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Research Article

Immunohistochemical Expression of CD56 in Thyroid Lesions and Its Possible Diagnostic Utility

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Abstract

Introduction: Thyroid nodules are very common among general population. Most of them are benign, however thyroid cancer (TC) represents 5% of these nodules. PTC is the most prevalent malignant thyroid neoplasm and its diagnosis is dependent on the presence of specific nuclear features, however diagnostic difficulties may arise in some cases. CD56 is a neural cell adhesion molecule that is expressed in different immune cells and neurons. Previous researches reported that lack of this marker has been linked to the malignant potentiality of tumor cells. **Aim of work:** Evaluate the diagnostic value of CD56 in distinguishing benign from malignant thyroid lesions. **Methods:** Seventy tissue blocks representing benign and malignant thyroid lesions were randomly selected for the current study. Among the forty selected malignant cases, 30 cases of papillary thyroid carcinoma and 10 cases of follicular carcinomas were included. Twenty cases of follicular adenomas and ten cases of nodular hyperplasia are included among the thirty benign lesions**. Results:** CD56 positive expression was found in 36 (51.4%) cases. A statistically significant relation was found between CD56 expression and histologic subtype and benign versus malignant lesions (p-value=<0.001 and <0.001 respectively). In PTC, CD56 negative expression was detected in 26 (86.7%) cases. A statistically significant relation was found between CD56 expression and site of lesion lymph node metastasis (p-value=0.029 and 0.009 respectively). **Conclusion:** CD56 can be a helpful immunohistochemical marker in distinguishing benign from malignant thyroid lesions.

Keywords: papillary thyroid carcinoma, thyroid cancer, CD56, immunohistochemistry.

Introduction

Thyroid nodules are a common entity which occur in up to 50% of adults. Although most thyroid lumps are benign (including thyroid adenoma, hyperplastic nodules and thyroiditis), 5% of thyroid nodules are malignant (including papillary thyroid carcinoma (PTC), follicular carcinoma (FC), anaplastic thyroid carcinoma (ATC), and poorly differentiated carcinoma) [(1,2).]

Thyroid cancer (TC) is the most prevalent endocrine malignancy. In 2020, it was the ninth most common cause of cancer, accounting for 586 000 cases worldwide. Majority of cases are women in whom TC was the fifth most common cancer in 2020 [(3,4).]

According to the data from the National Cancer Registry Program (NCRP), thyroid cancer represents about (1.5%) of all cancers and constitutes about (30%) of endocrine malignancies in Egypt. The rate in Egyptian females is 3.28% while 0.95% in males among different cancers [(5,6).]

Eighty percent of adult thyroid carcinomas are papillary thyroid carcinomas (PTCs), the most prevalent histological type of TC. Its diagnosis is dependent on architectural characteristics and nuclear features such as nuclear clearance, overlapping, and intra-nuclear grooves [(2)]. However, some of these morphological features can also be present in other benign or malignant

thyroid lesions, which may lead to diagnostic challenge. Therefore, various immune-histo-chemical and molecular studies have been developed [7,8].

CD56 is a glycoprotein which is expressed on the surface of neurons, glia and skeletal muscle[9]. CD56 signaling in neuronal cells has a crucial role in neurite outgrowth and synaptic plasticity beside its role as an adhesion molecule [10]. CD56 is considered to be the most sensitive neuroendocrine marker [11]. Aberrant CD56 expression is detected in various solid tumors as ovarian cancer, lung cancer, and neuroblastoma, and in some hematological malignancies such as leukemia and multiple myeloma [12].

In thyroid, CD56 is found to be expressed in normal follicular cells and in nearly all benign thyroid tumor cells. Frequently, decreased immune expression of CD56 has been found in malignant thyroid tumors, especially in PTC, and research has been conducted to evaluate the diagnostic value of CD56 and pathogenic connections among thyroid carcinomas [13].

The aim of the present study is to assess the diagnostic value of immunohistochemical marker CD56 to distinguish benign from malignant thyroid lesions.

Materials and Methods

1-Tissue specimens

Seventy formalin-fixed and paraffin embedded tissue blocks representing benign and malignant thyroid lesions were randomly selected for the current study. Among the forty selected malignant cases, 30 cases of papillary thyroid carcinoma and 10 cases of follicular carcinomas were included. Twenty cases of follicular adenomas and ten cases of nodular hyperplasia are included among the thirty benign lesions. The studied clinical data are: age of the patient, sex, size of lesion in the greatest dimension, site of lesion, type of operation. The studied histopathological data are: background, histo-pathologic subtype, laterality, focality, LVI, capsular infiltration, extrathyroidal extension, LN metastasis, pathological tumor Stage and tumor necrosis **(Table 1)**.

