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Original Article

UTILIZATION OF CK19 AND CD56 EXPRESSION IN DIFFERENTIATING MALIGNANT FROM BENIGN LESIONS OF THYROID

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ABSTRACT

BACKGROUND: Thyroid cancer accounts for majority of the endocrine cancer and is showing a rising trend. Precise pathological diagnosis is essential for optimal management of thyroid tumours and to avoid unwanted complications. Though histopathology is the main stay of diagnosis, ancillary diagnostic markers may be helpful in some cases with overlapping features or diagnostic discrepancies. The purpose of this study was to evaluate the diagnostic value of CK19 and CD56 immunohistochemical staining in distinguishing between benign and malignant thyroid lesions.

MATERIAL & METHODS: A total of 36 cases of thyroid lesions from January 2021 and August 2022 were taken for the study. After histopathological analysis representative sections were subjected for IHC using CK19 and CD56. Statistical analysis was done to observe frequency and significance.

RESULTS: Out of 36 cases taken for the study, 16 cases were malignant thyroid neoplasm and 20 cases were benign thyroid lesions. All the malignant cases included in the study were Papillary thyroid carcinoma, its variants and Non invasive follicular neoplasm of thyroid with papillary like nuclear features. The benign lesions included in the study were nodular goitre, adenomatoid nodule and follicular adenoma. CK19 was positive in 93.75% cases of malignant neoplasm. PTC and its variants showed loss of expression of CD56 in 81.25% of cases, while 75% cases of benign thyroid lesion showed positive staining for the same

CONCLUSION: It was found that CK19 was very specific but less sensitive marker to differentiate benign from malignant neoplasm and CD56 was more sensitive and specific as a marker of benign thyroid lesion. Hence, the use of these markers together could be a useful and reliable diagnostic approach for differentiating malignant from benign thyroid lesions.

Keywords: *Thyroid neoplasm, papillary thyroid carcinoma, nodular goitre, adenomatoid nodule, CK19, CD56*

INTRODUCTION

Thyroid cancer is the most common endocrine cancer and accounts for more than 90% of the same with a raising trend.[1] Papillary thyroid carcinoma (PTC) is the most common among them with an increasing frequency over the last two decades.[2]

A solitary thyroid nodule (STN) is a palpable distinct swelling within a thyroid gland and has higher rate of malignancy than multinodular goiter which has sparked increased worry.[3] For early treatment plan and improved patient management, it is crucial to distinguish patients with benign STN from the malignant ones.[4] Traditional diagnosis currently relies on histomorphologic assessment of routine Haematoxylin and Eosin (H&E) stained slides, however there is well-known inter-observer or intra-observer discrepancies in the diagnosis of papillary and follicular thyroid lesions which necessitates the use of novel IHC markers like CK19 and CD56.[1]

Cytokeratin Polypeptide 19 (CK19) is a type I intermediate filament protein and is the smallest known keratin synthesized in simple and stratified epithelia. Normal thyroid follicle is often negative for CK19, however it is expressed in malignant cases.[5,6]

CD56 is a neural cell adhesion molecule (NCAM) which is expressed normally in thyroid follicular cells. Reduced CD56 expression is correlated with tumour progression of patients with cancer. Its expression is reduced or totally lost in case of PTC, Follicular Carcinoma (FCa) and Anaplastic Carcinoma.[7,8]

The aim of this study was to analyze the usefulness of CK19 and CD56 in differentiating malignant thyroid nodules from benign and to correlate it with the histopathology

METHODS

A total of 88 cases of thyroidectomy specimens were received during the period of 2 years from January 2021 to August 2022 of which 36 cases were selected for the study according to inclusion and exclusion criteria. Surgically resected thyroid specimens from patients of all age groups and both sexes were included. Specimen from post chemotherapy and radiotherapy patients were excluded.

Of the taken samples, 16 cases were malignant and 20 cases were benign lesions. Detailed clinical history and investigations related to the case were obtained and noted. The specimens were processed as routine histopathological specimen and reported according to WHO criteria.

