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Original Research

The Role of CD56, HBME-1, and CK19 Immunohistochemical Markers in the differential Diagnosing of Thyroid Neoplasms

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Abstract

Background: The diagnosis of thyroid neoplasms is steadily increasing due to the widespread use of sensitive diagnostic techniques. While histopathologic evaluation using Hematoxylin and Eosin (H&E) staining is considered the "gold standard," it often faces challenges due to morphological overlap between benign and malignant follicular patterned lesions. This led to diagnostic uncertainties, underscoring the need for Immunohistochemistry (IHC) as a valuable adjunct. This study aims to evaluate the expression of IHC markers, Hector Battifora Mesothelial Cell-1 (HBME-1), Cluster of Differentiate (CD56 also known as Neural Cell Adhesion Molecule) and Cytokeratin-19 (CK19), in follicular patterned neoplasms of thyroid to aid in the diagnosis of malignant thyroid neoplasms

Methodology: The study was a descriptive analysis and it included 60 thyroidectomy specimens diagnosed as neoplastic by histopathology were studied after satisfying the inclusion and exclusion criteria. The IHC results were interpreted semi-quantitatively. Statistical analysis was performed using Chi-square test and Fisher's-exact tests. P-value of <0.05 was considered as significant. Sensitivity and specificity for each marker and their combination in diagnosis were calculated.

Results: Among the sixty cases, 31.67% were benign neoplasms, and 68.33% were malignant. Loss of CD56 expression was noted in 75.68% of malignant cases. The specificity of CD56, HBME-1, and CK19 in identifying malignant neoplasms was 84.21%, 84.21%, and 89.47%, respectively. The accuracy of CD56 and CK19 in diagnosing follicular variant papillary thyroid carcinoma (FVPTC) from follicular adenoma (FA) was 79.31% and 93.10%, respectively. The specificity of CK19 in distinguishing FVPTC from FA was 89.47%. The specificity of CD56, CK19, and HBME-1 in diagnosing follicular thyroid carcinoma (FTC) from FA was 84.21%, 85%, and 84.21%, respectively.

Conclusions: Our study highlights the diagnostic utility of CD56, CK19, and HBME-1 in thyroid neoplasms incorporating these markers into routine diagnostic panels can significantly enhance the accuracy and reliability of thyroid malignancy assessments.

Keywords: Papillary Thyroid Carcinoma; Follicular Adenoma; Follicular Thyroid Carcinoma; Follicular Patterned Neoplasm.

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Introduction

Thyroid nodules often attract attention due to their visibility and potential malignancy. While most are non-neoplastic, a significant proportion are neoplastic. The incidence of thyroid neoplasms has steadily risen globally over recent decades[1].In India, the incidence rate of thyroid cancer reached 2.5% in 2022, with notable increases from 2.4 to 3.8 in females and from 0.9 to 1.2 in males between 2005 and 2022[2]. This rise is partly attributed to improved diagnostic techniques such as neck ultrasonography (USG) and fine-needle aspiration (FNA), which detect smaller nodules and subclinical diseases like small papillary tumours, leading to earlier diagnoses and increased reported cases[3,4].

Surgical excision of the thyroid, whether total or hemi-thyroidectomy, is commonly performed for suspected thyroid nodules, with histopathological evaluation using Hematoxylin and Eosin (H&E) staining remaining the gold standard for detecting neoplasms. Diagnosing the classical variant of Papillary Thyroid Carcinoma (CPTC) is straightforward due to its distinct papillary structures and complete nuclear features. However, morphological overlap occurs among various follicular-patterned thyroid lesions, including follicular variant papillary thyroid carcinoma (FVPTC), follicular adenoma (FA), follicular thyroid carcinoma (FTC), and non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) poses challenges. The subtle differences between these subtypes often require additional diagnostic techniques, such as immunohistochemistry (IHC), for definite diagnosis[5,6].

Studies have reported a wide range of sensitivity and specificity values of various IHC markers over time[7-9]. Given their availability and affordability in resource-constrained settings, CK19, HBME-1, and CD56 have been selected for assessment in this study.

The neural adhesion molecule CD56, a member of the glycoprotein family, is crucial for cell-cell and cell-matrix adhesion, thereby limiting tumour invasion. It is typically expressed in neural and muscle tissues, as well as in natural killer (NK) and activated T-cells. Studies have shown diffuse membranous staining of CD56 in normal and benign thyroid follicular epithelium, with low or absent expression in malignant thyroid lesions. Loss of CD56 expression correlates with metastatic potential and poor prognosis[7,9,10].

