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Application of CK 19 and CD 56 Immunohistochemical Markers in the Diagnosis of Thyroid Tumors

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Abstract
Objectives: *Immunohistochemical expression of CK19 and CD56 was studied in the differential diagnosis of thyroid tumors as Papillary Carcinoma is the most common thyroid cancer which needs to be differentiated from other Benign follicular lesions and to identify Follicular Variant of Papillary Carcinoma. The aim of this study is to evaluate the immunohistochemical expression of CK19 and CD56 and its correlation with histopathological profile of thyroid tumors.*
Methods: *The study was carried out at SGT Medical College and Hospital, Gurugram which included 24 cases of thyroidectomy specimens (including Follicular Adenoma, Hurthle Cell Adenoma, Papillary Carcinoma) over a time period of two years. Cases of Follicular Carcinoma and Hurthle Cell Carcinoma were also included. Hematoxylin and Eosin staining and immunohistochemical staining for CK19 and CD 56 were done as per standard protocol.*
Results: *The positive expression of CK19 in patients with Papillary Carcinoma was significantly higher than other thyroid lesions. CD56 expression was seen in 41% of benign neoplasms and in 8.4% of malignant neoplasms, out of all Neoplastic lesions. The sensitivity and specificity of CK19 and CD 56 found out to be statistically significant.*
Conclusion: *Expression of CK19 and CD56 is helpful in differentiating Papillary Carcinoma from other thyroid tumors.*
Keywords: *Benign thyroid lesions, CD56, CK19, Papillary carcinoma, Thyroid tumors*.

Introduction

Thyroid cancer accounts for > 90% of all the endocrine cancer and 63% of all the death due to the endocrine cancer death. Thyroid neoplasm present as thyroid nodules of which 90% thyroid nodules are benign.[1] Thyroid cancer is the seventh most common malignancy and Papillary Carcinoma (PC) is the most common cancer of thyroid.[2]

The diagnosis of PC is based on nuclear morphology of a thyroid neoplasm, described as grooved nucleus with conventional Hematoxylin and Eosin (H & E) stain. Morphologic similarities between benign and malignant lesions are frequent; papillary and follicular architectures and nuclear irregularity may be seen both in benign and malignant lesions.[3]

There are no consistent marker(s), that distinguish between PC, other Follicular Thyroid Lesions and tumors, although ancillary studies such as immunohistochemistry may be helpful.[4]

Cytokeratin polypeptide 19 (CK19) is a type I intermediate filament protein.[4] CK 19 expression in thyroid nodules is, in general, intense and diffuse cytoplasmic staining in PC and heterogeneous in FC and in FA, with nil or low expression in other benign lesions.[5] Upregulation of CK19 is connected with neoplastic transformation.[6]

CD56 is a neural cell adhesion molecule (NCAM).[4] CD56 expression is markedly reduced by malignant transformation as previously reported in cases of FC, Anaplastic Carcinoma, and PC.[7] CD56 expression consistently shows strong diffuse membranous expression in hyperplasia, thyroiditis, adenomas and non Papillary Carcinomas.[4]

The aim of this study is to evaluate the immunohistochemical expression of CK 19 and CD 56 and their correlation with histopathological profile of Neoplastic Thyroid lesions.

Material and Methods

The study was based upon retrospective and prospective thyroidectomy specimens received in the Department of Pathology, SGT Medical College and Hospital, Gurugram (Haryana). Study included cases operated during 2 years duration from 2014-2016.

A total of 24 cases of Neoplastic Thyroid Lesions were studied. Neoplastic lesions were further subdivided into Benign group (Follicular and Hurthle Cell Adenoma) and Malignant group (Papillary, Follicular and Hurthle Cell Carcinoma).

All thyroidectomy specimens were routinely processed and the histopathological diagnosis was made and representative sections from each case were stained with with CK19 and CD56 antibodies.