IHC was performed on formalin fixed, paraffin-embedded tissue using primary antibody to CD56 (RTU mouse monoclonal CD56, Clone: 123C3.D5) and CK19 (RTU mouse monoclonal CK19, Clone: A53-B/A2.26).

CD-56 expression in ≥10% of cells showing membranous positivity was considered as positive and <10% as negative.[9] Cytokeratin 19 was considered positive when membranous positivity was seen. Grading of expression for CK19 were taken as Grade 0- staining<10%, Grade 1- staining in ≥ 10% and ≤ 25% of the cells, Grade 2- staining in 25% and ≤ 50% of the cells, Grade 3- staining in > 50% and ≤ 75% of the cells and Grade 4- staining in > 75 % of the cells[1].

Positive staining intensity was categorized into 3 groups as weak, moderate and severe and final IHC staining value was obtained by multiplying the score of extent of positively stained cells and the score of staining intensity and categorized as 0-1: negative expression, 2-3: weakly positive (+), 4-8: moderately positive (++). Score of 9-12: strong positive (+++)[1].

STASTISTICAL ANALYSIS

Details of data tabulation and statistical analysis were used. Descriptive statistical analysis was carried out in the present study to explore the distributions of several characteristics of the cases studied. The statistical significance of difference of various categorical variables across two or more groups was tested using Chi-square test. The p-values less than 0.05 were considered to be statistically significant. The entire data was statistically analyzed using Statistical Package for Social Sciences (version 27).

RESULTS

Among the 36 cases studied, 16 cases were malignant and 20 cases were benign. The age of presentation varied from 12-75 years with a mean age of 42 years. The patient age groups were divided into 3 categories as <30 years, 31-60 years and >60 years. Maximum cases were in the age group 31 to 60 years (77.8%). In the present study, out of 36 cases, 88.9% cases were females with a female to male ratio were 8:1. Benign cases included in the study were multinodular/ nodular goitre (14 cases), adenomatoid nodule (5 cases) and follicular adenoma (1 case). Out of 16 malignant cases, 11 cases were classical variant of papillary thyroid carcinoma, 1 case was follicular variant of papillary thyroid carcinoma. There were 4 cases of NIFTP.

Out of 16 malignant cases, 5 cases were multifocal lesions and 6 cases had tumour size between 2-4cm. Capsular invasion was noted in 6 cases, of which 5 cases were classical variant of papillary thyroid carcinoma and 1 case was Follicular variant of PTC. Margins were involved by tumour in 4 cases. Angioinvasion and lymphatic invasion were seen in 8 and 9 cases respectively.

All 16 cases of thyroidectomy specimens were assessed for nuclear features of PTC including enlargement, crowding, ground-glass (optical clear/ Orphan Annie) nuclei, nuclear grooves and intranuclear inclusions and the distribution is given in table 1.

Table 1: Distribution of nuclear features in thyroid neoplasms (n=16).

NUCLEAR FEATUES	NUMBER OF CASES		PERCENTAGE (%)	
	PRESENT	ABSENT	PRESENT	ABSENT
ENLARGEMENT	14	02	87.5	12.5
CROWDING	11	05	68.75	31.25
GROUND-GLASS	12	04	75	25
NUCLEAR GROOVES	15	01	93.75	6.25
INTRANUCLEAR INCLUSIONS	09	07	56.25	43.75

Tumour staging was done based on pathological TNM staging. The tumors were divided into two categories based on pathological staging: early stage (T1/T2)and late stage (T3/T4). In the present study, 62.5% cases belonged to early stage and 37.5% cases were of late stage.

Among the 20 benign thyroid cases, 5 cases showed Hurthle cell changes, 8 cases had microfollicular pattern and 10 cases had aggregates of lymphocytes. Papillary hyperplasia was seen in 4 cases, of which nuclei of 3 cases also showed clearing and 1 case had calcification, while other nuclear features of PTC were not seen.