Hector Battifora Mesothelial-1 (HBME-1) is a membrane antigen present in mesothelial microvilli and certain epithelial tissues, including the trachea, breast, lungs, and pancreas. Notably, HBME-1 is absent in normal thyroid tissue. Its expression is a valuable biomarker in diagnosing thyroid malignancies, particularly in follicular differentiated neoplasms and papillary thyroid carcinoma (PTC)[7,8].

Cytokeratin 19 (CK19), a low-molecular-weight cytokeratin, is widely expressed in epithelial tissues, including both normal and neoplastic forms. While normal thyroid follicular cells typically do not express CK19, strong and diffuse staining is observed in papillary thyroid carcinoma (PTC), with follicular adenomas and follicular thyroid carcinomas showing focal and less intense staining[8,9].

The application of IHC markers in thyroid neoplasms remains an area of active research. This study aims to evaluate the expression of CD56, HBME-1, and CK19 IHC markers in PTC and other follicular-patterned neoplasms of the thyroid. Additionally, it seeks to determine the effectiveness of these markers in distinguishing between benign and malignant thyroid neoplasms

Methods

The study is a retrospective descriptive analysis, conducted on thyroidectomy specimens received at the department of pathology, in a tertiary teaching Hospital, India during the period from May 2017 to April 2018.

Cases were included in the study if the thyroid neoplasm is of primary origin, & the age of the patients ranges 20 to 76. Cases with thyroid neoplasms other than primary including any form of malignancy metastasizing to the thyroid and lymphomas were excluded from study.

Out of a total of 94 thyroidectomy specimens received during the study period, 60 cases were identified as neoplastic. Pathological and clinical information, including age, gender, and type of operation, were extracted from the histopathology lab files. Ethical approval for this study was obtained from the institute ethics committee (IEC/DM WIMS 2017/003).

Standard procedures were followed in the histopathology lab facility for sample collection, tissue processing, and Hematoxylin and Eosin (H&E) staining of the slides[11]. H&E-stained slides and pathology reports of all 60 neoplastic cases were re-evaluated to confirm the histological type, and neoplasms were classified according to the WHO Classification of Tumors of Endocrine Organs, Fourth Edition, released in 2017[12].

Immunohistochemistry (IHC)

The paraffin embedded tissue blocks from the representative area of all 60 cases were retrieved for IHC,3–4-µm thickness were cut from the selected blocks. The sections were deparaffinized using two changes of xylene and rehydrated through absolute alcohol. Antigen retrieval in citrate buffer was performed after the sections were treated in a microwave three times for 5 minutes, and the sections were then left to cool for 20 minutes. Peroxidase and protein blocking was done. Sections were incubated with primary antibodies against CD56 (Monoclonal Mouse Anti-Human,123C3 clone, Dako), CK19 (Monoclonal Mouse Anti-Human, RCK108 clone, Dako) & HBME-1 (Monoclonal Mouse Anti-Human, Dako) at 37^0c for one hour then washed with Phosphate Buffered Saline (PBS) buffer. This was followed by secondary antibody, Polymer Horse Radish Peroxidase (HRP) for 30 mins and washed in PBS buffer. The section was covered with one drop of freshly prepared DAB (diaminbenzidine tetrachloride) solution and counterstaining with Harris hematoxylin followed by dehydration, clearing, and mounting positive controls for CD56, CK19 and HBME-1 was tonsil, skin and pleura, respectively. Negative controls were obtained by eliminating the primary antibody.

Immunohistochemistry Interpretation

Semi-quantitative scoring was done as positive and negative under light microscopy based on the cytoplasmic and membranous staining for CD56, HBME-1 was positive predominantly in the cell membrane and cytoplasm and CK-19 showed cytoplasmic positivity. following staining patterns were considered positive. H&E and IHC-stained slides were re-evaluated together with the pathology reports. For all CK19 and HBME-1 antibodies, expressions were considered positive for the marker when at least 10% of the neoplastic cells showed immunoreactivity and for CD56 whereas <10% of cells showed immunoreactivity was considered positivity for malignancy.