Immunohistochemical analysis and interpretation

Immunohistochemical staining was performed using the peroxidase-antiperoxidase method [DAKO Envision]. Four µm-thick sections were prepared on adhesive slides coated with poly-L-lysine. After the sections had been deparaffinized and rehydrated in descending alcohol dilutions, antigen retrieval was performed in a microwave oven in citrate buffer pH 9.0. After cooling to room temperature, the sections were treated with blocking peroxidase for 5 min. Next step was incubation with primary antibody (Mouse Monoclonal Antibody to Cytokeratin 19 and CD 56). Thereafter, the sections were incubated with DAKO Envision/HRP for 30 min. Diaminobenzidine was used as a chromogen, and the sections were counterstained with Hematoxylin. After drying, the sections were sealed and covered with glass coverslips. Positive control was run with each batch of IHC staining.

The following pattern was considered positive: cytoplasmic staining of CK19. The extent of positively stained cells was estimated and classified on a five-point scale as follows: Grade 0 - Staining in < 10% of the cells; 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; Grade 4 - Staining in > 75% of the cells. Positive staining intensity was categorized into three groups: 1 - Weak; 2 - Moderate; 3 - Strong. A final IHS value was obtained by multiplying the score for the extent of positively stained cells and the score for staining intensity as follows:- 0-1 - Negative expression(-); 2-3 - Weakly positive expression(+); 4-8 - Moderately positive expression(++); 9-12 - Strongly positive expression(+++).

Expression of CD56 was evaluated based on the membranous staining. The percentage of positive stained cells was estimated semiquantitatively as follows:- Grade 0 - Staining in <10% of the cells; Grade 1 - Staining in 10–25% of the cells; Grade 2 - Staining in 26–50% of the cells; Grade 3 - Staining in >50% of the cells. The positive staining intensity was scored semiquantitatively into three groups (0-3 scale). Hence, a final IHS value was obtained by multiplying the score for the extent and the score for intensity.

Statistical analysis

Descriptive statistics was analyzed with SPSS version 17.0 software. The Pearson's chi-square test or the chi-square test of association was used to determine if there is a relationship between two categorical variables. The sensitivity, specificity, PPV and NPV was calculated to analyze the diagnostic accuracy of various variables correlating with malignancy. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

Observations and Results

In our case series, age of the patient ranged from 22-62 years.

The highest incidence of neoplastic lesions was seen in age group of 31-40 years (49.9%). Out of 24 cases, maximum number of 20 cases (83.2%) were reported in females with a male: female ratio of 1:5. Benign tumors were frequent in 31-40 years of age whereas malignant tumors were seen in all age groups equally.(Table 1)

Table 1: Correlation of Age, Sex and Histopathological diagnosis in Neoplastic thyroid lesions

Age Groups	Benign		Malignant	
	Male	Female	Male	Female
21-30 yrs	1 (4.2)	5 (20.7)	1 (4.2)	1 (4.2)
31-40 yrs	1 (4.2)	9 (37.5)	0	2 (8.2)
41-50 yrs	0	0	1 (4.2)	1 (4.2)
>50 yrs	0	1 (4.2)	0	1 (4.2)
Total	2 (8.4)	15 (62.4)	2 (8.4)	5 (20.8)

Follicular Adenoma (63%) was the most common lesion in Benign group and Papillary Carcinoma (21%) in Malignant group. (Table 2)

Table 2: Distribution of cases according to various histological diagnosis

Lesions	Frequency	Percentage
Neoplastic lesions (n=24)		
Benign neoplasm (n=17, 71%)		
Follicular Adenoma	15	63
Hurthle Cell Adenoma	2	8
Malignant neoplasm (n=7, 29%)		
Papillary Carcinoma	5	21
Follicular Carcinoma	1	4
Hurthle Cell Carcinoma	1	4
TOTAL	24	

Strong positive expression of CK 19 was seen in Papillary Carcinoma (5/5 cases). The result was statistically insignificant (p value of 0.662 > 0.05) among Benign lesions and was significant (p value of 0.007 < 0.05) among Malignant lesions. (Table3)

Table 3: Expression of CK 19 in Neoplastic lesions

	CK 19				p value
	-	+	++	+++	
Benign lesions					
Follicular Adenoma	8 (33.4)	3 (12.5)	4 (16.6)	0	0.662
Hurthle Cell Adenoma	2 (8.3)	0	0	0	
Malignant lesions					
Papillary Carcinoma	0	0	0	5 (20.8)	**0.007**
Follicular Carcinoma	0	1 (4.2)	0	0	
Hurthle Cell Carcinoma	1(4.2)	0	0	0	