The age of the patients was categorized into 2 groups; the 1st group is under 55 years and the 2nd age group ≥55 years according to previous studies [13-16]. As regards tumor size in cases of PTC, it was divided into 2 groups; the 1st group was defined as ≤1 cm and the 2nd group as >1 cm according to previous researches [17,18].

Table (1): Clinicopathological characteristics for all studied patients (N=70)

Variables		Number	%
Age (years)	**Median**	40	100%
	IQR	(29-50)	
Age group	**< 55**	57	81.4%
	≥ 55	13	18.6%
Sex	**Male**	12	17.1%
	Female	58	82.9%
Size of lesion (cm)	**Median**	3	100%
	IQR	(2-4)	
Site of lesion	**Right lobe**	29	41.4%
	Left lobe	24	34.3%
	Both lobes	17	24.3%
Background	**no pathological abnormality**	47	67.1%
	Nodular hyperplasia	14	20.0%
	lymphocytic thyroiditis	9	12.9%
Type of operation	**Total thyroidectomy**	56	80.0%
	Hemi thyroidectomy	14	20.0%
Histologic subtype	**Papillary thyroid carcinoma**	30	42.9%
	Follicular carcinoma	10	14.3%
	Follicular adenoma	20	28.6%
	Nodular hyperplasia	10	14.3%
In malignant cases (PTC and FC) (N=40)			
Laterality	**Unilateral**	33	82.5%
	Bilateral	7	17.5%
Focality	**Unifocal**	31	77.5%
	Multifocal	9	22.5%
Lymphovascular invasion	**Negative**	28	70%
	Positive	12	30%
Capsular infiltration	**Negative**	13	32.5%
	Positive	27	67.5%
Extrathyroidal extension	**Negative**	24	60%
	Positive	16	40%
Lymph node metastasis	**Negative**	17	42.5%
	Positive	23	57.5%
Pathological tumor stage	**pT1**	17	42.5%
	pT2	9	22.5%
	pT3	14	35%
Tumor necrosis	**Absent**	28	70%
	Present	12	30%

2-Immunohistochemical (IHC) procedure

On positively charged slides, five µm sections were prepared for immunohistochemical staining by primary antibody CD56 using the method of avidin biotin-peroxidase complex with diaminobenzidine (DAB) chromogen detection system. On positively charged slides, tissue sections were first deparaffinized and rehydrated. After that, the endogenous peroxidase was blocked by immersing it in a

3% hydrogen peroxide solution and allowing it to incubate for half an hour. The slides were submerged in a solution of citrate buffer (pH 6) twice for ten minutes each at 750 W to retrieve the antigen. The slides were treated by UV block to block nonspecific background staining. Primary antibody CD56 (monoclonal mouse antibody, 100 µ, concentrated, clone no. 123C3.D5, Dako; Agilent Technologies, Inc., USA) was added and tissue sections were allowed to sit at room temperature for one hour (dilution 1:100). After discarding the extra reagent, the slides were carefully washed for five minutes with buffer solution. Next, addition of secondary biotinylated antibody for each slide for thirty minutes. DAB substrate and chromogen solutions were added to every slide and then tissue sections were counter stained with Mayer's hematoxylin. Normal human brain tissue was the positive control for CD56. Negative control sections were prepared by omitting the specific primary antibody from the immunostaining procedure and replaced with PBS.

3-Scoring of CD56 immunostaining:

CD56 positive staining was membranous +/- cytoplasmic staining. Scoring of CD56 was based on the percentage of immunoreactive tumor cells. More than 10% of tumor cells expressing membranous staining, either with or without cytoplasmic staining, was considered positive for CD56 expression, while less than 10% was considered negative [2,14].

4-Statistical analysis:

The IBM SPSS 28.0 statistical package software (IBM; Armonk, New York, USA) was used to analyse the data. For qualitative data, the data were reported as both percentages and numbers, and the Fisher's exact test or the Chi-square test were used for analysis. P-values below 0.05 were regarded as significant.

