



Original Research Article

Diagnostic utility of CD56 in differentiating papillary thyroid carcinoma from other lesions of thyroid

Khatija Shameem¹, Syeda Khadija Fatima^{1,*}, Bhavani Myla¹¹Dept. of Pathology, Kamineni Institute of Medical Sciences, Nalgonda, Telangana, India

ARTICLE INFO

Article history:

Received 27-05-2020

Accepted 23-06-2020

Available online 19-11-2020

Keywords:

CD56

Immunohistochemistry

Papillary carcinoma of thyroid

Follicular variant of papillary thyroid carcinoma

ABSTRACT

Background: Thyroid cancer is one of the most common malignant neoplasm worldwide. Among Indians, thyroid cancer constitutes 3.96% of total cancers. Papillary thyroid carcinoma (PTC) is a malignant epithelial tumor with distinctive nuclear features. PTC represents, about 85% of all malignant thyroid neoplasm. Though histopathological diagnosis is the gold standard for PTC diagnosis, pathologists usually face difficulty due to morphologic overlap between follicular neoplasms and PTC, especially the follicular variant of PTC. CD56 is a neuroendocrine marker and an antigen important for the follicular epithelium differentiation. Recent studies have reported low or absent expression of CD56 in PTC and its presence in normal thyroid tissue, benign thyroid lesions, and most follicular non-PTC tumors.

Aims: This study aimed to assess the diagnostic utility of immunohistochemical marker, CD56 in distinguishing PTC from benign thyroid lesions and follicular neoplasms.

Materials and Methods: This was a prospective and retrospective case control study conducted at department of Pathology of our institute. All 125 thyroidectomy specimens received during a study period from January 2017 to December 2019 were studied and any already established recurrent case of PTC was excluded. After routine histopathological examination, the expression of CD56 was studied and statistically analyzed.

Results: The difference between expression of CD56 antibody in differentiating PTC from other thyroid lesions was found to be statistically significant ($p < 0.001$). The sensitivity of CD56 was 94.6%, and its specificity was 97.7%.

Conclusion: Thus, CD56 was found to be a valuable and sensitive biomarker even when used individually.

© This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>) which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

1. Introduction

Thyroid cancer is one of the most common malignant neoplasm worldwide.¹ Among Indians, according to National Cancer Registry Programme, thyroid cancer constitutes 3.96% of total cancers.² The age adjusted incidence rates of thyroid cancer per 100,000 are 1:1.8 for males and females respectively.³ Papillary thyroid carcinoma (PTC) is a malignant epithelial tumor with distinct nuclear features and architectural pattern.⁴ PTC represents, about 85% of all malignant thyroid neoplasm and occurs largely in young to middle aged adults with

a female: male ratio of 4:1.⁵ Although histopathological study is the “gold standard” for diagnosis of thyroid lesions, there exist certain morphologically overlapping features between the follicular lesions and the follicular variant of papillary thyroid carcinoma (FVPTC). In such cases a consistent diagnosis based merely on morphologic assessment is sometimes impossible. Consequently, immunohistochemical and molecular methods were investigated to aid in the diagnosis of these problematic case.^{6–8} CD56, is a neural cell adhesion molecule (NCAM), expressed in normal thyroid follicular cells with frequent low or absent expression in malignant thyroid tumors especially PTC.^{8–11} CD56 regulates cell motility and homophilic binding between neurons, hence its expression

* Corresponding author.

E-mail address: skhadija0605@gmail.com (S. K. Fatima).

may affect the migratory capacity of tumor cells.¹² Thus loss of CD56 can be associated with metastasis through blood and lymph nodes. Aim of this study was to assess the utility of CD56 in benign and malignant lesions of thyroid and to compare its expression in follicular thyroid neoplasia and PTC (including FV-PTC).

2. Materials and Methods

This was a prospective and retrospective case control study conducted over a period of 2 years starting from January 2017 to July 2019, in the histopathology department of pathology in our institution. Institutional ethical clearance was obtained. A total of 125 specimens of surgically removed, formalin-fixed and paraffin embedded thyroid tissue were included in the study. After routine histopathological examination, out of 125 cases, 83 were benign and 42 were malignant. Any already established recurrent case of PTC was excluded. Benign thyroid lesions were divided into nodular hyperplasia, hashimotos thyroiditis and follicular adenoma. Malignant cases included PTC and non PTC cases. Non PTC malignancies included follicular carcinoma and medullary carcinoma. We did not receive any anaplastic carcinoma during this tenure. Normal thyroid tissue sections from autopsy specimens was obtained as control and stained. Confirmation of the original diagnosis was achieved through separate revision of H&E stained slides by the two independent pathologists using the well established diagnostic criteria for each lesion. The major and minor histological criteria proposed by Chan was used to diagnose PTC.¹³

