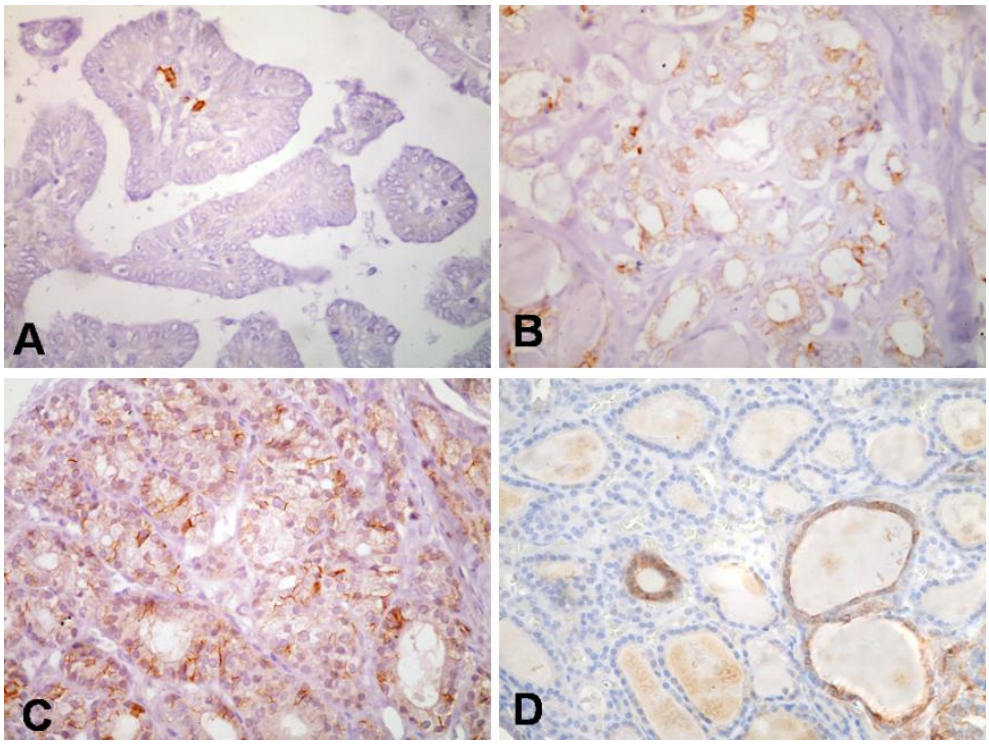

Fig. 4. CD117 expression (DAB immunoperoxidase). (A) Negativity with positive internal control in mast cells in the core of PTC (X400). (B) Mild to moderate focal membranous and cytoplasmic expression in FV PTC (X400). (C) Mild to moderate expression in a case of follicular adenoma (X400). (D) Moderate focal expression in a case of colloid goiter (X400)

Table 3. Sensitivity and specificity of Ck19, P63 and CD56 in diagnosis of PTC

IHC marker	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value(NPV)	Accuracy
CK19(+ve)	87.5%	77.1%	72.4%	90%	81.4%
P63(+ve)	54.2%	88.6%	76.5%	73.8%	74.6%
CD56(-ve)	83.3%	82.9%	76.9%	87.9%	83.1%
Combined 3 markers	54.2%	97.1%	92.9%	63 %	79.7%
Combined Ck19(+)ve CD56(-)ve	83.3%	97.1%	95.23%	89.5%	91.2%

PPV: Positive predictive value; NPV: Negative predictive value

4. DISCUSSION

Although the histopathological diagnosis of the PTC seems relatively easy due to papillary architecture, (FV/PTC) created some confusion among pathologists. The differential diagnosis includes follicular neoplasms, such as (follicular adenoma and follicular carcinoma), because the microscopic criteria of differential diagnosis are sometimes difficult to apply, and they are subject to a high degree of subjectivity on behalf of the pathologists. In addition, the existence of non neoplastic lesions as hyperplastic nodule or thyroiditis may create confusing diagnoses [5]. Immunohistochemical studies are helpful but there is no marker that can definitely differentiate PTC from other follicular thyroid lesions and is 100% consistent at present [15]. In our study, we selected only those papillary thyroid carcinomas with unequivocal criteria.