Results

CD56 expression was membranous +/- cytoplasmic staining. In normal thyroid tissue, CD56 showed positive membranous and/ or cytoplasmic expression. In our study, 34/70 cases (48.6%) revealed negative CD56 expression, whereas 36/70 (51.4%) revealed positive expression. On studying the association between CD56 immunohistochemical expression and clinicopathological variables in various thyroid lesions, a statistically significant relation was detected between CD56 expression and the histologic type in the studied cases where (86.7%) of PTC **(Figure 1)** and (70%) of FC **(Figure 3)** cases and 5% of FA **(Figure 6)** displayed negative expression, while 13.3% of PTC **(Figure** 2**)**, 30% of FC **(Figure 4)**, 95% of FA **(Figure 5)** and 100% of nodular hyperplasia **(Figure 7)** cases demonstrated positive expression (*P*-value <0.001). Moreover, a statistically significant difference was found between CD56 expression in benign and malignant lesions where (96.7%) of benign lesions showed positive expression while (82.5%) of malignant lesions exhibited negative expression (*p*-value <0.001). No significant relation was detected between CD56 expression and patient's age, sex, size and site of lesion, background, and type of operation (*p-value*= .099, .913, .140, .051, .152, and .282 respectively) **(Table 2)**.

Regarding CD56 expression and its relation with histopathological variables in malignant cases (PTC and FC), 33/40 cases (82.5%) showed negative CD56 expression, whereas 7/40 (17.5%) revealed positive expression. A statistically significant relation was found between CD56 expression and LN metastasis where most of cases (95.7%) with positive LN metastasis showed negative CD56 expression while (64.7%) of cases with negative nodal metastasis showed positive expression (*p*-value <0.011). No significant association could be found with other studied histopathological variables including laterality, focality, LVI, capsular infiltration, ETE, pT stage and tumor necrosis (*p-value*= 0.180, 0.567, 0.928, 0.807, 0.497, 0.676 and 0.928 respectively) **(Table 2)**.

Concerning CD56 expression and its relation with clinicopathological variables in PTC cases, 26/30 cases (86.7%) showed negative CD56 expression, whereas 4/30 (13.3%) exhibited positive expression. A statistically significant association was detected between CD56 expression and site of the lesion where 93.8% of lesions located in right lobe, 57.1% of lesions located in left lobe, and 100% of lesions located in both lobes showed negative CD56 expression (*p*-value <0.029). A statistically significant relation was detected also between CD56 expression and LN metastasis where most of cases (95.7%) with positive lymph node

metastasis showed negative CD56 expression while (42.9%) of cases with negative nodal metastasis showed positive expression (*p*-value <0.009). No significant association could be found between CD56 expression and other studied variables among cases of PTC (Table 3).

CD56 showed a sensitivity of 95%, specificity of 90%, positive predictive value (PPV) of 92.7%, negative predictive value (NPV) of 93.1%, and diagnostic accuracy of 92.9% (Table 4).

Table (2): Association between CD56 expression and Clinicopathological features for all studied patients (N=70)

Variables		CD56 Expression		*P*-value
		Negative Expression N=34 (48.6%)	Positive Expression N=36 (51.4%)	
Age groups	**< 55**	25 (43.9%)	32 (56.1%)	0.099
	≥ 55	9 (69.2%)	4 (30.8%)	
Sex	**Male**	6 (50%)	6 (50%)	0.913
	Female	28 (48.3%)	30 (51.7%)	
Size of Lesion (cm)	**Median**	2	3	0.140
	IQR	(1.5-4.1)	(2-4)	
Site of lesion	**Right lobe**	19 (65.5%)	10 (34.5%)	0.051
	Left lobe	8 (33.3%)	16 (66.7%)	
	Both lobes	7 (41.2%)	10 (58.8%)	
Background	**No pathological abnormality**	20 (42.6%)	27 (57.4%)	0.152
	Nodular hyperplasia	7 (50%)	7 (50%)	
	Lymphocytic thyroiditis	7 (77.8%)	2 (22.2%)	
Type of operation	**Total thyroidectomy**	29 (51.8%)	27 (48.2%)	0.282
	Hemi thyroidectomy	5 (35.7%)	9 (64.3%)	
Histologic subtype	**Papillary thyroid carcinoma**	26 (86.7%)	4 (13.3%)	**<0.001***
	Follicular carcinoma	7 (70%)	3 (30%)	
	Follicular adenoma	1 (5%)	19 (95%)	
	Nodular hyperplasia	0 (0%)	10 (100%)	
Benign Vs Malignant lesions	**Benign**	1 (3.3%)	29 (96.7%)	**<0.001***
	Malignant	33 (82.5%)	7 (17.5%)	

