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Role of CK-19, HBME-1 and Galectin-3 in Prediction of Prognosis of Papillary Thyroid Carcinoma – An Experience from a Tertiary Care Centre

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Results: Positive expression of CK19 and GAL-3 were correlated significantly with the total tumor diameter and capsular invasion. Positive expression of HBME-1 was correlated significantly with capsular invasion and lymph nodal metastasis. But none of them was found to be associated with age and sex of the patient.

Conclusion: High expression of CK19, GAL-3 and HBME-1 are found to be associated with high volume of total tumor diameter as well as capsular invasion and lymph nodal metastasis. Thus, these IHC markers could be used to assess the aggressive behavior of PTCs.

Keywords: papillary thyroid carcinoma (PTC), total tumor diameter (TTD), cytokeratin 19, prognostic markers.

I. Introduction

Papillary thyroid carcinoma (PTC) is the most common malignant neoplasm of thyroid follicular epithelium.[1] Its incidence has increased dramatically in past few decades reaching up to 80% of malignant thyroid tumors.[2,3,4] Despite the propensity for lymphovascular invasion, majority of the patients with this tumor, if properly treated, have an excellent long-term prognosis.[5] But appropriate treatment primarily depends on the ability of the pathologist to make an accurate diagnosis. Historically, diagnosis of PTC was based on the presence of the papillary architectures but currently it also includes the presence of nuclear features i.e. nuclear overlapping, optical clearing, macronucleoli, irregular contours with pseudoinclusion and grooving.[6] Identification of these features remains difficult and controversial when they are present focally, thus distinction of PTC from other thyroid lesions i.e. benign papillary hyperplasia, some forms of thyroiditis, variants of PTC may not be possible. In this regard, implication of immunohistochemical (IHC) markers are very useful. In this study, we have used a panel of three IHC markers – Cytokertain 19 (CK-19), Hector Battifora Mesothelial-1 (HBME-1) and Galectin-3 (GAL-3) to show their role as prognostic markers of PTC.

II. Materials and Methods

We have conducted a single institution based, retrospective study at a tertiary care centre of Eastern India. Patients with histologically confirmed papillary thyroid carcinoma treated between January 2017 and June 2018 were identified from the Department of General Surgery. All patients had undergone total thyroidectomy for the primary tumor. A total of 41 patients were reviewed for their clinical and pathological data. We have considered gender, age, total tumor diameter (TTD), capsular invasion and lymphnodal metastasis as the parameters to be studied. We have correlated the expressions of CK 19, GAL-3 and HBME-1 with those parameters to show their role in prognostication of PTC (weak and strong expression both considered as positive expression).

CK19 is a low molecular weight cytokeratin which presents widely in simple epithelia and basal cell layers of stratified epithelium.

HBME-1 is a monoclonal antibody generated against a membrane antigen of mesothelial cells.[7] It

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was originally found in malignant mesothelioma; several investigators showed that HBME-1 play an important role in diagnosis of papillary thyroid carcinoma.

GAL-3 is a member of oligosaccharide selective binding protein family known as lectins which plays an important role in the cell growth, apoptosis, cell-matrix interactions, neoplastic transformation and metastasis; and now it's been considered to be an effective indicator that can be available to distinguish the malignant thyroid nodules from the benign ones.[8]

The aim of present study was to investigate the relationship between the expression of CK19, HBME-1 and GAL-3 and the aggressive behavior of PTCs by correlating immunohistochemical results with the clinical features.

a) Statistical Analysis

The Kruskal–Wallis test was performed for comparisons between multiple groups. The χ^2 test was analysed for categorical evaluation. Correlations were evaluated using Spearman's rank correlation. *p*-value < 0.05 was considered as significant. Statistical software (GRAPHPAD PRISM 5) was used for analysis.

III. Results

In Table 1 we have shown the summary of the clinicopathological traits. Among 41 cases, the female: male ratio was 19.5:1 and 14.63% cases were more than 45 years old. 80.48% cases had total tumour diameter more than 1cm. capsular invasion and lymphovascular invasion were found to be present in 26.82% and 31.70% cases respectively.

In Table 2-4 we have summarized the results showing correlation of the IHC markers with five prognostic factors. All the cases with PTC were divided into positive and negative expression groups.