2.1. Immunohistochemistry

All 125 samples were subjected to IHC. The tissue was paraffin embedded and cut into 4mm thick tissue sections. They were then passed through xylene and absolute alcohol for deparaffinization and rehydration respectively. Microwave method was used for antigen retrieval using 0.01 citrate buffer (pH6) after heating the sections at 98°C for 5–6 min, then kept at room temperature for 10 min. Peroxidase and protein blocks were done. Monoclonal mouse anti human CD56 antigen, 6ml (antibody dilution 1/100, Clone 123 C3, Pathnsitu Biotechnologies, India) was used as primary antibody. After that the slides were incubated overnight with the primary antibodies, it was followed by the secondary biotin conjugated antibody and peroxidase conjugated streptavidin for 1 h each. After treating the sections with diaminobenzidine tetrachloride for 25 min, slides were counterstained in Harris hematoxylin for 5mins, followed by dehydration, clearing and mounting. Positive control for CD56 antibody was endometrial stromal cells and skin biopsy as negative control. Negative controls were done by

excluding the primary antibody and its replacement with a non-immune antibody.

2.2. Interpretation of immunohistochemical staining of CD56

The results were assessed by two independent pathologists with a pentaheaded microscope and a common consensus was reached regarding any doubtful cases. According to Park, strong, diffuse complete membranous expression of more than 10% of cells with or without cytoplasmic staining of the cells qualified the case as positive for CD56 and less than 10% was taken as negative expression.^{14,15}

2.3. Statistical analysis

The statistical analysis was performed by the aid of the SPSS version 17. Sensitivity, specificity, positive predictive value, and negative predictive value of CD56 protein were assessed in PTC and compared with non-PTC thyroid lesions. The Chi-square test was used to assess the differences between groups. The threshold for statistical significance was set at $p < 0.05$.

3. Results

There were total 125 cases out of which 83 cases were benign lesions showing 93.9% (78) females and 6% (5) males. Among the 42 malignant lesions, 92.8% (39) were females and 7% (3) males. There was female preponderance among all the lesions. Majority of the patients were in the third to sixth decade of life. The age wise incidence of thyroid lesions showed both benign malignant lesions to be more common in less than 55 years of age group. (Figure 1) Both age and gender distribution was not found to be significant in benign ($p=0.68$, $p=0.442$) and malignant lesions ($p=0.513$, $p=0.338$) (Table 1 Age and gender wise incidence of different thyroid lesions).

Most common lesion among the benign thyroid lesions was nodular hyperplasia -54 cases (65.06%) followed by hashimotos thyroiditis- 20 cases (24.09%). Of the 42 malignant cases, 37 cases (88.0%) were papillary thyroid carcinomas (PTC), which included 10 cases of classic PTC, 18 cases Follicular variant PTC, six cases of Encapsulated variant, two cases of micro PTC and one case of Solid variant of PTC. Non PTC cases included one (2.3%) case of follicular carcinoma (FC), four cases (11.9%) of medullary thyroid carcinomas (MC).

3.1. Results of CD56 immunostaining

CD56 expression was studied, along with positive and negative controls, in 83 benign and 42 malignant thyroid lesions. CD56 was positively expressed in 80/83 (96.3%) of benign specimens and 7/42 (16.6%) of malignant cases. (Table 2 Expression of CD56 immunohistochemical marker

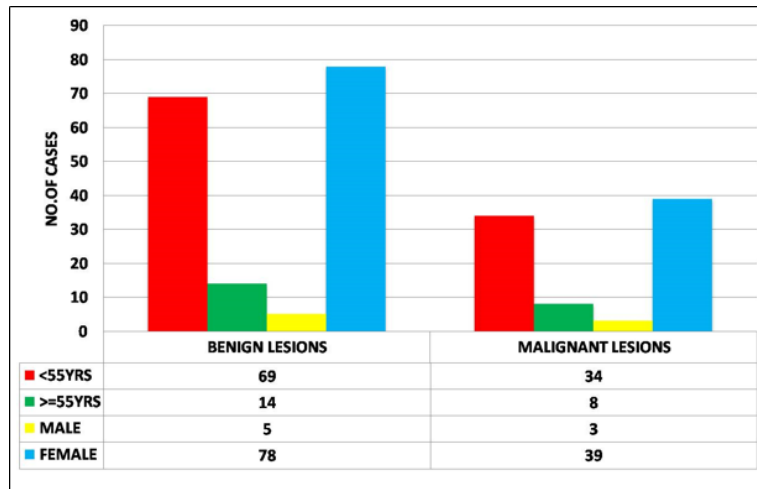


Fig. 1: Age and gender wise distribution of thyroid lesions

in benign and malignant thyroid lesions).