EXPRESSION OF CYTOKERATIN 19 IN THYROID NEOPLASMS

Cytokeratin-19 immunohistochemistry was done on all 36 cases of thyroidectomy specimens. Out of these 36 cases, positive staining of 1+, 2+ or 3+ are seen in 11/20 benign cases and 15/16 malignant cases. Negative staining with same is seen in 9/20 benign cases and 1/16 malignant cases.

Among the 11cases of classical variant of papillary carcinoma thyroid, 4 cases had 2+ positive expression for CK-19, 6 cases had 3+ positivity and only 1 case showed negative expression for the same. There was only 1 case diagnosed as FVPTC, it had 2+ positivity for CK-19. NIFTP cases showed equal distribution of cases having 2+ and 3+ positivity in 2 cases each as shown in Figure 1.

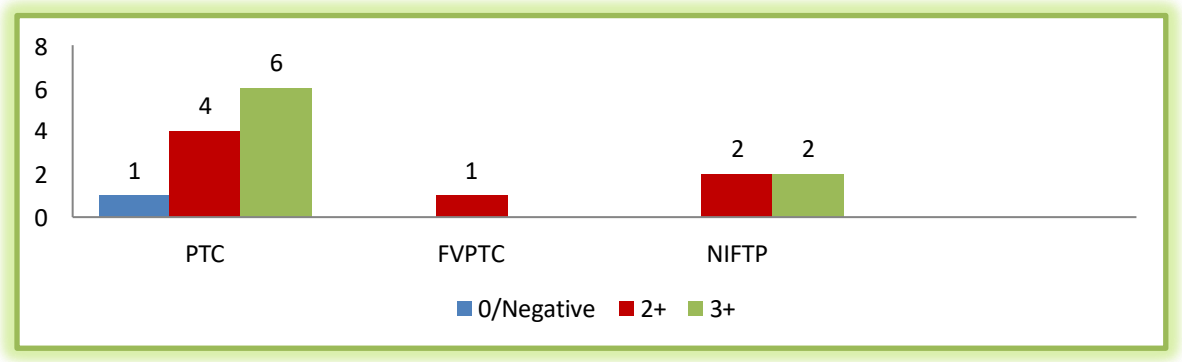

Figure 1: CK19 positivity score in malignant thyroid lesions (n=16).

Out of 9/20 positive benign cases, there were 2 cases with 1+ staining and 9 cases with 2+ positivity. No benign cases showed 3+ positivity. Case was distribution is shown in Figure 2.

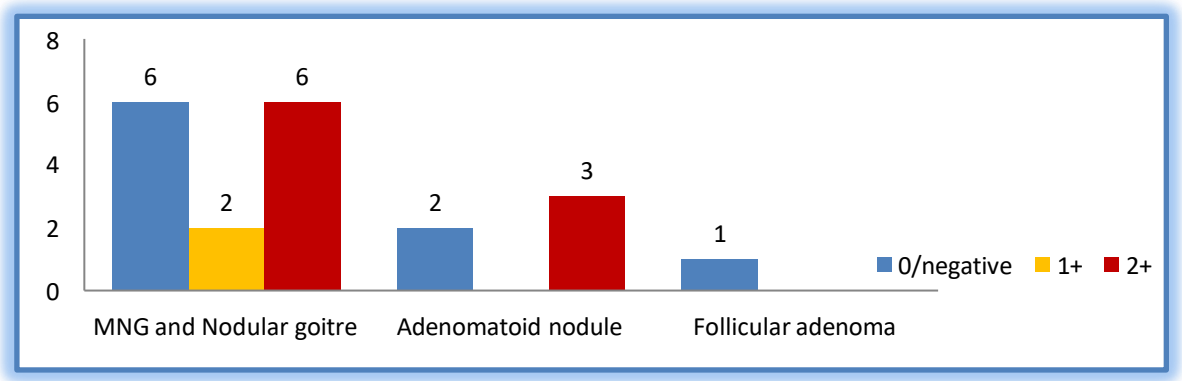

Figure 2: CK19 positivity score in benign thyroid lesions (n=20).