In malignant cases (PTC and FC) (N=40)				
Laterality	**Unilateral**	26 (78.8%)	7 (21.2%)	0.180
	Bilateral	7 (100%)	0 (0%)	
Focality	**Unifocal**	25 (80.6%)	6 (19.4%)	0.567
	Multifocal	8 (88.9%)	1 (11.1%)	
Lymphovascular invasion	**Negative**	23 (82.1%)	5 (17.9%)	0.928
	Positive	10 (83.3%)	2 (16.7%)	
Capsular infiltration	**Negative**	11 (84.6%)	2 (15.4%)	0.807
	Positive	22 (81.5%)	5 (18.5%)	
Extrathyroidal extension	**Negative**	19 (79.2%)	5 (20.8%)	*0.497*
	Positive	14 (87.5%)	2 (12.5%)	
Lymph node metastasis	**Negative**	11 (64.7%)	6 (35.3%)	**0.011***
	Positive	22 (95.7%)	1 (4.3%)	
Pathological tumor stage	**pT1**	15 (88.2%)	2 (11.8%)	0.676
	pT2	7 (77.8%)	2 (22.2%)	
	pT3	11 (78.6%)	3 (21.4%)	
Tumor necrosis	**Absent**	23 (82.1%)	5 (17.9%)	0.928
	Present	10 (83.3%)	2 (16.7%)	

**** P - value <0.05 are considered statistically significant according to Chi-Square test and Fisher's exact test.***

Table (3): Association between CD56 expression and Clinicopathological features for patients with papillary thyroid carcinoma (N=30)

Variables		CD56 Expression		*P*-value
		Negative Expression N=26 (86.7%)	Positive Expression N=4 (13.3%)	
Age groups (years)	< 55	22 (88%)	3 (12%)	0.631
	≥ 55	4 (80%)	1 (20%)	
Sex	Male	4 (100%)	0 (0%)	0.399
	Female	22 (84.6%)	4 (15.4%)	
Size of Lesion (cm)	≤1	6 (85.7%)	1 (14.3%)	0.933
	>1	20 (87%)	3 (13%)	
Site of lesion	Right lobe	15 (93.8%)	1 (6.2%)	***0.029****
	Left lobe	4 (57.1%)	3 (42.9%)	
	Both lobes	7 (100%)	0 (0%)	
Background	No pathological abnormality	13 (92.9%)	1 (7.1%)	0.150
	Nodular hyperplasia	7 (70%)	3 (30%)	
	Lymphocytic thyroiditis	6 (100%)	0 (0%)	
Type of operation	Total thyroidectomy	22 (84.6%)	4 (15.4%)	0.399
	Hemi thyroidectomy	4 (100%)	0 (0%)	
Laterality	Unilateral	19 (82.6%)	4 (17.4%)	0.236
	Bilateral	7 (100%)	0 (0%)	
Focality	Unifocal	19 (86.4%)	3 (13.6%)	0.935
	Multifocal	7 (87.5%)	1 (12.5%)	
Lymphovascular invasion	Negative	20 (87%)	3 (13%)	0.933
	Positive	6 (85.7%)	1 (14.3%)	
Capsular infiltration	Negative	11 (84.6%)	2 (15.4%)	0.773
	Positive	15 (88.2%)	2 (11.8%)	
Extrathyroidal extension	Negative	17 (85%)	3 (15%)	*0.704*
	Positive	9 (90%)	1 (10%)	
Lymph node metastasis	Negative	4 (57.1%)	3 (42.9%)	***0.009****
	Positive	22 (95.7%)	1 (4.3%)	
Pathological tumor stage	pT1	15 (88.2%)	2 (11.8%)	0.417
	pT2	5 (100%)	0 (0%)	
	pT3	6 (75%)	2 (25%)	
Tumor necrosis	Absent	20 (87%)	3 (13%)	0.933
	Present	6 (85.7%)	1 (14.3%)	

**** P - value <0.05 are considered statistically significant according to Chi-Square test and Fisher's exact test.***

Table (4): The diagnostic characteristics of CD56 immunohistochemistry for differentiating benign from malignant thyroid lesions

Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
95%	90%	92.7%	93.1%	92.9%

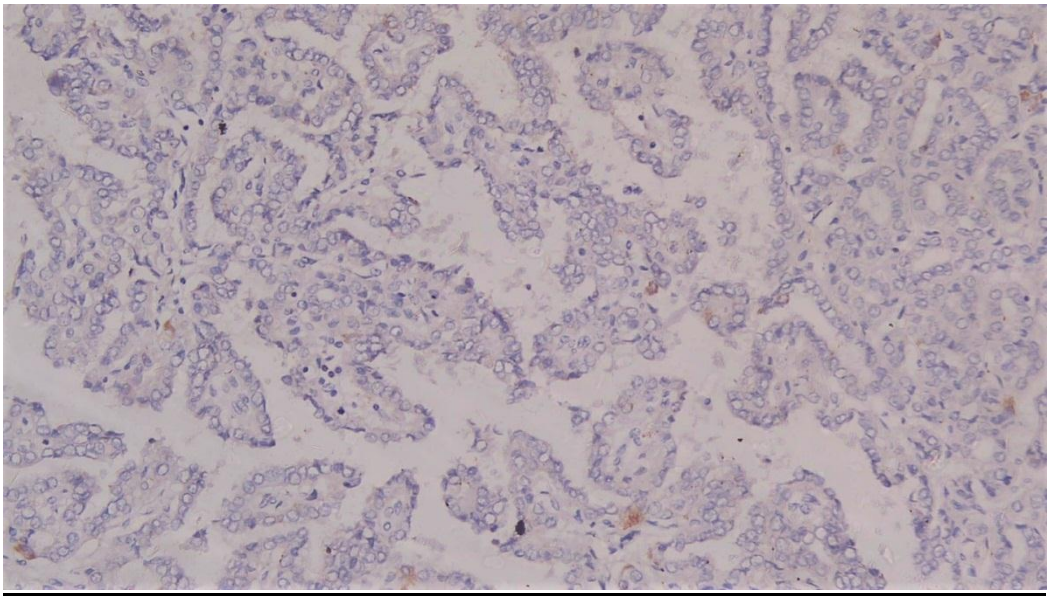

Figure 1: Negative CD56 expression in papillary thyroid carcinoma (IHC, 200X)

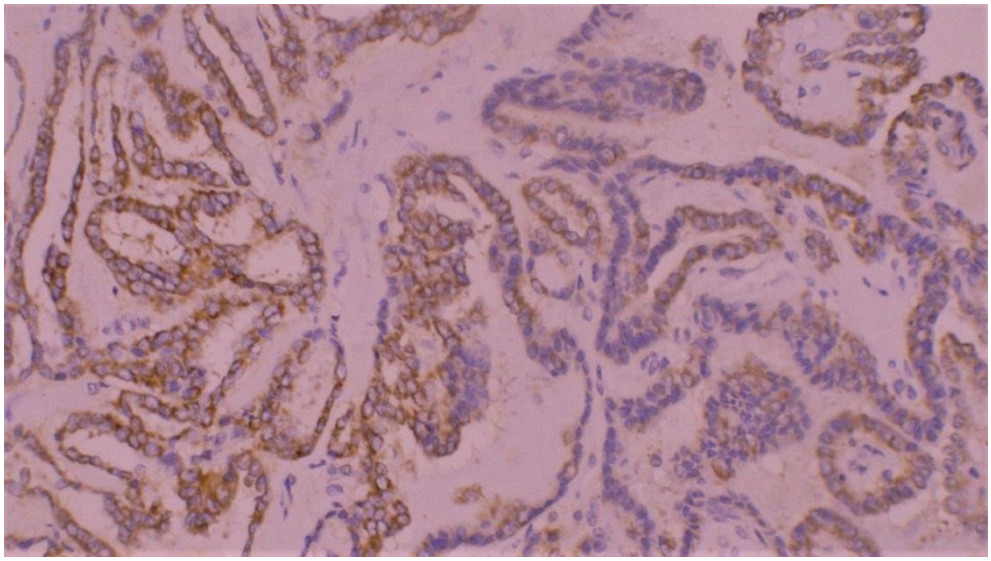

Figure 2: Positive CD56 expression in PTC (IHC, 200X)