3.2. CD56 expression in Non neoplastic benign lesions: (Figures 2 and 3)

CD56 expression was strongly positive in these cases (Figure 2 A, B and Figure 3 A, B) except for one case of nodular hyperplasia (Figure 2 C, D) and one case of hashimotos thyroiditis which showed a suspicious focus of microcarcinoma (Figure 3C, D).

3.3. CD56 expression in neoplastic follicular lesions: (Figures 4 and 5)

Follicular type lesions included in our study were benign follicular adenoma, follicular carcinoma and follicular variant of papillary carcinoma (FVPTC). The follicular adenoma and follicular carcinoma showed intense and diffuse staining in tumor cells (Figure 4 A, B, Figure 5 A, B, C) when compared to the normal surrounding thyroid tissue. 1/9 cases of follicular adenoma showed less intense staining.

In follicular lesions causing morphological confusion in the diagnosis of PTC, CD56 helped in exclusion. All 18 cases of FVPTC showed 100% negative expression (Figure 5 D, E, F). No statistical significance was observed when CD56 expression of NH and HT was compared with FA. ($c^2=0.109$, $p = 0.74$). CD56 expression in FVPTC was compared with non PTC follicular lesions (FA+FC) and benign lesions (FA+ NH+ HT) and the difference between expressions was statistically significant ($c^2=19.92$ and $c^2=77.6$ respectively).

3.4. CD56 expression in papillary neoplastic lesions: (Figure 6)

In 35 out of the 37 cases (97.3%) of PTC, CD 56 expression was negative in all areas of tumor tissues including the

centre and periphery (Figure 6 A, B, C). In the remaining two cases, one of them turned out to be hyperplastic nodular goiter with papillary areas on H&E stained slide, originally diagnosed as classic PTC, which showed >50% expression of CD56 in follicles. Another was initially diagnosed as EVPTC on H&E, which revealed positive expression of CD56 in >50% of the tumor cells and was later changed to follicular adenoma after IHC and confirmed by Cytokeratin 19 marker.

A significant relationship was found between CD56 staining of PTC and benign follicular lesions ($c^2=93.73$, $p = < 0.0001$). No statistically significant difference was found between FVPTCs and other PTCs as regards to CD56 expression ($c^2=0.47$, $p = 0.49$).

3.5. CD56 expression in non PTC malignant cases. (Figure 6)

All cases of follicular carcinoma and medullary carcinoma showed strong positivity with CD56. A case of medullary carcinoma showed areas of papillary pattern with typical nuclear features of PTC on H&E which were CD56 positive (Figure 6 D, E, F). Using Fisher's exact test, CD56 distinguished PTC from non PTC tumors which was statistically significant ($c^2=21.97$, $p = < 0.0001$). The sensitivity for expression of CD56 in separating benign thyroid lesions from malignant lesion (PTC) was 94.6%, and its specificity was 97.3%. The positive and negative predictive values of this test were 97.3%, and 94.6%, respectively.

4. Discussion

PTC diagnosis is, usually but not always, easily achieved with almost minimal inter observer variability. However, in the absence of papillary architecture, it becomes challenging