Moderate expression of CD 56 was seen in 8 cases and strong expression in 3 cases of Neoplastic lesions. Papillary Carcinomas were negative for CD 56. The result was statistically insignificant (p value of 0.356 > 0.05) among Benign lesions but was significant (p value of 0.030 < 0.05) among Malignant lesions. (Table 4)

Table 4 : Expression of CD 56 in Neoplastic lesions

	CD 56				p value
	-	+	++	+++	
Benign lesions					
Follicular Adenoma	5 (20.8)	1 (4.2)	6 (25)	3 (12.5)	0.356
Hurthle Cell Adenoma	2 (8.3)	0	0	0	
Malignant lesions					
Papillary Carcinoma	5 (20.8)	0	0	0	**0.030**
Follicular Carcinoma	0	0	1 (4.2)	0	
Hurthle Cell Carcinoma	0	0	1 (4.2)	0	

Sensitivity and specificity of CK 19 for diagnosis of malignant lesions was 71.4 and 100%, respectively. (Table 5)

Table 5 : Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CK 19

	Sensitivity	Specificity	PPV	NPV	Accuracy
CK19	71.40%	100.00%	100.00%	94.70%	97.60%

Sensitivity and specificity of CD 56 for diagnosis of malignant lesions was 71.4 and 80.6%, respectively. (Table 6)

Table 6: Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CD 56

	Sensitivity	Specificity	PPV	NPV	Accuracy
CD 56	71.40%	80.60%	41.70%	93.50%	81.00%

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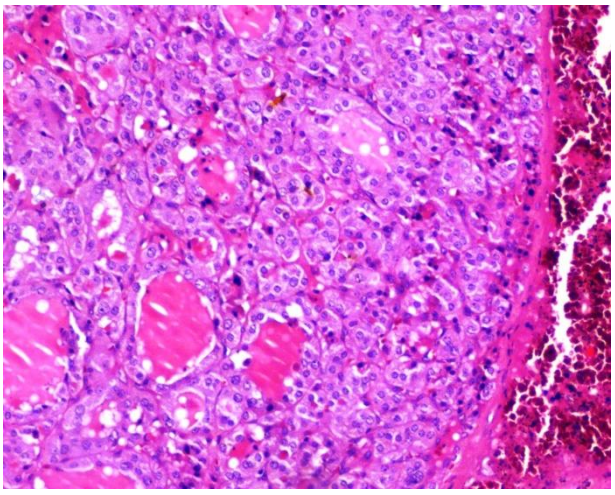

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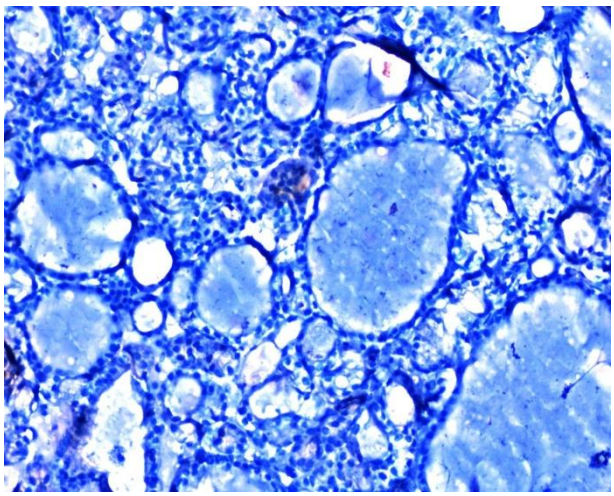