There was no significant correlation between the expression of CK 19 and various histomorphological features in malignant thyroid lesions though higher the tumour stage was, more was the intensity of staining for CK19 as shown in Table 2.

Table 2: Histomorphological features of malignant neoplasm and expression of CK19.

	negative	1+	2+	3+	P value
Age group					0.572
<30 years	0	0	1	3	
31-60 years	1	0	6	4	
>60 years	0	0	0	1	
Gender					0.319
Female Male	1	0	7	6	
	0	0	0	2	
Tumour size					0.622
<2cm 2-4cm	0	0	3	2	
>4cm	0	0	2	4	
	0	1	2	2	
rchitecture Papillae					0.611
Follicular	0	0	1	2	
Both	0	0	3	1	
	1	0	3	3	
Angioinvasion	0	0	2	4	0.504
Lymphatic invasion	0	0	4	5	0.493
ımour stage Stage 1					0.481
Stage 2	0	0	3	2	
Stage 3	0	0	1	4	
Stage 4	1	0	2	1	
	0	0	1	1	

EXPRESSION OF CD56 IN THYROID NEOPLASMS

There were 16 malignant neoplasm, out of which 13 cases expressed <10% of staining pattern which was considered negative. It comprised of 9 cases of classical variant of PTC, 1 case of FVPTC and 3 cases of NIFTP. Only 3 cases expressed >10% of staining pattern, of which 1 case each of PTC and NIFTP showed 1+ positivity, while 1 case of PTC showed 2+ positivity. In this study, the negative expression of CD56 in malignant cases showed a statistical significance with p value of <0.001. The case wise distribution of CD56 expression score in malignant lesion is given in Table 3.

Table 3: CD56 staining score in malignant thyroid neoplasm (n=16).

CD56	Negative	1+	2+	3+	p value
<10%	**13**	**0**	**0**	**0**	
>10%	**0**	**2**	**1**	**0**	**<0.001**

EXPRESSION OF CD56 IHC IN BENIGN THYROID LESIONS.

Out of 20 benign lesions, 15 cases expressed >10% staining pattern of which 11 cases were nodular goiter, 3 cases were adenomatoid nodule and 1 case of follicular adenoma. Oot of the positive 5 cases, 9 cases had a score of 3+. Of the 5 cases which expressed <10% staining, 3 cases were nodular goiter and 2 cases were adenomatoid nodule. The positive staining of CD56 in benign lesions were found to be statistically significant with a p value<0.001. The case wise distribution of CD56 expression score in benign lesion is given in Table 4.

Table 4: CD56 staining score in benign thyroid neoplasm (n=20).

CD56	Negative	1+	2+	3+	p value
<10%	**5**	**0**	**0**	**0**	

>10%	**0**	**1**	**5**	**9**	**<0.001**

So, in this study, 15/16 malignant thyroid neoplasm showed positive staining of varying intensity for CK19 while only 11/20 benign cases showed positivity for the same. Loss of CD56 expression was seen in 13/16 malignant neoplasm while positive staining for the same was seen in 15/20 benign cases.

In this study, we also found out that, CK 19 had 93.8% and 45% sensitivity and specificity respectively for malignant cases with a positive predictive value of 57.7%, negative predictive value of 90% and accuracy of 66.67%. CD56 had 81.2% and 75% sensitivity and specificity respectively for benign cases with a positive predictive value of 72.2%, negative predictive value of 83.3% and accuracy of 77.78%.