In our study, CK19 strongly immunoreacted with (87.5%) cases of PTC; while negative cases (3 cases) show focal immunoreactivity in less than 10% hence considered negative. As shown in Table 4 previous studies reported CK19

expression in most of their studied PTC cases, ranging from 75.9% to 100% [16-21].

The current study pointed that; the expression of CK19 in PTC including FVPTC was significantly higher than in other thyroid lesions including follicular neoplasms and hyperplastic nodules. Palo and Biligi and Siderova et al. reported similar relation supporting that it can serve to differentiate PTC from follicular neoplasm [19,21]. However, other studies found higher expression of Ck19 in follicular neoplasm and hyperplastic nodules [18,20].

The sensitivity of CK19 expression in diagnosis of Papillary carcinoma as recorded by previous researchers ranged from70% to 85% [22-24]. The present study reported a higher sensitivity reaching 87.5% encouraging the use of Ck19 taking into account the intensity and distribution of expression in the tumor.

As demonstrated in Table 5, various studies have reported no p63 staining or rare weak staining in normal thyroid tissue and non-PTC lesions while PTC cases frequently showed areas of focal staining [3,5,15,25] with high specificity [5,26]. Nuclear p63 staining was present in 54.17% of the currently studied PTC cases while follicular non-PTC lesions showed focal staining at a rate of 11.43% with high specificity reaching 88.6%, yet less sensitive than Ck19.

We found a statistically significant difference in P63 expression between PTC cases and other follicular non-PTC lesions (p=0.000). This results and literature data [3,5,15,25] proposed that P63 may be an additional marker for PTC.

CD56 has been reported to be an antigen related to the differentiation of the follicular epithelium [27] and many previous studies reported high CD56 expression in normal thyroid tissue and benign thyroid follicular lesions as follicular adenoma and nodular hyperplasia [28].

Negative CD56 was reported in 83.33% of all studied PTC cases with focal weak positivity in 4 PTC cases compared to other studied follicular lesions. Similarly, previous studies, as demonstrated in Table 6, reported weak or negative CD56 expression in all or most of their studied PTC cases [3,5,27-29]. In accordance with previous studies, the present study also confirmed the strong and diffuse positive CD56 expression in 82.86% of the follicular patterned thyroid lesions (Follicular neoplasms, hyperplastic nodules, thyroiditis and colloid goiter).

The sensitivity and specificity of CD56 as a negative marker of PTCs was 83.3% and 82.9% respectively however different studies recorded higher sensitivity and specificity reaching 100% [10,28,30].

Table 4. Comparison of CK19 immunostaining results with previous studies

Study (year)	Number of positive cases/total number of cases (percentage)		
	Papillary carcinoma	Follicular neoplasm	Hyperplastic nodule
Nasr et al (2006)[16]	30/30(100%)	5/6(83.3%)	5/10(50%)
Murphy et al (2008)[17]	22/29(75.9%)	10/29(34.5%)	0/11(0%)
Saleh et al (2010)[18]	27/32(84.4%)	32/68(47.1%)	8/52(15.4%)
Siderova et al (2013)[19]	16/17(94.1%)	4/15(26.7%)	-
Alshenawy (2014)[20]	22/22(100%)	12/22(54.5%)	-
Palo and Biligi 2017)[21]	27/31(87.1%)	4/18(22.2%)	2/10(20%)
Present study	21/24(87.5%)	3/14(21.43%)	2(28.57%)