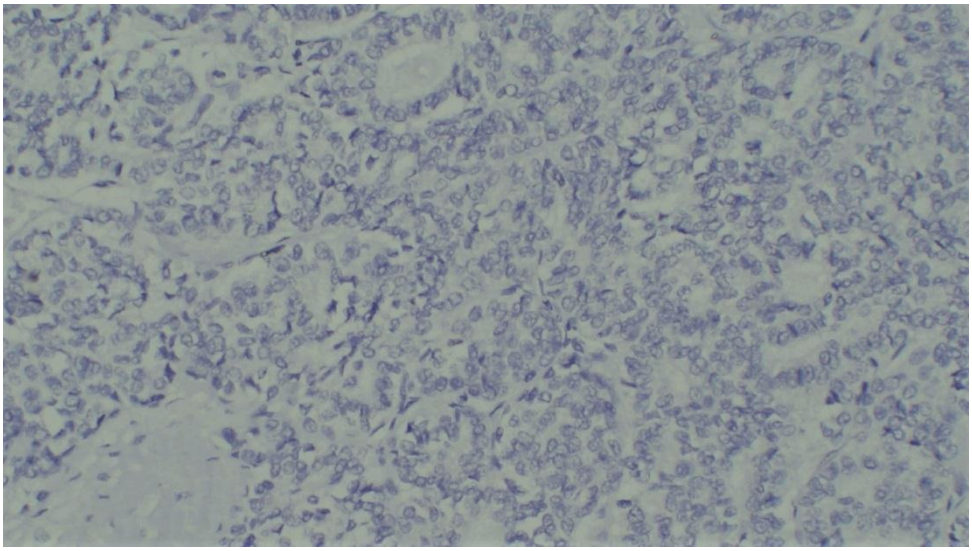

Figure 3: Negative CD56 expression in follicular carcinoma (IHC, 200X)

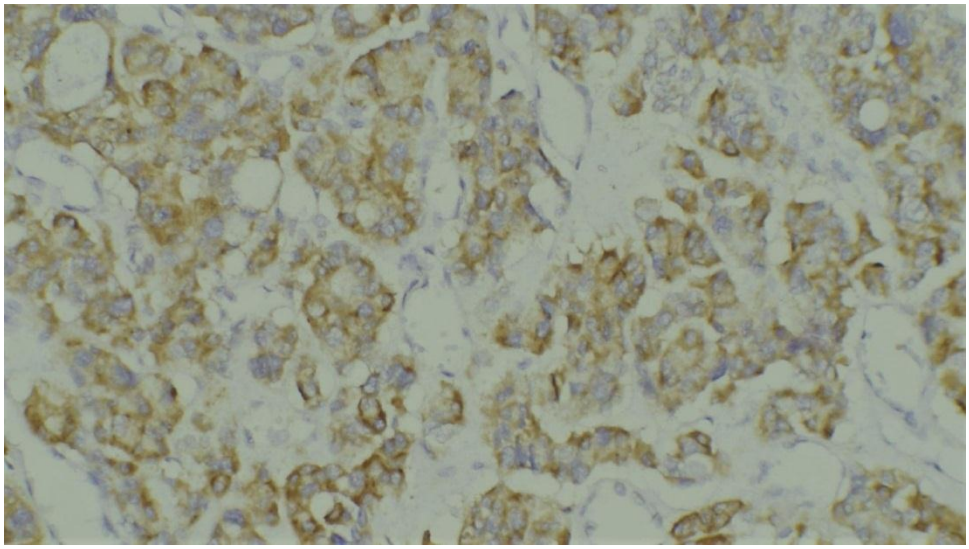

Figure 4: Positive CD56 expression in follicular carcinoma (IHC, 200X)

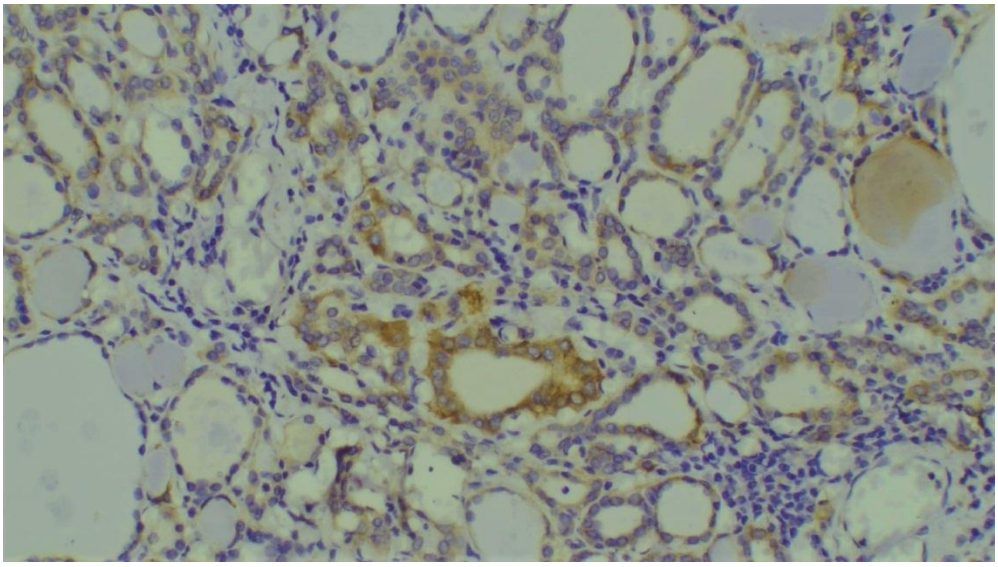

Figure 5: Positive CD56 expression in follicular adenoma (IHC, 200X)