Statistical analysis

Data were entered into Microsoft Excel 2019 (Microsoft Corp, Redmond, WA, USA). Categorical variables were expressed as proportions, while continuous variables were presented as mean ± standard deviation. Associations between the intensity of staining of immunoreactive cells and their percentage

distribution patterns were evaluated using 2 × 2 contingency table analysis, with the Chi-square test applied where appropriate. Statistical significance was set at a p-value <0.05, with all analyses conducted at a 95% confidence interval. Additional statistical methods included Pearson's Chi-square test and Fisher's exact test.

Results

All sixty cases were subjected to IHC analysis with three biomarkers CK19, HBME-1 and CD56. Of the 60 cases, 55 (91.67%) were female and 5 (8.33%) were male, resulting in a male-to-female ratio of 0.09:1, showing a marked female preponderance. Among the 5 male cases, three were CPTC, one was FVPTC, and one was FA. Among the 55 female cases, there were 18 FA, 19 CPTC, 9 FVPTC, 5 FTC, and 4 NIFTP. The distribution of neoplasm according to the histological type was shown in table I.

Table I: Distribution of thyroid neoplasm according to the histological type

Neoplasm	**Histopathological type**
Benign 19(31.67%)	FA 19(31.67%)
Malignant 41(68.33%)	CPTC 22 (36.67%) FVPTC 10 (16.67%) FTC 5 (8.33%) NIFTP 4 (6.67%)

FA: Follicular Adenoma, CPTC: Classical Variant of Papillary Thyroid Carcinoma, FVPTC: Follicular Variant of Papillary Thyroid Carcinoma, FTC: Follicular Thyroid Carcinoma, NIFTP: Non-Invasive Follicular Tumour with Papillary like nuclear features

CD56 exhibited high immunoreactivity among benign neoplasm cases, with 13 out of 19 (68.42%) cases of FA. Conversely, CD56 showed loss of expression in most malignant thyroid neoplasms, with 28 out of 37 (75.68%) cases, including FTC, FVPTC, and CPTC (Table II). The sensitivity, specificity, and accuracy of CD56 in detecting malignant neoplasms of the thyroid were 75.68%, 84.21%, and 78.57% respectively, with a chi-square test value of 18.218, which is significant (p = 0.0014). Follicular patterned neoplasms of the thyroid were classified separately as FA, NIFTP, FVPTC, and FTC, while CPTC was the only entity in the non-follicular thyroid neoplasms. CD56 demonstrated high sensitivity, specificity, and accuracy in detecting follicular patterned malignant thyroid neoplasms, with greater sensitivity and accuracy in detecting FTC than HBME-1. In the detection of FVPTC, CD56 showed slightly lower sensitivity, specificity, and accuracy compared to CK19. In contrast, most non-follicular patterned neoplasms (CPTC) showed CD56 positive malignant immunoreactivity, with 18 out of 22 cases (81.82%) being positive, which is statistically significant (p = 0.0087).

Table II: Comparison of the immunohistochemical panel results between Benign and Malignant thyroid neoplasm

Diagnosis	**CD56**			**CK19**			**HBME-1**		
	Positive No. (%)	Negative No. (%)	Pvalue	Positive No. (%)	Negative No. (%)	Pvalue	Positive No. (%)	Negative No. (%)	Pvalue
Benign	06 (31.58)	13 (68.42)	P<0.01	02 (10.53)	17 (89.47)	P<0.01	03 (15.79)	16 (84.21)	P<0.01
FA	06 (31.58)	13 (68.42)		02 (10.53)	17 (89.47)		03 (15.79)	16 (84.21)	
Malignant	29 (78.37)	08 (21.62)	P<0.01	35 (94.59)	02 (5.41)	P<0.01	31 (83.78)	06 (16.22)	P<0.01
CPTC	18 (81.82)	4 (18.18)		22 (100)	0 (0)		21 (95.45)	01 (4.55)	
FVPTC	08 (80)	02(20)		10 (100)	0 (0)		07 (70)	03 (30)	
FTC	04 (80)	01 (20)		03 (60)	02 (40)		03 (60)	02 (40)	
NIFTP	2 (50)	2 (50)		03 (75)	1 (25)		02 (50)	02 (50)	

FA: Follicular Adenoma, CPTC: Classical Variant of Papillary Thyroid Carcinoma, FVPTC: Follicular Variant of Papillary Thyroid Carcinoma, FTC: Follicular Thyroid Carcinoma, NIFTP: Non-Invasive Follicular Tumour with Papillary like nuclear features

Table III Immunohistochemical panel results between Malignant Follicular Patterned thyroid neoplasm