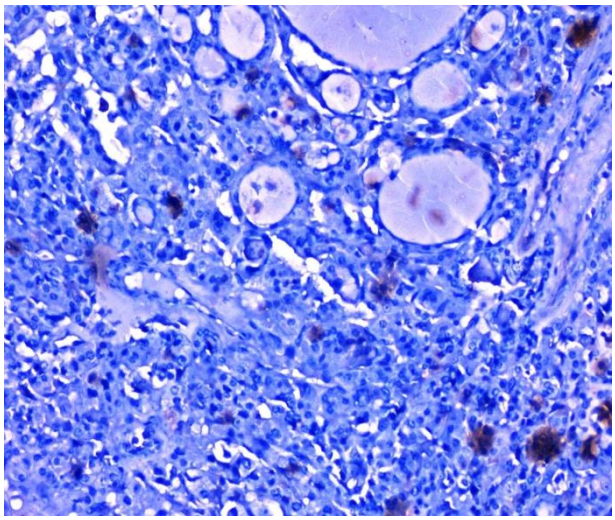
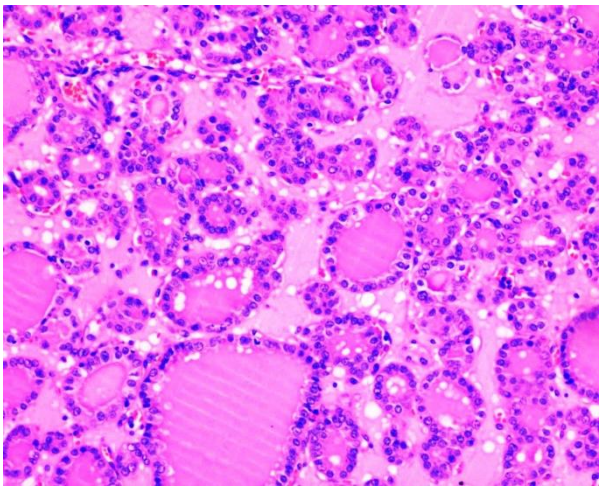
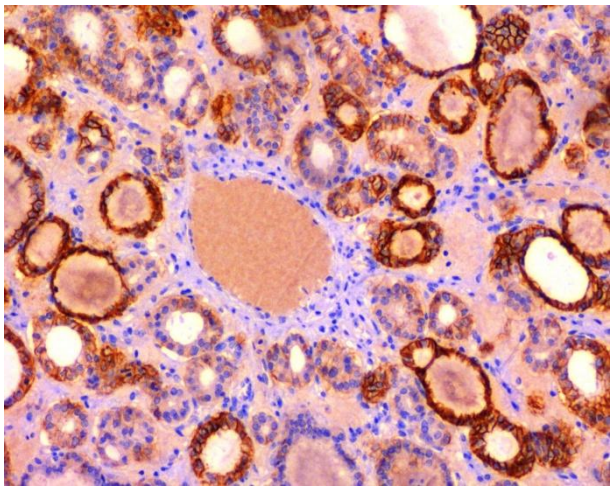
C 

Figure 1 : (A) Case of Hurthle Cell Adenoma (H & E, 100x), **(B)** CD 56 showing negative expression in Hurthle Cell Adenoma (IHC, 100x), **(C)** CK 19 showing negative expression in Hurthle Cell Adenoma (IHC, 100x)