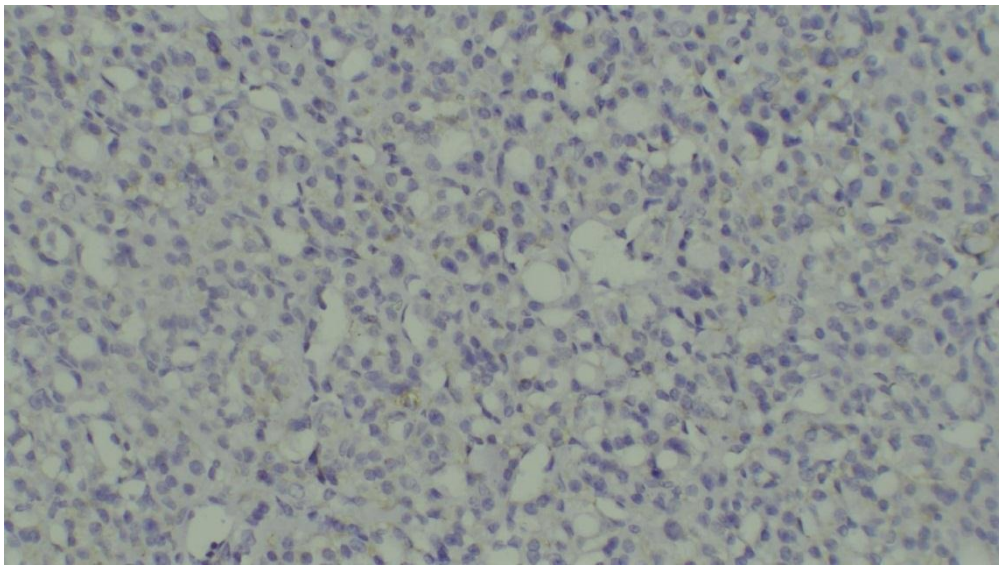

Figure 6: Negative CD56 expression in follicular adenoma (IHC, 200X)

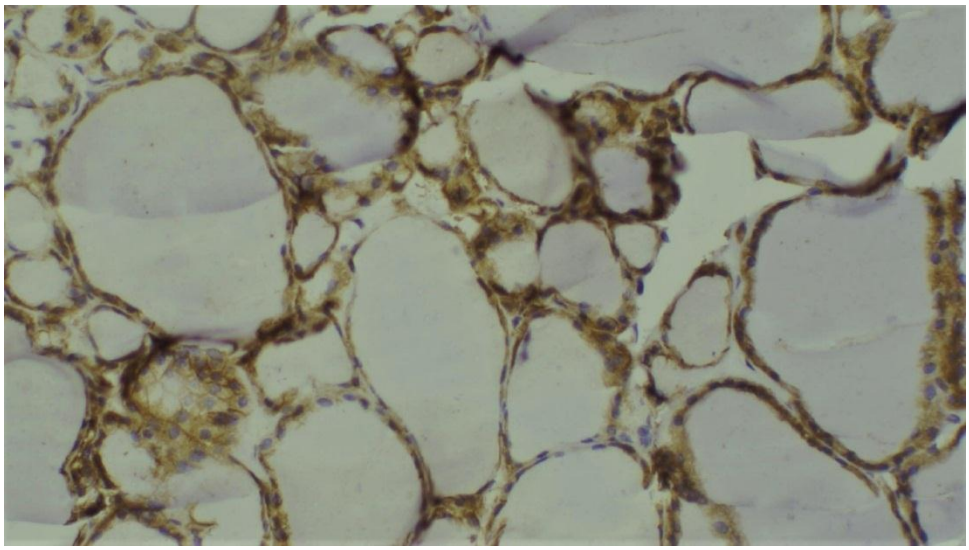

Figure 7: Positive CD56 expression in nodular hyperplasia (IHC, 200X)

Discussion

In our current study, we analyzed the diagnostic utility of CD56 in differentiating benign from malignant thyroid lesions. Regarding CD56 expression, it was expressed in the cell membrane +/- cytoplasmic staining. Normal thyroid tissue showed positive membranous and/ or cytoplasmic expression. Regarding CD56 expression in different thyroid lesions, 48.6% of cases showed negative CD56 expression while 51.4% of cases showed positive expression. This was similar to what was reported by Mahmoud et al., 2022, who reported CD56 positivity in 52% of cases [(2)].