Diagnosis	**IHC**	**Positive Staining No. (%)**	**Negative Staining No. (%)**	**Sensitivity**	**Specificity**	**Accuracy**	**pValue**
Follicular Patterned Malignant Thyroid Neoplasm	CD56	11(73.33)	04(26.67)	73.33%	78.26%	76.32%	0.0082
	CK19	13(86.67)	02(13.33)	86.67%	73.91%	78.95%	0.0006
	HBME-1	10(66.67)	05(33.33)	66.67%	78.26%	73.68%	0.0082
FVPTC vs FA	CD56	07(70)	03(30)	70.00%	84.21%	79.31%	0.0108
	CK19	10(100)	0	100.00%	89.47%	93.10%	<0.0001
	HBME-1	07(70)	03(30)	70.00%	84.21%	79.31%	0.0035
FTC Vs FA	CD56	04(80)	01(20)	80.00%	84.21%	83.33%	0.0422
	CK19	03(60)	02(40)	60.00%	85.00%	80.00%	0.0154
	HBME-1	03(60)	02(40)	60.00%	84.21%	79.17%	0.0422

IHC: Immunohistochemistry, FVPTC: Follicular Variant of Papillary Thyroid Carcinoma, FTC: Follicular Thyroid Carcinoma

Most benign neoplasms, specifically 17 out of 19 (89.47%) cases of FA, showed negative expression for CK19. Conversely, CK19 positivity was observed in the majority of malignant thyroid neoplasms, with 35 out of 37 (94.59%) cases, including all cases ofCPTC and FVPTC cases being positive (Table II). CK19 demonstrated high expression in CPTC, FVPTC, and NIFTPs. The sensitivity, specificity, and accuracy for CK19 in detecting malignant neoplasms were 94.59%, 89.47%, and 92.86%, respectively, at a 95% confidence interval, with a chi-square test value of 39.577, which is statistically significant ($p < 0.0001$).CK19 exhibited good sensitivity and accuracy in diagnosing follicular patterned malignant thyroid neoplasm with statistical significance of 0.0006. Additionally, CK19 showed high sensitivity, specificity, and accuracy in detecting FVPTC which is statistically significant (p value= <0.0001), However, in detecting FTC, CK19 demonstrated slightly lower sensitivity and accuracy compared to CD56, indicating lower statistical significance.

HBME1 expression was found to be significantly higher in malignant thyroid neoplasms compared to benign neoplasms. The results are summarized in Tables II. The sensitivity, specificity, and accuracy for HBME1 in detecting malignant neoplasms were 83.78%, 84.21%, and 83.93%, respectively, at a 95% confidence interval, with a chi-square test value of 24.332 and a p-value of <0.0001. However, HBME1 demonstrated lower sensitivity and accuracy compared to CD56 and CK19 in detecting follicular patterned malignant thyroid neoplasms, with a statistical significance of 0.0082, Similarly, in detecting FVPTC, HBME1 showed lower sensitivity and accuracy than CK19, with a statistical significance of 0.0035. In detecting FTC, HBME1 also exhibited lower sensitivity and accuracy compared to CD56, with a statistical significance of 0.0422 (table III).

Discussion

In the study, the patients showed a wide range of age varying between 20 to 76 years. The mean age (in years) of clinical presentation was 42 (SD 12.64). This finding is consistent with other studies[13-14]. The current study also demonstrated a marked female predominance, which aligns with similar studies in the literature[14-16].

The only benign thyroid neoplasm present was follicular adenoma, which accounted for 19 (31.67%) cases in our study, while malignancy was diagnosed in 41 (68.33%) cases of the total thyroid lesions. Studies by Muthusamy et al.[10] and Yang et al.[17] showed a similar prevalence rate for malignant cases. PTC accounted for 78.05% of all malignant lesions encountered in our study, followed by FTC at 12.2%. This predominance of PTC aligns with studies by Cheung et al.[18] and Palo et al.[19].

Loss of CD56 expression was observed in malignant thyroid neoplasms, while high CD56 expression was noted in benign neoplasm cases, specifically in FA. This difference is statistically significant and aligns with findings from other studies in the literature[20-23]. Complete loss of CD56 expression was noted in 18 cases (78.13%) of PTC. Studies by Nechifor-Boila et al.[7], Abouhashem et al.[23], and Huang et al.[24] reported loss of expression in 84.8%, 81.8%, and 90% of PTC cases, respectively. One case of FTC exhibited high CD56 immunoreactive expression, which is consistent with Priyadarshini et al.[20], who reported a 33.34% CD56 expression. This indicates that while CD56 loss is prevalent in malignancy, its presence does not entirely rule out malignancy. Definite histopathological correlation is essential in such cases. The high specificity and accuracy of CD56 in detecting malignant thyroid neoplasms underscore its potential as a marker for distinguishing benign from malignant thyroid neoplasms.

