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CD56 – A NEURAL ADHESION MOLECULE AS A MARKER FOR THYROID CARCINOMA

Y. Shreya, G. Jayalakshmi*
Sri Lakshmi Narayana Institute of Medical Sciences, Kudupakkam Post, Puducherry - 605 502, India

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ABSTRACT

Thyroid neoplasms are the most frequently encountered endocrine neoplasms in clinical and surgical pathology practice. It has been suggested that a number of markers, including Cytokeratin-19, HWCK, HBME-1, GAL-3, CD57, CITED-1, CD15, Fibronectin-1, CD44, and PDGF, are important in the diagnosis of papillary cancer. A neural cell adhesion molecule is CD56. Its expression may affect the migratory capability of tumor cells. Therefore, it is not unexpected that CD56 depletion corresponds with the propensity for metastasis and a poor prognosis in several cancers.

Corresponding Author:

Dr. G. Jayalakshmi,
Sri Lakshmi Narayana Institute of Medical Sciences,
Kudupakkam Post,
Puducherry - 605 502, India.
Email: jayalakshmi.2k15@gmail.com

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1. INTRODUCTION

The most prevalent malignant endocrine tumour is thyroid cancer. These days, the most effective diagnostic methods for thyroid lesions are tissue biopsy and pathological evaluation. Pathology must differentiate between adenomas and the follicular type of papillary thyroid cancer (PTC). The thyroid gland's nodular follicular lesions can be either benign or malignant tumours, as well as various types of hyperplasia. A solid nodule, a multinodular gland, Grave's disease, or thyroiditis are all examples of follicularly generated thyroid illness. Thyroglobulin, TTF-1, Pan-Cytokeratin, and PAX-8 are typical markers for papillary cancer [1, 2]. Most of these neoplasms arise from follicular epithelial cells. They encompass a wide variety of benign & malignant neoplasms. Papillary carcinoma of the thyroid (PTC) is the most prevalent among these, constituting about 80% of all thyroid neoplasms [3, 4]. Thyroglobulin, TTF-1, Pan-Cytokeratin, and PAX-8 are typical markers for papillary cancer. Cytokeratin-19, HWCK, HBME-1, GAL-3, CD57, CITED-1, CD15, Fibronectin-1, CD44, and PDGF are only a few of the markers that have been shown to be significant in the diagnosis of papillary cancer [5-8]. The reported incidence of thyroid neoplasms has significantly increased on a global scale. [9-11], since the introduction of high-resolution imaging techniques (thyroid ultrasonography). Almost all of the tumors accounting for this recent increase are of the papillary type [12-14].The increased incidence may be the result of an actual increase in the incidence of PTC. However, a minor component has been attributed to over diagnosis of PTC. The diagnostic criteria for PTC have been established for more than 50 years. However, it appears that its application, especially with regard to quantization, is still not sufficiently established. Quite a few cases do spark debate. To call it PTC, or not to call it PTC, is quite often the question that surgical pathologists face.

Unfortunately, such controversy is not a rarity, even among expert thyroid pathologists. Inter-observer disagreements among pathologists have been documented quite frequently. Studies show that CD56 is expressed in normal thyroid follicular cells, as well as in benign and malignant follicular lesions, but not in PTC. The loss of CD56 expression has displayed reasonably high sensitivity and specificity in differentiating PTC from other follicular neoplasms. However, it is a negative marker for PTC. CK19, HBME-1 and P63, are positive markers, which have proven to be valuable in the distinction of PTC from other thyroid follicular lesions [9-12). This study is aimed at evaluating the efficacy of CD56 as an immunomarker to aid in the diagnosis of papillary thyroid carcinoma. CD56 being a negative marker for PTC, CK19 has also been included in the study.

2. METHOD

2.1. Sample Size

A total of 30 cases of surgically resected follicular cell derived thyroid lesions that include both benign and malignant neoplasms were collected. The followed inclusion and exclusion criteria.

2.2. Processing of Specimens

The specimens were received in 10% formalin. They were allowed to fix over a period of 24 hours. After formalin fixation, gross examination of the specimens was done. The role of immunohistochemical staining with CD56 and CK19 in differentiating papillary thyroid carcinoma and its variants from other follicular patterned thyroid lesions is evaluated and the results are compared with those reported in the literature.