According to our results in Table 2, positive expression of CK19 was correlated significantly with the total tumor diameter ($p < 0.001$). This finding indicated that the larger volume of the total tumor diameter is more likely to express CK19. Positive expression of CK19 was also correlated significantly with the capsular invasion ($p < 0.007$) which denotes that CK19 positivity stands for more aggressive behavior of PTC. On the other hand, expression of CK19 had no significant relationship with age, sex and lymph nodal metastasis.

In Table 3, we have shown the correlation of expression of Galectin 3 with the prognostic parameters. Similarly expression of GAL-3 was correlated significantly with total tumor diameter ($p < 0.005$) and capsular invasion ($p < 0.007$) in all the PTC cases, whereas its expression was found to be not related to patient's age, sex and lymph nodal metastasis.

In Table 4, correlation between the expression of HBME-1 and the prognostic parameters is shown. Expression of HBME-1 was found to be significantly correlated with capsular invasion ($p < 0.01$) and lymph nodal metastasis ($p < 0.002$).

Table 1: Summary of clinicopathological traits

Parameter	% (No. of cases)
Age (Yr)	
≤ 45	85.36 (35/41)
> 45	14.63 (6/41)
Gender	
F	95.12 (39/41)
M	4.87 (2/41)
Total Tumor Diameter	
≤ 1 cm	19.51 (8/41)
> 1 cm	80.48 (33/41)
Capsular Invasion	
Present	26.82 (11/41)
Absent	73.17 (30/41)
Lymph Node Metastasis	
Present	31.70 (13/41)
Absent	68.30 (28/41)

Table 2: Prediction of some clinicopathological characteristics of PTC based on immunohistochemical expression of CK19

Prognostic Factors		CK 19 (N=41)		P Value
		Positive	Negative	
Mean Age		33.88	34.78	0.76
Sex	Male	2	0	0.53
	Female	25	14	
Diameter	≤ 2 cm	2	12	*<0.001**
	>2 cm	25	2	

Capsular Invasion	Present	11	0	*0.0071**
	Absent	16	14	
Lymph Node Metastasis	Present	9	4	1.00
	Absent	18	10	

Table 3: Prediction of some clinicopathological characteristics of PTC based on immunohistochemical expression of Galectin-1

Prognostic Factors		Galactin-3 (N=41)		P Value
		Positive	Negative	
Mean Age		33.18	36.14	0.33
Sex	Male	2	0	0.53
	Female	25	14	
Diameter	≤ 2 cm	4	10	*0.005*
	>2 cm	23	4	
Capsular Invasion	Present	11	0	*0.0071*
	Absent	16	14	
Lymph Node Metastasis	Present	11	2	0.1559
	Absent	16	12	

Table 4: Prediction of some clinicopathological characteristics of PTC based on immunohistochemical expression of HBME-1

Prognostic Factors		HBME-1(N=41)		P Value
		Positive	Negative	
Mean Age		35.54	32.29	0.26
Sex	Male	0	2	0.16
	Female	24	15	
Diameter	≤ 2 cm	6	8	0.18
	>2 cm	18	9	
Capsular Invasion	Present	10	1	*0.01*
	Absent	14	16	
Lymph Node Metastasis	Present	13	0	*0.002*
	Absent	11	17	

IV. Discussion

Primary thyroid cancers comprise the largest group among malignancies of the endocrine system. 120,000 new cases are added each year. Thyroid carcinomas usually present in the 40-60 age group. Environmental, genetic and hormonal factors have been considered in the etiology of thyroid carcinomas. Many benign conditions like thyroidal adenomas, multi-nodular goiter, thyroiditis, thyroidal cysts, thyroidal malformations and focal granulomatous diseases occur clinically as solitary nodules and malignancy is found in 0.1-0.2% of these conditions.[9]

Cytokeratin-19 (CK-19) expression in thyroid nodules is in general intense and diffuse in papillary carcinoma and heterogeneous labeling in follicular carcinoma and in follicular adenoma, with nil or low expression in other benign lesions.[10,11] Galectins, especially galectin-3, are suggested to play a role in the pathogenesis of well differentiated thyroid carcinoma, particularly in papillary carcinoma.[12]Therefore, it is one of the markers most commonly used to assist in distinguishing thyroid lesions. Hector Battifora mesothelial-1 (HBME-1) has been demonstrated to be important as a thyroid marker of follicular origin, with greater affinity to malignant lesions when compared to benign lesions.[13]