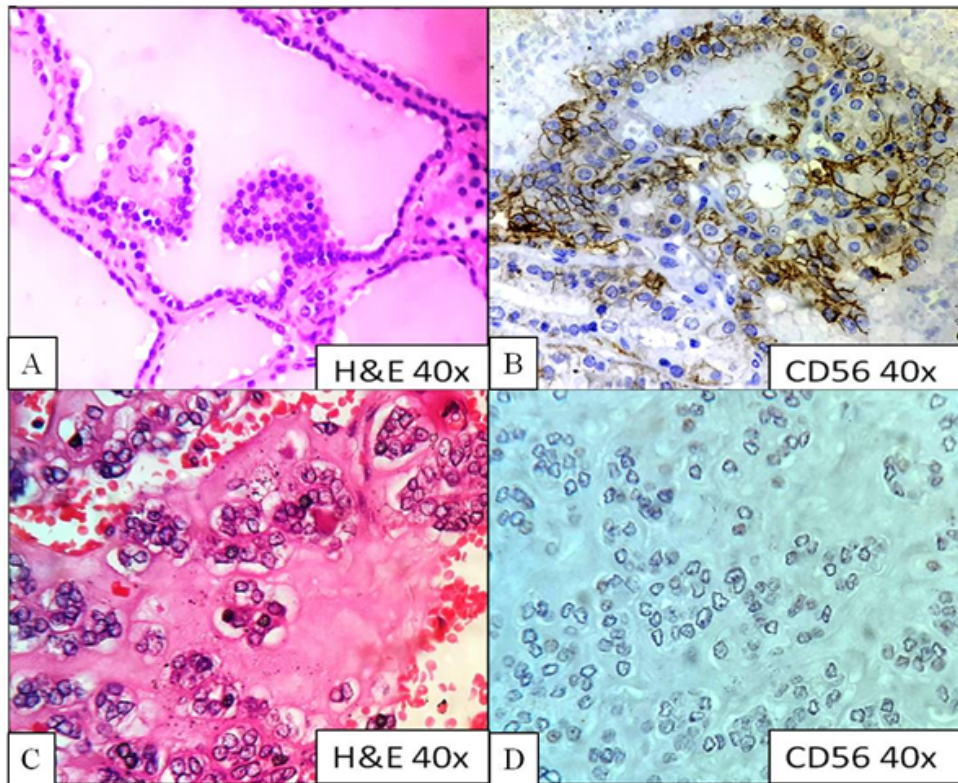


Fig. 2: A, B: In nodular hyperplasia, follicles and hyperplastic papillae (H&E 40X) showed an positive membranous CD56 staining throughout the lesion.(CD56 40X). C, D: A nodular adenomatous goiter with lack of papillary architecture and nuclear features(H&E 40X) suspicious of PTC showed absence of staining for CD56.(CD56 40X)

Table 1: Age and gender wise incidence of different thyroid lesions.

		Benign			Total	P value	Malignant			Total	P value
		HT	NH	FA			PTC	FC	MC		
Age	<55	14	47	8	69	0.44	29	1	4	34	0.51
	=>55	5	8	1	14		8	0	0	8	
Gender	M	1	4	0	5	0.66	2	0	1	3	0.33
	F	18	51	9	78		35	1	3	39	
Total		19	55	9	83		37	1	4	42	

FA= Follicular adenoma, NH= Nodular hyperplasia, HT = Hashimoto thyroiditis, PTC=Papillary thyroid carcinoma, FC= Follicular carcinoma, MC=Medullary carcinoma)

to differentiate a follicular adenoma from the FVPTC.¹⁶ Routine histopathological examination stands as the gold standard in arriving at a diagnosis in thyroid follicular tumors. Although several IHC methods are being used, there is no marker that can exactly differentiate PTC from follicular lesions of thyroid.^{11,17}

CD56 belongs to the Ig-superfamily. It is a homophilic binding glycoprotein whose antibody targets an NCAM isoform that is expressed normally in activated T cells, large granular lymphocytes, natural killer cells, specific endocrine cells and brain tissues.^{9,11,14} Reduced CD56 expression has been implicated in tumor progression of patients with cancer. Normal thyroid follicular cells also express CD56 but its expression is markedly reduced

by malignant transformation as in follicular carcinoma, papillary carcinoma and anaplastic carcinoma.^{6,9,11,14–16,18} In our study we have used CD56 marker to determine its diagnostic value in assessing a series of benign thyroid lesions, non PTC malignancies and PTC.

In the present study, maximum number of cases diagnosed with PTC was in the third to sixth decade of life with females predominating over males with a ratio of 7:1. Frazell and Carcangiu, also observed the maximum incidence of papillary thyroid carcinoma in the third to sixth decade of life along with female preponderance.^{19,20} Among the benign cases, Ponnuswamy et al recorded most common non neoplastic cases as colloid nodular goiter and autoimmune thyroiditis.²¹ In our study also we