3. RESULTS

This retrospective case-control study includes a total of 30 cases of follicular cell-derived thyroid neoplasms. We selected 15 cases of unequivocal PTCs as the study group. These included 9 cases of classical PTC and 6 cases of follicular variant of PTC. We selected 15 cases of follicular neoplasms (other than PTCs) as the control group. These included 11 cases of follicular adenoma and 4 cases of follicular carcinoma. For the purpose of this study, we have assigned scores 0 and 1 as lack of expression of the immunomarker. We have considered scores 2 and 3 as positive expression of the marker. The mean age in our study was 43.53 years. The youngest patient in our study population was 23 years old and the oldest was 68 years old.

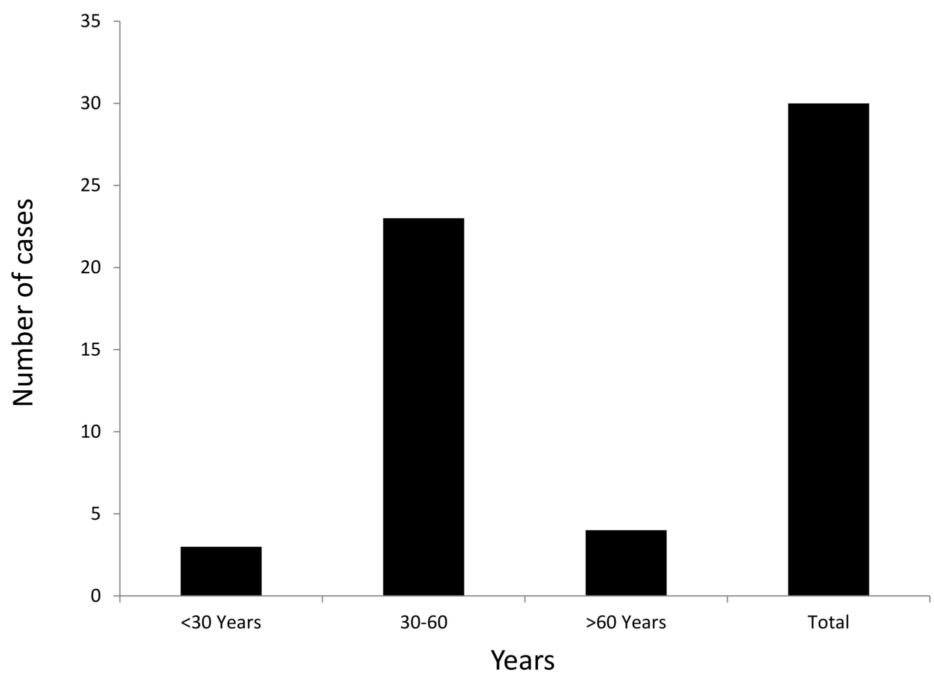

Figure 1: Age distribution

CD56 demonstrated an excellent positive predictive value (PPV) of 100% in diagnosing PTCs.

Table 1: PPV of CD56, CK19 & CD56 / CK19 Panel

Immunomarker	CD56	CK19	CD56 / CK19
PPV	**100.00%** (76.60% – 100%)	**77.80%** (61.00% – 83.00%)	**100.00%** (74.20% – 100%)

CD56 recorded a very high diagnostic accuracy of 90.00%, while CK19 had a lower diagnostic accuracy of 83.30%.

Table2: Accuracy of CD56, CK19 & CD56 / CK19 Panel

Immunomarker	CD56	CK19	CD56 / CK19
Accuracy	**90.00%** (71.30% – 90.00%)	**83.30%** (63.20% – 89.60%)	**86.70%** (67.80% – 86.70%)

Table 3: Diagnostic validity of CD56 in PTCs

CD56	*Ma H et al.*	*Ceyran AB et al.*	*Mi Kyung Shin et al.*	Our Study
Sensitivity	79.10%	91.10%	95%	**80.00%**
Specificity	100%	91.70%	72.73%	**100.00%**
PPV	64%	85.90%	92.68%	**100.00%**
NPV	100%	94.80%	80%	**83.30%**
Accuracy	84.70%	91.30%	90.20%	**90.00%**