A 

B 

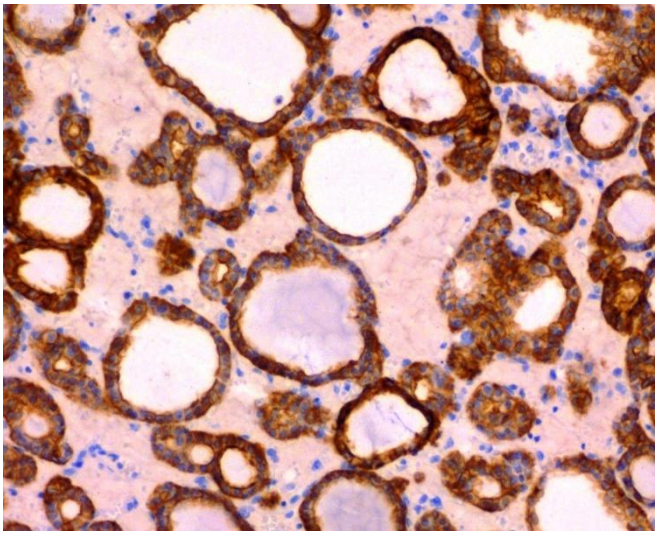
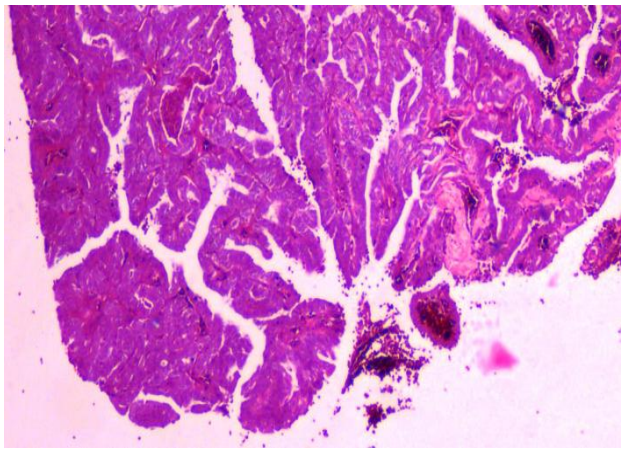
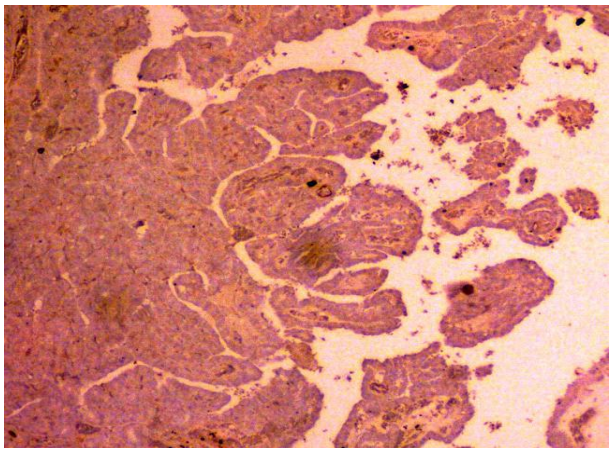
C 

Figure 2 : (A) Case of Follicular Adenoma (H & E, 100x), **(B)** CD 56 showing focal and moderate positive expression in Follicular Adenoma (IHC, 100x), **(C)** CK 19 showing focal and moderate positive expression in Follicular Adenoma (IHC, 100x)

A  B 

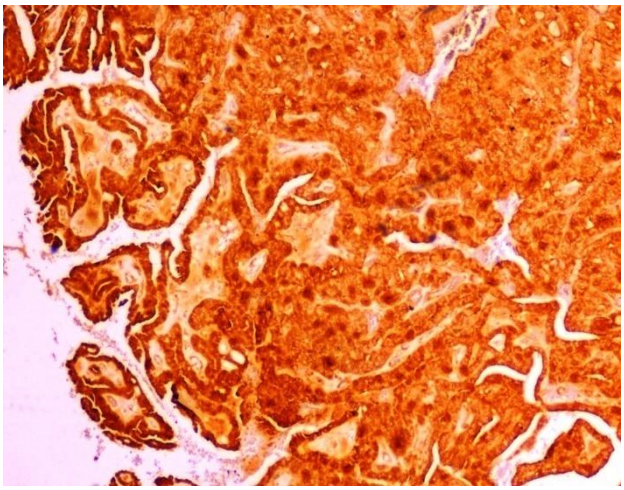
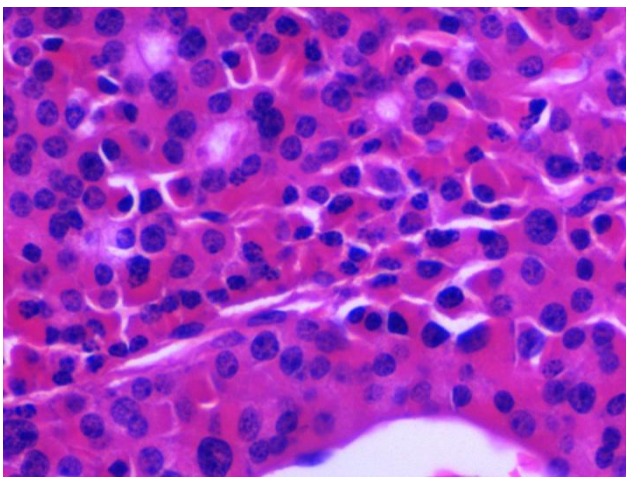
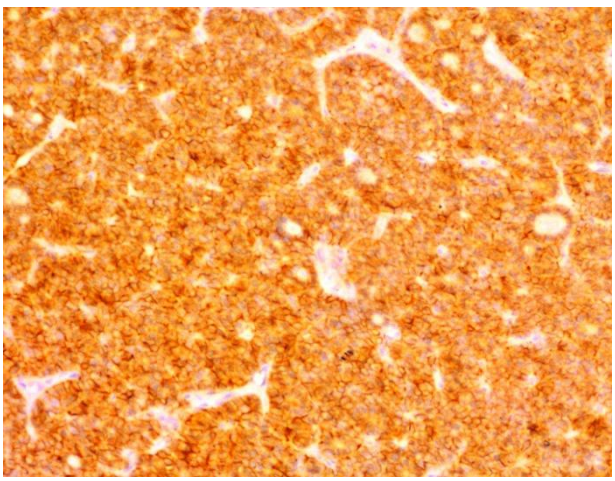
C 