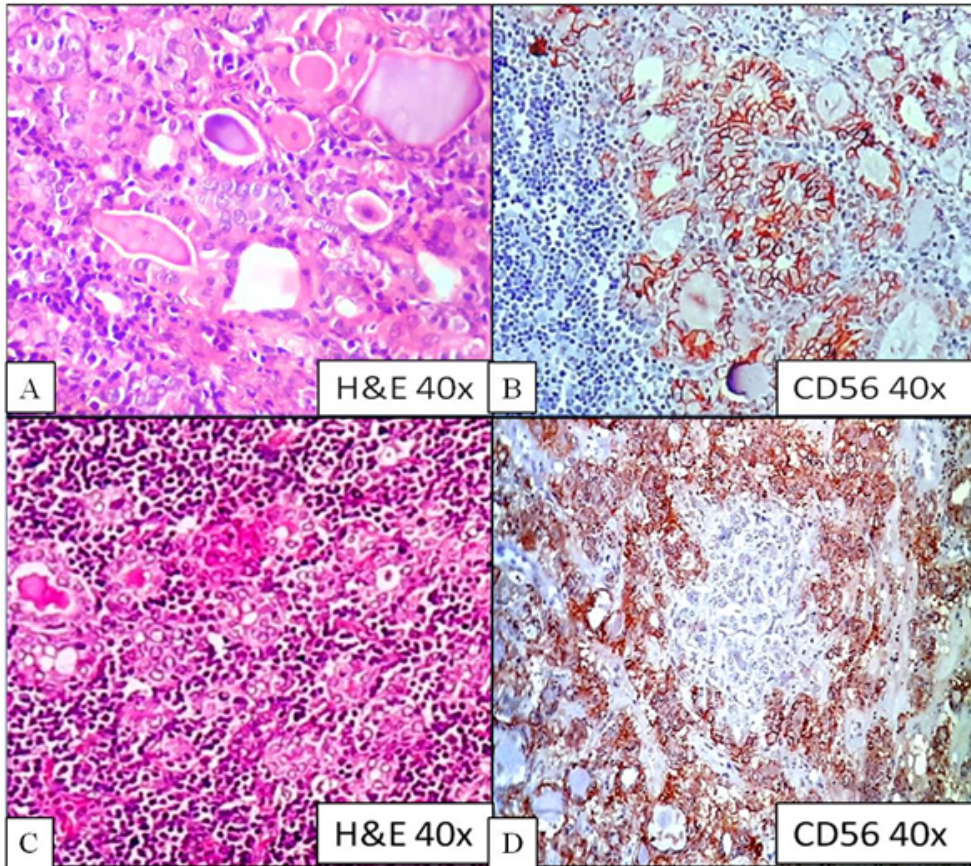


Fig. 3: A, B: In hashimotos thyroiditis, atrophic follicles with intervening lymphoid collections(H&E 40X) showed diffuse and strong CD 56 membranous positivity.(CD56 40X). **C, D:** Suspicious microcarcinoma focus in a hashimotos thyroiditis having papillary configuration and typical nuclear features(H&E 40X) showed negative CD56 staining (CD56 40X)

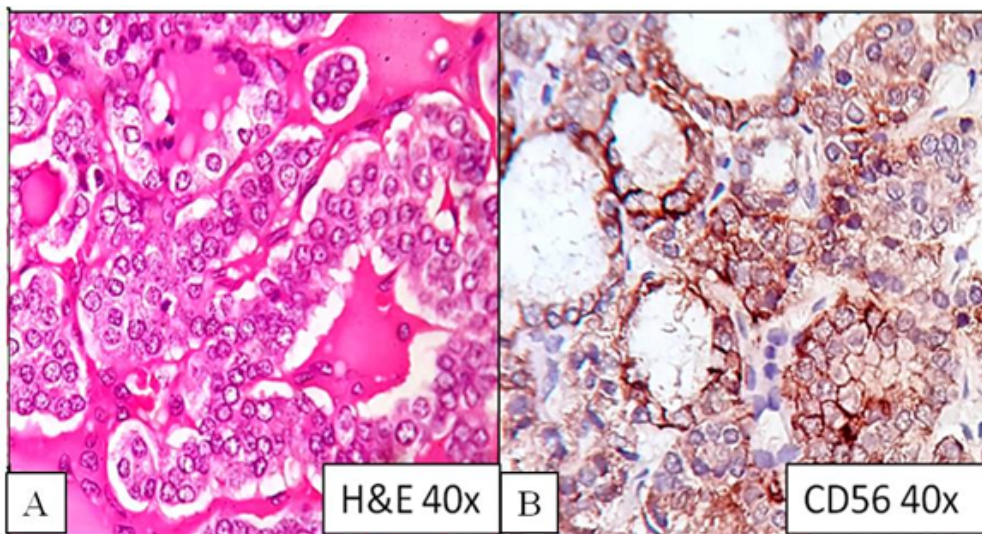


Fig. 4: A, B: Follicular adenoma of thyroid showing microfollicular pattern (H&E 40X) showed high membrane positivity >50% for CD56 staining (CD56 40X)