Table 5. Comparison of P63 immunostaining results with previous studies

Study (year)	Number of positive cases/total number of cases (percentage)		
	Papillary carcinoma	Follicular neoplasm	Hyperplastic nodule
Etem et al., 2010[15]	12/40 (30.5%)	3/40 (7.5%)	-------
Jeong et al., 2016[3]	19/129 (14.7%)	1/80 (1.25%)	0/40 (0%)
El Demellawy et al., 2008[5]	50/72 (70%)	0/34 (0%)	-----
Bonzanini et al., 2008[25]	20/27 (74.1%)	-------	1/22 (4.5%)
Present study	13/24 (54.17%)	3/14 (21.43%)	1/7 (14.29%)

Table 6. Comparison of CD56 immunostaining results with previous studies

Study (year)	Number of positive cases/total number of cases (percentage)		
	Papillary carcinoma	Follicular neoplasm	Hyperplastic nodule
Jeong et al., 2016 [3]	69/129 (53.5%)	41/80 (51.25%)	31/40 (77.5%)
Park et al. 2009 [28]	5/67 (7.5%)	33/38 (86.84%)	19/21 (90.48%)
Abd Elatti and Shash L 2012 [27]	5/29 (17.2%)	14/15 (93.33%)	28/32 (87.5%)
Shin et al. 2011 [29]	4/80 (5%)	5/5 (100%)	-----
El Demellaway et al. 2008 [5]	0/72 (0%)	34/34 (100%)	-----
Present study	4/24 (16.67%)	10/14 (71.43%)	6/7 (85.71%)

As a result, a statistically significant difference between PTC and non- PTC follicular lesions as regards CD56expression was found (P <0.001) proposing that lack of CD56 expression in the PTCs could be helpful in discrimination from other follicular lesions. On the other hand, Etem et al. [15] found no statistically significant difference between his studied group of PTCs and the other group of follicular tumors as regards CD56 expression. The differences might be due to factors like antibodies used, dilution and antigen retrieval methods, type of tissue fixative used, time of fixation and histological types of tumor.

Previous researches on CD117 in thyroid lesions were controversial. In 2004 Mazzanti et al. detected c-KIT by microarray assay as one of the most significantly down-regulated genes in PTC compared to other thyroid lesions [31], moreover, in 2012 Tomei et al., confirmed the down-expression of c-KIT mRNA in PTC highlighting its importance as a diagnostic marker in thyroid FNAC[11]. More recently, other studies have been published showing a decreased CD117 expression in PTC compared to normal thyroid tissues [2,32]. Moreover, Pusztaszeri et al., 2014 stated that negative CD117 is highly specific and sensitive differentiating PTC from other thyroid lesions [2].

On the other hand, Aydin et al. stated that CD117 staining of neoplastic and inflammatory lesions were found to be higher than the reactive and normal groups furthermore, within the neoplastic group, papillary carcinomas express higher ratio of CD117 positivity [14].

On the contrary, the current study reported negative CD117 in most of the studied thyroid lesion with weak focal positivity in one FV-PTC, 3 follicular neoplasms and one goiterous nodule with no significant difference.

Based on the previously mentioned results and in the light of our findings, we suggest that immunohistochemical analysis of 2 or 3 protein markers is necessary for the diagnosis of PTC, especially in the paucity of significant diagnostic morphological features. However, our study still have some limitations such as data from single center, the number of patients is relatively small, the need of more protein markers for evaluation.

5. CONCLUSION

CK19 is a useful marker for PTC in distinguishing from other thyroid lesions, and a cocktail with other markers including CD56 and P63 can further improve diagnostic accuracy. P63 is highly specific but less sensitive marker for PTC than CK19. CD56 is more sensitive than P63, however it is a negative rather than a positive marker for PTC. Combined CK19 expression and CD56 loss might be useful in the diagnosis of PTC with sensitivity 83.3% and specificity 97.1% with improved accuracy (91.2%).CD117 is of limited value in the diagnosis of thyroid lesions/tumors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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