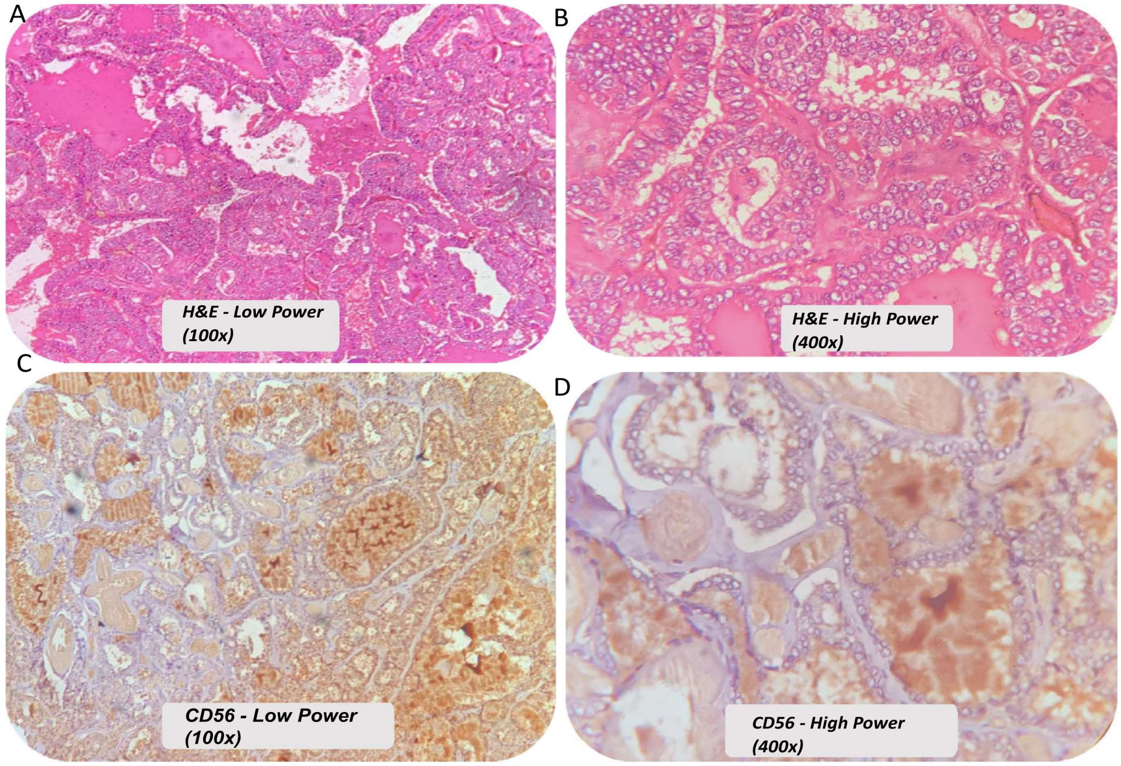

Figure 2: A. Classical PTC with papillary architecture. B. Classical PTC with characteristic nuclear features. C. Negative expression of CD56 in classical PTC, and d. Negative expression of CD56 in classical PTC.

4. DISCUSSION

It has been speculated that this may be the reason for elevated CD56 expression observed in some cases of PTC. The extrapolation of this hypothesis points at the probability of a more aggressive and metastatic phenotype being encountered in such cases [22-26].We observed a statistically significant difference between PTCs & other follicular neoplasms with regard to the CD56 expression ($p < 0.001$). Thus, the loss of CD56 expression in the FVPTCs can be utilized in distinguishing them from other follicular patterned lesions. However, Etem el al. found no statistically significant difference between his study group of FVPTCs and his control group of follicular tumours (Follicular adenomas, FTUMPs and follicular carcinomas) with regard to the expression of CD56 [26]. We compared the validity of CD56 as a diagnostic immunomarker for PTCs with results from similar studies done previously. The results from these studies, in comparison with our study, have been tabulated and represented graphically below.

We recorded a fairly good sensitivity of 80% and negative predictive value of 83.30% in our study. Ceyran AB et al. and Mi Kyung Shin et al. reported similar values [18-20]. However, Ma H et al. had reported a negative Predictive value of 100% [19]. We recorded excellent specificity (100%) and positive predictive value (100%) of CD56 in distinguishing PTCs from other follicular patterned lesions of the thyroid. While Ma H et al. had reported a similar specificity in their study, they reported a much lower PPV of 64% [19]. In our study, we found CD56 to have a diagnostic accuracy of 90%, which was in close agreement with those reported by Ceyran AB et al. (91.30%) and Mi Kyung Shin et al. (90.20%) [18, 20]. CK19 has shown great promise as a diagnostic immunomarker for PTC, thus its expression in PTC has been studied extensively over the past two decades. While few studies have reported very good sensitivity as well as specificity with CK19, most studies have noted a poor specificity [16, 17, 27].