Figure 3 : (A) Case of Classical Papillary Carcinoma (H & E, 40x), **(B)** CD 56 showing negative expression in Classical Papillary Carcinoma (IHC, 40x), **(C)** CK 19 showing diffuse and strong positive expression in Classical Papillary Carcinoma (IHC, 40x)

A  B 

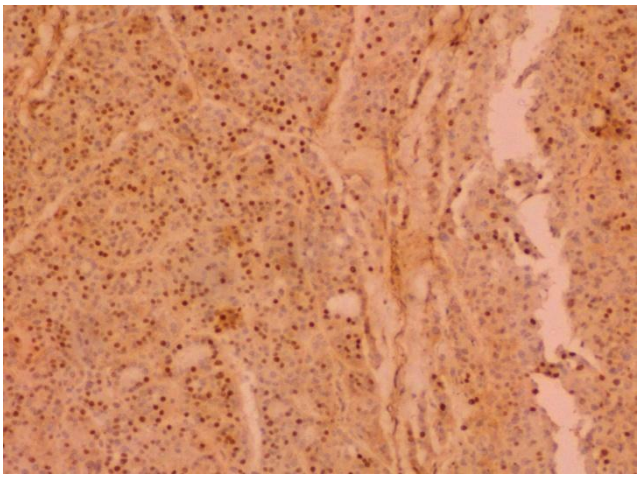
C 

Figure 4: (A) Case of Hurthle Cell Carcinoma (H & E, 400x), **(B)** CD 56 showing diffuse and moderate positive expression in Hurthle Cell Carcinoma (IHC, 100x), **(C)** CK 19 showing negative expression (as it is showing nuclear staining instead of cytoplasmic staining) in Hurthle Cell Carcinoma (IHC, 100x)

Discussion

Thyroid nodules are common lesions in clinical practice, but only a minority are malignant or suspicious for Malignancy that require surgery.[8] Currently, the gold standard for the diagnosis of thyroid lesions, particularly PC, is histology. Using morphological criteria, most papillary cancers can be diagnosed with ease, except cases in which there is a paucity of diagnostic nuclear features. Some ancillary approaches (such as immunohistochemistry and molecular techniques) have been explored.[9]

In our study, the highest frequency of cases (49.9%) was seen in 31-40 years of age group. These findings are in concordance with the studies done by Ramesh et al,[10] Wani et al[11] and Kolur et al.[12] Wani et al and Ramesh et al analyzed that the relative peak incidence was seen in 30-39 years age group.[11,12] Kolur et al also observed that the maximum number of cases seen in 31-40 years.[12] Incidence in early age group is high as the Sub-Himalayan belt is one of the most endemic areas for iodine deficiency diseases.

In this study, female preponderance (83.2%) was observed with male : female ratio of 1:5. This was in agreement with studies of Kolur et al,[12] Wani et al[11] and Rahman et al,[13] although the variable male : female ratio of 1:7.6 and 1:8.4 was reported by Ramesh et al[10] and Joseph et al[14] respectively. It is due to the fact that females are more prone to the thyroid disorders.