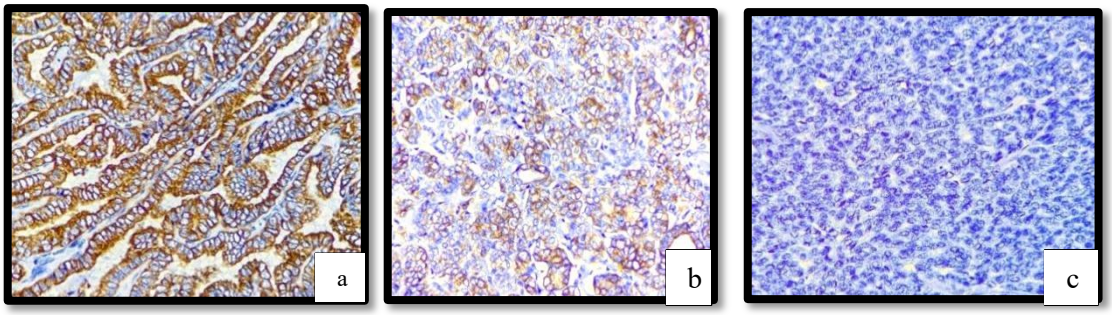

Figure 3. fig a- shows 3+ positivity of CK19 in PTC, fig b- shows 2+ positivity in PTC, fig c- shows negative stauining of CD56 in PTC

DISCUSSION

PTC is the most common thyroid malignancy. In 2020, according to national cancer institute in US, 52,890 new cases of thyroid carcinoma were reported and there were 2180 deaths due to the same.[10] Thyroid neoplasm usually present as thyroid nodules of which 90% are benign.[11] It is also necessary to differentiate benign from malignant lesion to avoid unnecessary thyroidectomy procedure resulting lifelong hypothyroidism and lifelong dependency to medical treatment. PTC is usually diagnosed based on nuclear morphology. In some cases, morphologic similarities are seen between benign and malignant lesions. Both in benign and malignant lesions papillary and follicular architectures along with nuclear irregularity may be seen.[5] About 20% of indeterminate thyroid nodules actually harbour a malignancy. The increased detection of benign nodules and microcarcinomas in these nodules reinforces the need for improved methods to differentiate benign from malignant disease.[12,13] So to aid in making diagnosis, IHC can pave the road for confirmation.

Thyroid carcinoma occurs in persons of all ages, but is most often diagnosed between the ages of 45–54 years; median age at diagnosis is 51 years. In the present study, age range for patients with thyroid lesion was between 12 to 75 years and the mean age of the presentation was 42 years.

In our study, female to male ratio was 8:1. On comparing the gender distribution in various studies to our study, we found that female preponderance was noted in all the studies but the male: female ratio was found to be variable. On the other hand, study conducted by Rahman MM et al [14] showed almost equal distribution among males and females with a ratio of 0.9:1.

We studied the expression of CK19 and CD56 in both malignant and benign thyroid lesion and correlation of their expression in both malignant and benign cases.

CK19 Expression in thyroid lesions

Cytokeratin is a family of water-insoluble intracytoplasmic structural proteins that are the dominant intermediate filament proteins of epithelial and hair forming cells; also present in epithelial tumours[15]. Based on their molecular weight, several keratin subtypes are categorized, of which CK19 is the smallest known keratin. It has a molecular weight of 40 kDa. It is involved in organization of myofibrils by linking contractile apparatus to dystrophin in striated muscles.[16] Normal thyroid follicle is often negative for CK19, although focal staining for CK19 can be identified in the compressed thyroid parenchyma surrounding nodules and in follicular cells within lymphocytic thyroiditis[17]. Even the reactive follicular epithelium within thyroid nodules around the site of degeneration and at the site of a previous needle biopsy can also show CK19 positivity[6]. Papillary thyroid carcinoma show diffuse and intense positivity but focal staining for CK19 does not rule out the diagnosis as nuclear features might be present only focally.[6,9] CK19 is also a useful ancillary tool for the diagnosis of papillary carcinoma in FNAC, especially in cytologically indeterminate cases.[6]

This study has concluded that staining features of Ck19 may be helpful in differentiating PTC from multinodular goitre showing papillary areas as the later show focal and pale staining. Cerilli LA et al[18] illustrated strong, diffuse CK19 expression in the vast majority of PTCs, as well as the follicular, Hürthle cell, and sclerosing variants of this tumour. Non papillary carcinomas and adenomas showed CK19 staining, but the pattern and intensity were clearly different. Lam KY et al[19] concluded that CK19 is strongly and highly expressed in papillary carcinoma and were often focally stained or negative in over 60% of follicular carcinomas. But, diffuse CK19 staining was found in follicular carcinomas, poorly differentiated carcinomas and anaplastic carcinomas. So, strong CK19 staining is not entirely specific for papillary carcinoma.