We observed diffuse positivity of CK19 in 14 (93.30%) of the 15 cases of PTC under study. However, we also noted positive expression of CK19 in 4 (26.67%) of the15 cases of other follicular neoplasms studied. It has been suggested that though CK19 is also noted in follicular adenomas, the intensity and proportion of staining were different compared to PTCs. Cheung CC et al. and F Noroozinia et al. reported diffuse staining in PTCs and focal staining in Fas [15, 21]. We observed a similar trend in our study, with 2+ staining noted in 4 (36.37%) out of the 11 cases of FA compared to the 3+ staining noted in most PTCs.Thus, if we consider only diffuse staining pattern as positive expression, PTCs would be the only ones displaying CK19 positivity. So, a higher threshold for assigning positivity may improve the specificity of CK19.We compared the validity of

CK19 as a diagnostic immunomarker for PTCs with results from similar studies done previously. The results from these studies, in comparison with our study, have been tabulated and represented graphically.

Table 4: Diagnostic validity of CK19 in PTCs

CK19	*Ma H et al.*	*Ceyran AB et al.*	*Mi Kyung Shin et al.*	Our Study
Sensitivity	100%	84.20%	100%	**93.30%**
Specificity	56.25%	36.70%	36.36%	**73.30%**
PPV	86%	69.10%	85.11%	**77.80%**
NPV	100%	57.80%	100%	**91.70%**
Accuracy	88.10%	72.70%	86.27%	**83.30%**

We found CK19 to be a highly sensitive marker for PTC, with a sensitivity of 93.30% and a high negative predictive value of 91.70%. Ma H et al. & Mi Kyung Shin et al. had both reported an excellent sensitivity, as well as an excellent negative predictive value, of 100% in their studies [19, 20]. On the other hand, Ceyran AB et al. had reported a slightly lower sensitivity of 84.20% and a poor negative predictive value of 57.80% [18]. While CK19 was among the most sensitive markers for diagnosing PTC in most studies, the other diagnostic parameters were not as impressive. In our study, we recorded a poor specificity of 73.30%. This was in line with the specificity recorded in the other studies [18-20]. In our study, CK19 had a positive predictive value of 71.10% and a diagnostic accuracy of 76.70%. This was in keeping with the other studies, which also reported similar values [19-20]. The immunopanel of CD56 & CK19 demonstrated excellent specificity and positive predictive value of 100%. The panel had a sensitivity of 73.30%, negative predictive value of 78.90% and diagnostic accuracy of 86.70%. The efficacy of the panel may be attributed to the combination of two complementary markers. The high sensitivity of CK19 complements the highly specific CD56.

The negative expression of CD56 was found to be statistically significant ($p<0.001$) in distinguishing PTCs from follicular neoplasms. CD56 was negatively expressed in 12 (80%) of the 15 cases of PTC, while all 15 cases (100%) of follicular neoplasms diffusely expressed CD56. In our study, the loss of CD56 expression demonstrated a reasonably good sensitivity of 80% and negative predictive value of 83.30%.The negative expression of CD56 recorded excellent specificity (100%) and positive predictive value (100%) in distinguishing PTCs from follicular neoplasms. We calculated a diagnostic accuracy of 90% for CD56 in the diagnosis of PTC. The positive expression of CK19 was found to be statistically significant ($p<0.001$) in distinguishing PTCs from follicular neoplasms. CK19 was diffusely positive in 14 (93.30%) of the 15 cases of PTC under study. CK19 also positively expressed in 4 (36.37%) of the 11 cases of follicular adenomas studied. However, the staining patterns were different. A lower proportion, as well as, intensity of staining, was noted. CK19 was a highly sensitive marker for PTC, with a sensitivity of 93.30% and a fairly good negative predictive value of 91.70%. CK19 demonstrated a poor specificity of 73. 30%, a satisfactory positive predictive value of 77.80% and a diagnostic accuracy of 83.30%.The immunopanel of CD56 & CK19 demonstrated excellent specificity and positive predictive value of 100%. The panel had a sensitivity of 73.30%, a negative predictive value of 78.90% and a diagnostic accuracy of 86.70%.

5. CONCLUSION

CK19 showed very good sensitivity; however, the other diagnostic parameters were quite poor. CK19 was expressed in follicular neoplasms but to a lesser degree. Setting the cut-off for positive expression of CK19 at 3+ would increase the specificity of the marker. We recorded excellent specificity & positive predictive values with CD56. The other diagnostic parameters were also quite impressive. Taking into account our relatively small sample size, we suggest evaluation of the immunohistochemical expression of CD56 and CK19 by a group of expert thyroid pathologists in a more extensive study, with focus on the recently introduced borderline categories of follicular neoplasms (FTUMPs, WDTUMPs & NIFTP).

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ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

COMPETING INTEREST

The authors declare no conflict of interest.

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