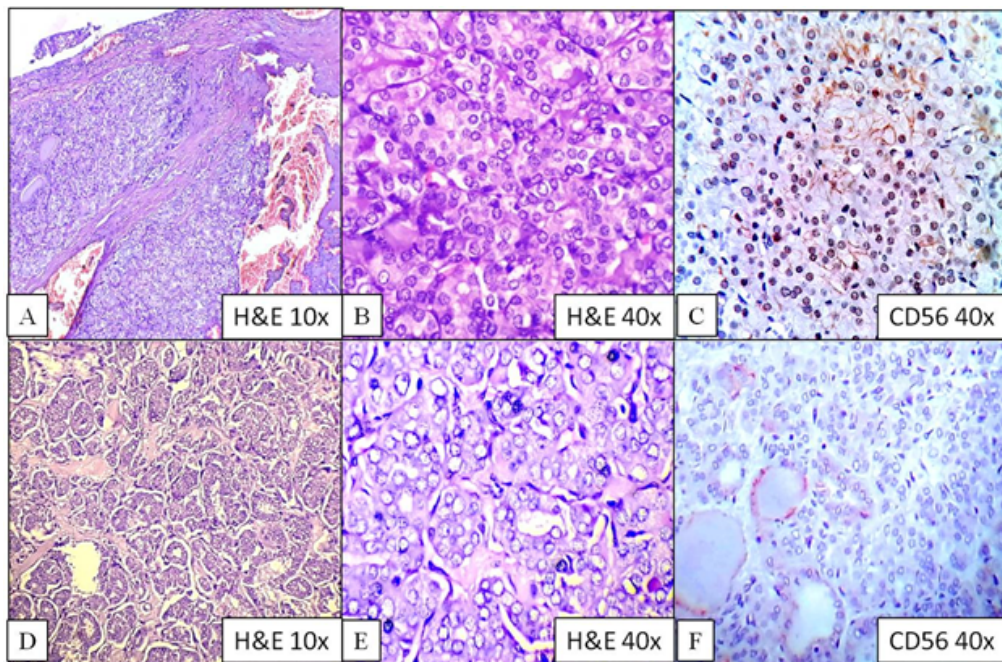


Fig. 5: A, B, C: Follicular carcinoma of thyroid with doubtful capsular invasion shows compact microfollicular pattern with atypical nuclear features (H&E 10X,40X) expressing $<50\%$ membrane positivity for CD56 staining.(CD56 40X). D, E, F: In follicular variant of PTC with nuclear features of PTC(H&E 10X,40X), there was absence of CD 56 expression throughout the lesion with few intervening benign glands serving as positive internal control.(CD5640X)

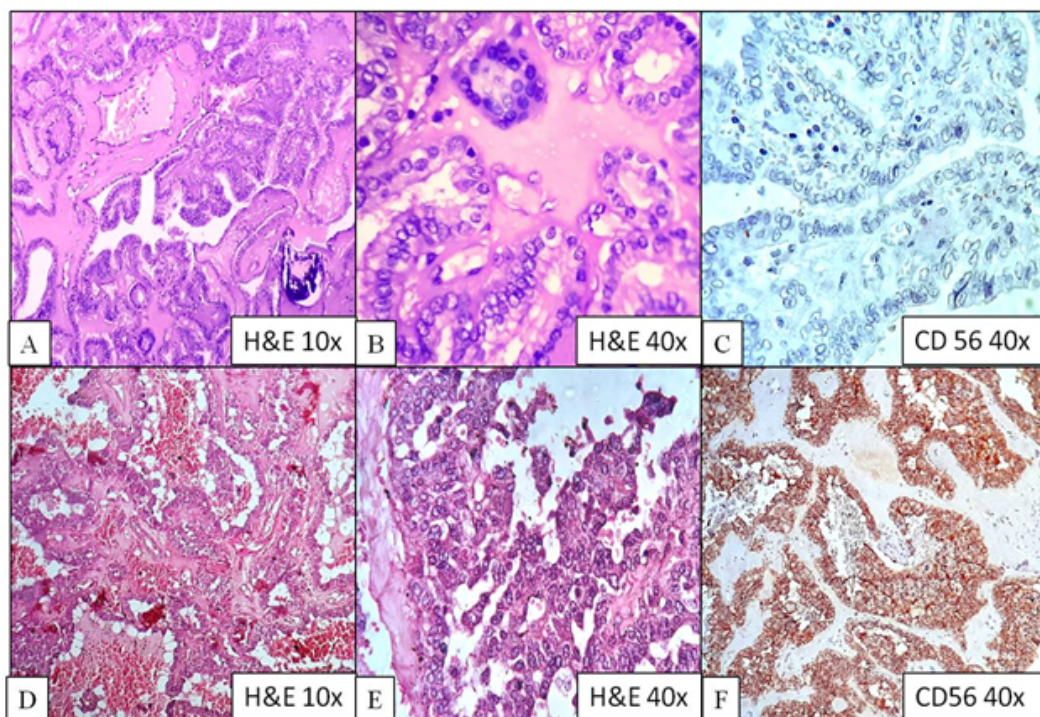


Fig. 6: A, B, C: Papillary carcinoma with areas showing typical architectural and nuclear features (H&E 10X, 40X). CD 56 expression was negative ($<10\%$)in all areas of tumor tissues (CD56 40X). D, E, F: Medullary carcinoma with areas showing papillary architectural and nuclear features.(H&E 10X,40X) CD 56 expression was highly membranous positive in all areas of tumor tissues(CD56 40X).