On studying the association between CD56 immunohistochemical expression and different clinicopathological variables among various thyroid lesions, we detected a statistically significant relation between CD56 expression and the histologic type in the studied cases where the majority of PTC cases and FC cases showed negative expression, while majority of cases of follicular adenoma and nodular hyperplasia showed positive expression (P-value <0.001). This was in agreement with Muthusamy et al., 2018 who reported negative CD56 expression in 90.3% in PTC and 9.1% of FC while all cases of follicular adenoma and

nodular hyperplasia showed positive expression except one case in each type displayed negative expression (p-value = 0.01) [13]. Mahmoud et al., 2022 also found negative CD56 expression in 91.3% in PTC and 14.3% of FC while 90% of FA and all cases of nodular hyperplasia showed positive expression (p-value =0.000) [2].

Variations in the percentages could result from variations in the number of studied cases. Furthermore, in the comparison between. CD56 expression in benign and malignant lesions, we found that 96.7% of benign lesions showed positive expression while 82.5% of malignant lesions demonstrated negative expression and the difference was statistically significant (p-value <0.001). This goes in line with Cha et al., 2018, Shameem et al., 2020 and Mahmoud et al., 2022 who also reported significant difference with similar percentages [19,14,2]. A statistically significant association was found between CD56 expression and lymph node metastasis where most of cases with positive lymph node metastasis showed negative CD56 expression (p-value <0.011). This coincides with what was reported by Mahmoud et al., 2022 who also reported a significant difference (p-value =0.024) [2]. The possible explanation for this finding is that changes in CD56 expression may impact the migratory potential of tumor cells and trigger β1-integrin-mediated cell-matrix adhesion by activation of fibroblast growth factor receptor signaling; so, decreased expression of CD56 can raise the possibility of metastasis via stimulation of lymphangiogenesis [20].

Moreover, Scarpino et al., 2007 found that modifications of CD56 immunohistochemical expression can lead to down regulation of vascular endothelial growth factor C (VEGF-C) and VEGF-D factors that stimulate lymphangiogenesis in PTC [21].

On the contrary, Muthusamy et al., 2018 documented an insignificant difference (p-value =0.076), which may result from using antibodies of different nature [13]. Regarding CD56 expression and its relation with clinicopathological features in cases of PTC, a statistically significant relation was found between CD56 expression and site of the lesion where 93.8% of lesions located in right lobe showed negative CD56 expression (p-value <0.029). Also, when we compare CD56 expression and lymph node metastasis in PTC cases, we found a significant difference where most of cases with positive lymph node metastasis showed negative CD56 expression (p-value <0.009). This is the first study that evaluated the relation between CD56 expression and site of the lesion and lymph node metastasis among PTC cases Up to our knowledge as other studies evaluated differences in CD56 expression among different benign and malignant thyroid lesions as mentioned above. No significant relation could be found between CD56 expression and other studied clinic-pathological variables among PTC cases.

The diagnostic characteristics of CD56 for differentiating benign (FA and NH) from malignant thyroid lesions (PTC and FC) were a sensitivity of 95%, specificity of 90%, positive predictive value (PPV) of 92.7%, negative predictive value (NPV) of 93.1%, and diagnostic accuracy of 92.9%. This was similar to what was reported by Mokhtari et el., 2013 who reported sensitivity of 98.6%, specificity of 95.8% [20], and by Shameem et al., 2020 who reported sensitivity of 94.6%, specificity of 97.3%[14]. On the other hand, one study has demonstrated 100% sensitivity and specificity for CD56 [22].

In conclusion, these results indicate that decreased CD56 immunohistochemical expression was much higher in malignant tumors, such as follicular carcinoma and papillary thyroid carcinoma, than in nodular hyperplasia and follicular adenoma. Therefore, CD56 immunohistochemistry can be a helpful marker in discriminating benign from malignant thyroid lesions.

Ethical consideration

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Approvals were obtained from the Ethics Committee of Faculty of Medicine, Minia University (Approval No. 404/04/2021).

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Conflicting Interests: The authors declare that there is no conflict of interest.

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