These findings can suggest the use of CK 19 to differentiate small foci of papillary carcinoma from benign hyperplastic thyroid lesion. El Demellawy D et al[5] conducted a study on expression of CK19 in PTC and other thyroid neoplasm and CK 19 showed positive expression in 85% PTC and also in 26% of cases of non-PTC lesions/tumours.

Out of 20 benign cases, papillary hyperplasia was seen in 4 benign cases, of which 3 cases showed 2+positivity for CK19. Both the 2 benign cases with nuclear clearing also showed 2+ positivity for the same.

In contrast to this were the findings from the study conducted by Nechifor-Boilă et al[20] which showed only 45.5% positivity for CK19 in PTC cases and none of the benign cases was positive for the same.

There was no significant statistical correlation between the tumour size and the intensity of CK19 staining in our study unlike the study conducted by Liu Z et al[21] where positive expression of the CK19 was correlated significantly with the tumour diameter ($P < 0.05$) and concluded that larger is the tumour diameter, higher was the intensity of CK19staining.

CD56 Expression in thyroid lesions

The Neural Cell Adhesion Molecule (NCAM), also known as CD56, is a member of the immunoglobulin super family that engages in both homophilic and heterophilic interactions. Originally thought to as a mediator of cell-cell adhesion, CD56 is now understood to be a signalling receptor that affects synaptic plasticity as well as cellular adhesion, migration, proliferation, and death.[22,23] CD56 is also expressed in normal thyroid follicular cells, has been connected to the differentiation of the follicular epithelium. CD56 expression was initially studied in Hashimoto's thyroiditis and Grave's disease and it was shown that thyrocytes from autoimmune glands had higher CD56 expression. This finding suggests that locally released cytokines may have contributed to this increase. Later research revealed that PTC frequently had low CD56 expression and that elevated CD56 expression was detected in thyroid follicular lesions like nodular hyperplasia, follicular adenomas, and follicular cancer.The progression of thyroid tumour has been linked to decreased CD56 expression in the thyroid gland.[24]

Dina El Demellawy et al[5] showed CD56 was positive in all thyroid lesion except Papillary thyroid carcinoma cases. In this study CD56 was extremely useful in distinction between Papillary thyroid carcinoma. Young park et al[25] showed that CD56 has an important role as a negative diagnostic marker for PTC and differentiation from other malignant and benign lesions. In this study, positive expression of the CD56 in benign lesions was seen in 75%, while it was positive only in 18.75% of malignant lesions (PTC).

Similar study conducted by Shin MK et al[7] and Shahebrahimi et al[9] showed loss of CD56 expression in malignant thyroid lesions in 95% and 94.87% of cases.

In a similar study conducted by Erdogan-Durmus S et al[26], 100% of benign cases showed positive staining and Dunderovic D et al[27] showed positive staining for 92.4% of benign cases for same in contrast to the study done by Dalal N et al[1], in which only 41.1% benign cases showed positive staining for CD56.

In this study, Ck19 staining was significantly seen more in malignant cases than in benign cases, both in intensity and by number of cases. CD56 staining was significantly seen more in benign cases when compared to malignant cases, both in intensity and by number of cases with a statistical significance . Hence, we suggest the usage of immunohisochemistry to aid the diagnosis.

CONCLUSION

Positive Expression of CK19 had a sensitivity of 93.8 % and specificity of 45% to diagnose PTC with positive predictive value of 57.7% and Negative predictive value of 90%. CD56 immunostaining had a sensitivity of 81.2 % and specificity of 75% to diagnose benign thyroid lesions. The test has a positive predictive value of 72.2% and Negativepredictive value of 83.3%. Thus using these marker together will increase the diagnostic utility.

LIMITATION

The limitation of the study was that the sample size was small (36 cases) and is a single institutional study.

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