Table 2: Expression of CD56 immunohistochemical marker in benign and malignant thyroid lesions. CD56 Expression

Diagnosis		Before CD56 staining	Positive	Negative	After CD56 staining	Compared to (p value)
Benign thyroid Lesions	NH	54	53	1	56	FA (p=0.74)
	HT	20	19	1	19	PTC (p<=0.0001)
	FA	9	8	1	8	FVPTC (p<=0.0001)
	FVPTC	18	0	18	19	FA+FC (p=0.00) NH+HT+FA(p=0.0001)
Malignant thyroid lesions	PTC	19	2	17	19	FVPTC(p=0.49) NH+HT+FA(p=0.0001)
	Non PTC tumors (FC+MC)	5	0	0	5	PTC (p<-0.0001)
		125	38	87	125	

FA= Follicular adenoma, NH= Nodular hyperplasia, HT= Hashimotos thyroiditis, PTC= Papillary thyroid carcinoma, FC= Follicular carcinoma, MC= Medullary carcinoma)

had nodular hyperplasia (65.06%) followed by hashimotos thyroiditis (24.09%). The CD56 expression was evaluated in normal thyroid, among which 83 cases were of benign thyroid lesions and 42 cases of thyroid follicular tumors. A constant diffuse membranous CD56 expression in normal thyroid follicular epithelium, non neoplastic and neoplastic epithelium except in PTC and its variants, including FV-PTC was seen in Immunohistochemical staining of the sections with anti-CD56 antibody (Clone 123 C3). However, we had 2 cases of PTC which showed greater than 10 percent of tumor cells expressing weakly stained cytoplasmic positivity. One case of FVPTC membranous positivity of >30% seen, similar to a study conducted by Abd El Atti and Shash, which had CD56 positivity in three cases of FV-PTC.⁷ Statistics for the CD56 staining was derived and the p value was found to be statistically significant between benign thyroid lesions and PTC as well as FA and FVPTC. No statistical difference was noted between FVPTC and PTC.

In our study, CD56 marker showed a sensitivity of 94.59% and specificity of 97.3%. A study conducted by Park, also showed 92.5% sensitivity and 86.4% specificity as a sole marker.¹⁴ A study has demonstrated 95.8% (70/73) positive and 98.63% (72/73) negative CD-56 expression for non-papillary thyroid lesions and PTC cases respectively.¹⁵ Hence, in several studies including ours, sensitivity and specificity of CD56 expression were not 100% when used individually, but it may improve by using in combination with other markers.⁷ Nonetheless, a study showed 100% sensitivity and specificity of CD56 marker.¹¹

Several studies were conducted in which CD56 immunohistochemistry has differentiated PTC from benign thyroid lesions like FA, NH, and HT, the differences being statistically significant (p= < 0.0001).²² Similar results were also obtained in our study (p=< 0.0001). No statistical significance was observed by comparing CD56 expression of NH and HT with FA. (c²=0.109, p = 0.74). CD56 has helped to differentiate FV-PTC from

other thyroid nodular lesions having follicular pattern, such as in hyperplastic/adenomatous nodules, FA, and follicular tumors, the results obtained was being statistically significant (p=<0.0001). There was no difference between CD56 expression in FVPTCs and classic PTC (c²=0.47, p = 0.49) similar to a study conducted by Abd El Atti and Shash.⁷ The difference of expression of CD56 was significant when original diagnosis was compared with IHC assisted diagnosis (c²=103.213, p=<0.0001). Our study was limited by the less number of cases and the using a single IHC marker. Hence, depending on our findings we conclude that CD56 protein expression was strong and intense in benign thyroid lesions and non PTC tumors, while it was low or absent specially in papillary carcinoma thyroid. It is a valuable biomarker with a very good sensitivity and specificity as it can differentiate PTC from other thyroid lesions especially inconclusive or doubtful cases.

5. Source of Funding

No financial support was provided.

6. Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

We are grateful to the institutional head, department of pathology and its staff along with technicians for helping us in completing this research.