In general, the prognosis of PTC is favorable and ten-year survival rate for PTCs is greater than 90%.[14] However, about 20% of the differentiated thyroid cancer will present with metastasis. So accurate biomarkers which can predict the aggressive behavior of thyroid carcinoma is critical for clinical management.[15]

Tijana *et al* reported that the CK19 was a useful marker for the identification of PTCs and they suggested that the high expression of the CK19 is a predictor for the aggressive behavior of PTC and could help to identify a particular subgroup of PTCs which had a potentially worse prognosis.[16] GAL-3 could be a important tool for guiding therapeutic decisions in patients with thyroid nodules.[17]

The significance of the biomarkers, such as CK19, HBME-1, GAL3, have been widely explored and debated for the differential diagnosis of thyroid neoplasms but the value of these biomarkers as prognostic factors for PTCs is not clear.[16] Thus, in our study, we attempted to investigate whether the expression of the CK19,HBME-1 or GAL3 is linked to the aggressive behavior in papillary thyroid carcinoma.

In a study performed by Prasad *et al.* consisting of 85 carcinoma and 21 adenoma cases, all carcinomas showed different percentage and intensity of staining and 24% of adenomas showed poor intensity of staining with HBME-1. It was concluded that HBME-1 was a very useful marker in malignancies arising from follicular cells and its negativity in benign lesions has a specificity of 94%.[18] In a study performed by Pisani *et al.*, specific cytoplasmic staining with galectin-3 was observed in a suspicious cell population in fine needle aspiration biopsy of a thyroid nodule. Occult papillary carcinoma was found in the operation material of this case andgalectin-3 was concluded as a marker of malignancy.[19]

Thus, in our study we can conclude that this triad of IHC markers – CK19, GAL-3 and HBME-1 could be used in the prognostication of papillary thyroid carcinoma. The positive expressions of these markers have been significantly correlated with total tumor diameter, capsular invasion and lymph nodal metastasis in this study.

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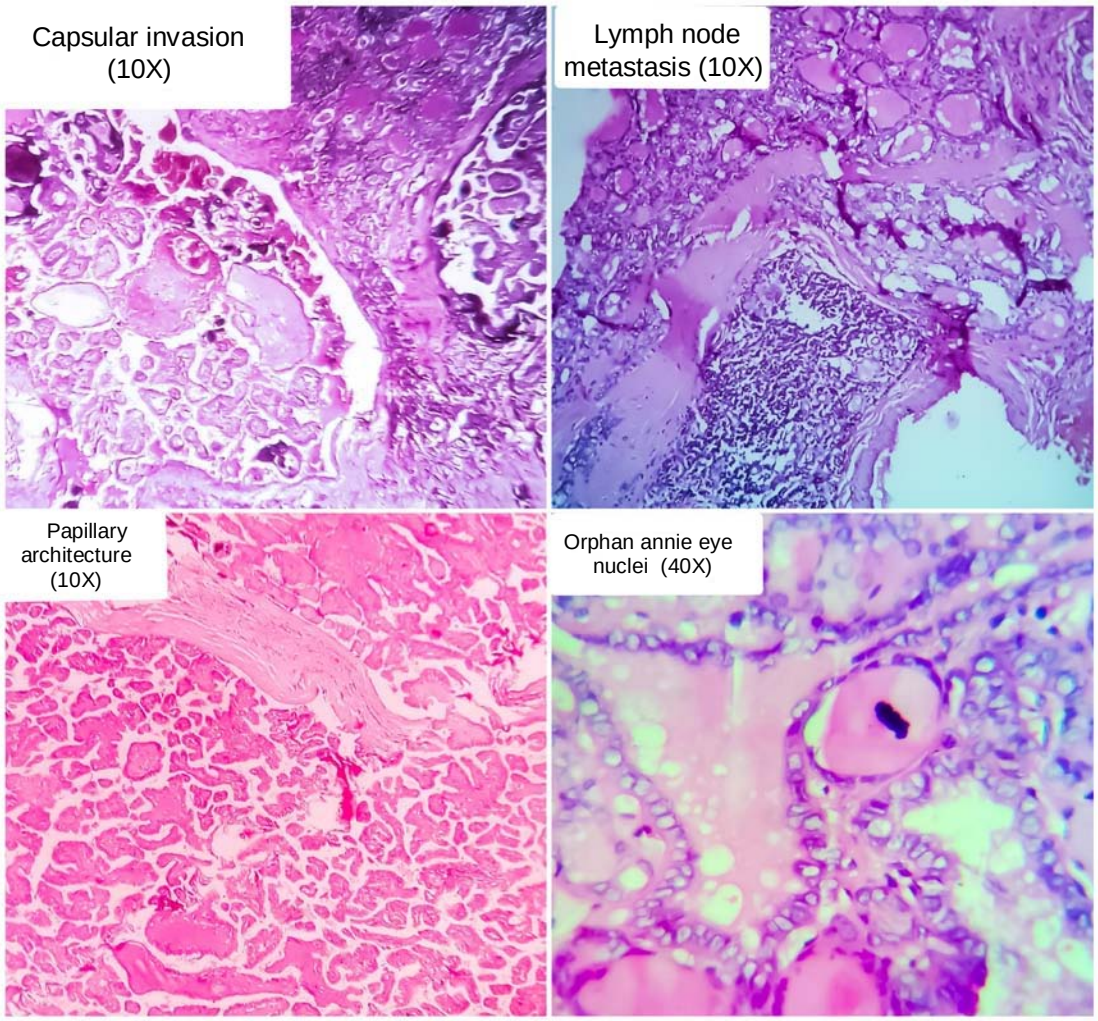