In the present study, Follicular Adenoma (35%) was the most common with female preponderance in the age group of 31-40 years followed by Papillary Carcinoma (12%). In malignant group, 21-50 years age group showed equal number of cases with less number in age > 50 years. This study is in agreement with the study of Rahman et al,[13] Gupta et al[15] and Patil et al.[16] They observed that Follicular Adenoma was the most common lesion followed by Papillary Carcinoma with the female preponderance.

Studies have demonstrated that CK 19 expression is strongly and diffusely expressed in Papillary Carcinoma, whereas it is usually absent or focally expressed in Follicular Carcinoma and Benign Hyperplastic Nodules.[17-21] In our study, 29.1% cases of Follicular Adenoma revealed positive expression and weak intensity in most of the cases (+ in 3 cases and 2+ in 4 cases) and 4.2% cases of Follicular Carcinoma showed weakly positive expression. This is in concordance with the result of Sahoo et al[22] and Saleh et al.[23] Sahoo et al reported that 25% of their Follicular Adenomas had extensive immunoreactivity for CK19 (2+ in 1, 3+ in 4 of 20 Follicular Adenomas).[22] Saleh et al observed that 85.1% of all the malignant tumors were positive for CK19 (diffusely and strongly), 50% of the Adenomas were also positive (but

more focal and less intense) and positivity of CK19 in Adenomas was more focal and weak than in Carcinomas.[23] In the present study, CK 19 expression showed positivity in 54.1% cases All cases of Papillary Carcinoma showed diffuse and strong positive expression. The result was statistically significant in malignant lesions (p=0.007). It was shown that CK 19 had high specificity (100%), sensitivity (71.4%) and positive predictive value (100%) for diagnosing Papillary Carcinoma. This result is in agreement with most of the studies done by Demellawy et al,[4] Zhu et al[24] and Krzeslak et al[25] which showed that CK 19 was strong and diffuse in Papillary Carcinoma cases and that there was either none or only weak immunostaining in Benign lesions. In the present study it was observed that diffuse and strong expression of CK19 is characteristic of Papillary Carcinoma. Although weak CK19 staining is common in Benign lesions. A negative stain is a good evidence against Papillary Carcinoma.

CD56 has been reported to be an antigen related to the differentiation of the follicular epithelium.[26] Many previous studies reported high CD56 expression in normal thyroid tissue and benign thyroid follicular lesions as Follicular Adenomas and Nodular Hyperplasias.[4,7,27,28] In our study, moderate to strong staining intensity was seen in 41% cases of Benign lesions and negative expression in 29% cases. All cases of Papillary Carcinoma showed negative expression. Cases of Follicular and Hurthle Cell Carcinoma showed moderate positive expression. Statistically significant result was seen in Malignant lesions (p=0.030). CD 56 has shown low positive predictive value (41.7%), sensitivity (71.4%) and specificity (80.6%) for diagnosing Malignant lesions. The present study is in agreement with studies of Atti et al[26] and Shahebrahimi et al.[29] Atti et al reported a high positive CD56 expression in normal thyroid tissue compared to PC cases. They also observed strong and diffuse positive CD56 expression in 89.4% of the solitary follicular patterned thyroid nodules. Negative CD56 expression in 82.8% of all Papillary Carcinoma cases.[26] Shahebrahimi et al observed that CD56 was expressed in 93% of all Benign lesions, while it was only found in 5% of Malignant thyroid lesions (PC).[29] Similarly, previous studies by Demellawy et al,[4,28] Park et al,[27] and Shin et al[7] reported that negative CD56 expression in all or most of their studied PC cases and also observed that CD56 expression was more reduced in Papillary Carcinomas in respect to Follicular Carcinomas and Follicular Adenomas. In the present study, it was observed that high positive CD56 expression is seen in Benign lesions. On the other hand, negative CD56 expression was observed in Papillary Carcinoma.

Conclusion

Immunoexpression of CK19 and CD 56 is a supplementary test in the diagnosis of thyroid neoplasms, albeit it does not replace the conventional histomorphological examination. No marker by itself has a superior diagnostic value, a combination of markers may be more accurate than any single marker. Though the study is limited by a small sample size, it is suggested that immunohistochemical panel for diagnosing Papillary Carcinoma should include CK19 as positive markers and CD56 as negative marker in equivocal histological diagnosis.

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