In our study, CD56 demonstrated high specificity in diagnosing FVPTC and FTC from FA. These findings were similar to the study by Muthusamy et al.[10], Tastekin et al.[21], Pyo et al.[25], and Cho et al.[26]. CD56 was the most sensitive and accurate marker in detecting FTC from FA.CD56 loss was more pronounced in CPTC than in follicular patterned neoplasms, corroborating findings from other

studies[20,23,24]. These results underscore CD56's reliability in distinguishing follicular patterned neoplasms from CPTC and identifying follicular patterned malignant thyroid neoplasms.

In our study, CK19 emerged as the most sensitive and specific marker for identifying malignant thyroid neoplasms, particularly PTC. High rates of CK19 positivity in PTCs were also observed by El Demellawy et al.[9], and Abouhashem et al.[23], supporting our findings. All FVPTC cases in our study expressed CK19, consistent with the results of Cheung et al.[18]and Sahoo et al.[27]. Our findings showed 60% CK19 positivity in FTC, aligning with Priyadarshini et al.[20], who reported a 66.67% expression rate. CK19 demonstrated the highest sensitivity and specificity in detecting FVPTC.

In our study, PTC exhibited high-level immunoreactivity of HBME-1, demonstrating significant sensitivity for detecting PTC. This finding aligns with several previous studies, by Tastekin E et al.[21], Dunđerović et al.[22], and Dağlar Aday et al.[28]. HBME-1 was the second most sensitive and specific marker is detecting thyroid malignancy. Additionally, HBME-1 demonstrated lower immunoreactivity in detecting NIFTP compared to CK19. Also, HBME-1 due to the smaller number of FTC and NIFTP cases in our study, a definitive conclusion for these subtypes is challenging, and further studies with larger sample sizes are recommended. The higher expression of HBME-1 in malignant versus benign thyroid lesions was statistically significant, with a p-value of <0.0001, consistent with the findings of Nasr et al[29]. HBME-1 also showed good specificity in detecting follicular-patterned malignant thyroid neoplasms, including follicular variant PTC and FTC, in line with the study by El-Mahdy et al[30].

We found that loss of expression of CD56 and increased expression of CK-19 and HBME-1 is detected in malignant thyroid neoplasms.CK19 and HBME-1 negative expressions were observed in 2 (5.41%) and 6 (16.22%) cases of malignant thyroid neoplasms, respectively, suggesting that negative staining does not rule out malignancy. However, the sequential use of CK19 and HBME-1 may be useful in confirming the malignant diagnosis in such cases. HBME-1 demonstrated a balanced performance with good sensitivity and specificity in detecting PTC among other thyroid neoplasms. Additionally, two (10.53%) and three (15.79%) cases of FA showed positive immunoreactivity with CK19 and HBME-1 respectively, Therefore, we recommend that cases of FA showing immunoreactivity with CK19 and HBME-1 be re-scrutinized histopathologically for nuclear features and capsular/vascular invasion.

The study's limitations include a small sample size and its single hospital-based design. Future research could build on this study by conducting multicentric studies with larger sample sizes. Expanding the range of IHC markers and including diverse populations would enhance the generalizability and robustness of the findings.

Conclusion

Our study recommends the use of CD56, CK19, and HBME-1 for diagnosing thyroid malignancies and for differentiating follicular patterned thyroid neoplasms. Increased CD56 expression supports benign lesions, while its loss indicates malignancy. CD56 demonstrated highest sensitivity and accuracy in differentiating FTC and FA. Positive staining with CK19 and HBME-1 is a strong indicator of malignancy, although negative staining does not rule it out. CK19 is the single most sensitive and specific marker for the diagnosis of PTC. HBME-1 proved to be a reliable diagnostic marker of CPTC, and second most sensitive and specific marker is detecting thyroid malignancy and balanced marker in differentiation of follicular patterned malignant thyroid neoplasm. Combining these markers in dual or triple panels enhances diagnostic accuracy and reliability. Thus, we advocate for the routine use of these markers in assessing thyroid malignancies, with all immunohistochemical results correlated with conventional histopathological findings.

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