Figure 1

Upper left: Capsular invasion in papillary thyroid carcinoma in H & E (×100)
Upper right: Capsular invasion in papillary thyroid carcinoma in H & E (×100)
Lower left: Papillary architecture in papillary thyroid carcinoma in H & E (×100)
Lower right: Intranuclear clearing in papillary thyroid carcinoma in H & E (×400)

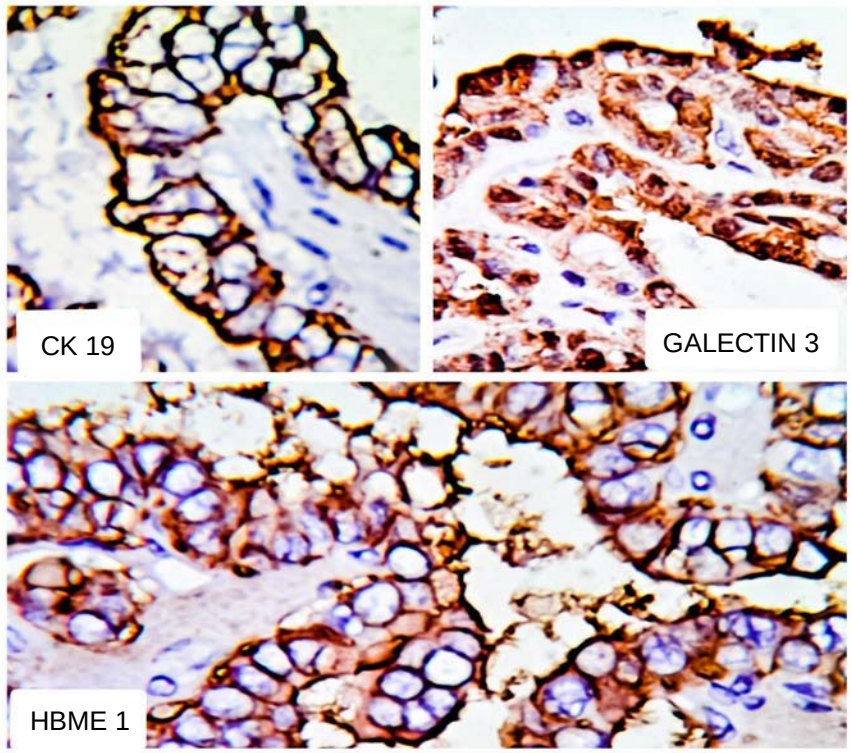

Figure 2

Upper left: CK19 immunostain in papillary thyroid carcinoma (×400)
Upper right: Galectin-3 immunostain
Lower: HBME immunostain in papillary thyroid carcinoma (×400)