References

1. Horner MJ, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlader N, et al.. SEER Cancer Statistics Review, 1975-2006. National Cancer Institute. Available from: https://seer.cancer.gov/csr/1975_2006/.
2. National Centre for Disease Informatics and Research. Trend over time for all sites and on selected sites of cancer and projection of burden of cancer. National Cancer Registry Programme. Indian

- Council for Medical Research 3 Year Report of Population Based Cancer Registries. Ch. 10. National Centre for Disease Informatics and Research; 2016.
3. Unnikrishnan AG, Menon UV. Thyroid disorders in India: An epidemiological perspective. *Indian J Endocrinol Metab.* 2011;15(6):78–81.
 4. Thompson LDR, Wenig BM. *Diagnostic Pathology: Head and Neck.* 2nd ed. Salt Lake City, UT: Elsevier; 2016.
 5. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. American Thyroid Association Guidelines Taskforce. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2006;16(2):109–42.
 6. Demellawy DE, Nasr AL, Babay S, Alowami S. Diagnostic utility of CD56 immunohistochemistry in papillary carcinoma of the thyroid. *Pathol - Res Pract.* 2009;205(5):303–9.
 7. Atti RMAE, Shash LS. Potential diagnostic utility of CD56 and claudin-1 in papillary thyroid carcinoma and solitary follicular thyroid nodules. *J Egypt Natl Cancer Inst.* 2012;24(4):175–84.
 8. 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(1):48–57.
 9. Satoh F, Umemura S, Yasuda M, Osamura RY. Neuroendocrine Marker Expression in Thyroid Epithelial Tumors. *Endocr Pathol.* 2001;12(3):291–9.
 10. Scarpino S, Napoli AD, 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(4):411–9.
 11. Demellawy DE, Nasr A, Alowami S. Application of CD56, P63 and CK19 immunohistochemistry in the diagnosis of papillary carcinoma of the thyroid. *Diagn Pathol.* 2008;3(1):5.
 12. Huerta S, Srivatsan ES, Venkatesan N, Peters J, Moatamed F, Renner S. Alternative mRNA splicing in colon cancer causes loss of expression of neural cell adhesion molecule. *Surg.* 2001;130(5):834–43.
 13. Chan J. Strict criteria should be applied in the diagnosis of encapsulated follicular variant of papillary thyroid carcinoma. *Am J Clin Pathol.* 2002;117(1):16–8.
 14. 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 the thyroid gland. *Basic Appl Pathol.* 2009;2:63–8.
 15. 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(12):1046–50.
 16. Nasr MR, Mukhopadhyay S, Zhang S, Katzenstein ALA. Immunohistochemical markers in diagnosis of papillary thyroid carcinoma: utility of HBME1 combined with CK19 immunostaining. *Mod Pathol.* 2006;19(12):1631–7.
 17. Ozolins A, Narbutis Z, Strumfa I, Volanska G, Gardovskis J. Diagnostic utility of immunohistochemical panel in various thyroid pathologies. *Langenbeck's Arch Surg.* 2010;395(7):885–91.
 18. 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(1):23–30.
 19. Frazell EL, Foote FW. Papillary cancer of the thyroid. A review of 25 years of experience. *Cancer.* 1958;11:895–922.
 20. Carcangiu ML, Zampi G, Pupi A, Castagnoli A, Rosai J. Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy. Wiley; 1985. Available from: [https://dx.doi.org/10.1002/1097-0142\(19850215\)55:4<805::aid-cncr2820550419>3.0.co;2-z](https://dx.doi.org/10.1002/1097-0142(19850215)55:4<805::aid-cncr2820550419>3.0.co;2-z). doi:10.1002/1097-0142(19850215)55:4<805::aid-cncr2820550419>3.0.co;2-z.
 21. Karkuzhali P. An Indian Tertiary Care Hospital Scenario of Papillary Carcinoma of Thyroid. *J Clin Diagn Res.* 2017;11(6):26–9.
 22. Vlad MM, Golu I, Dema A, Moleriu LC, Tudor A, Iacob M, et al. The absence of CD56 expression can differentiate papillary thyroid carcinoma from other thyroid lesions. *Indian J Pathol Microbiol.* 2017;60(2):161–6.

Author biography

Khatija Shameem, Associate Professor

Syeda Khadija Fatima, Assistant Professor

Bhavani Myla, Professor and HOD

Cite this article: Shameem K, Fatima SK, Myla B. Diagnostic utility of CD56 in differentiating papillary thyroid carcinoma from other lesions of thyroid. *Indian J Pathol Oncol* 2020;7(4):582-589.