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Original Article

Cytokeratin 19, thyroperoxidase, HBME-1 and galectin-3 in evaluation of aggressive behavior of papillary thyroid carcinoma

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Abstract: Objective: To assess usefulness of cytokeratin 19 (CK19), thyroperoxidase (TPO), Hector Battifora mesothelial epitope-1 (HBME-1) and galectin-3 (GAL3) in evaluation of aggressive behavior of PTCs. Methods: All available clinical and pathological data were reviewed in 168 papillary thyroid cancer patients; while the values as predictive markers of PTC were tested by univariate and multivariate analysis. Results: According to the univariate set of tests, positive expression of CK19 and negative expression of TPO correlated significantly with total tumor diameter ($P < 0.05$); But there was no association of positive CK19 expression and negative expression of TPO with gender, age, capsular invasion or lymph node metastasis. Moreover, there was no association of positive HBME-1 and galectin-3 expression with clinical aggressive behavior of PTCs. Conclusion: High expression of CK19 and negative expression of TPO indicate total tumor diameter of PTC, but expression of CK19, TPO, HBME-1 and GAL3 has no values in the identification of PTCs with other potentially aggressive behavior.

Keywords: CK19, TPO, HBME-1, galectin-3, aggressive behavior, papillary thyroid carcinoma

Introduction

Papillary thyroid cancer (PTC) is the most common malignant neoplasm of the endocrine system and the incidence of thyroid cancer has increased dramatically [1, 2]. In recently, many studies focus on the roles of CK19, TPO, HBME-1 and GAL-3 in malignant and benign tumors.

CK19 is a low molecular weight cytokeratin which presents widely in simple epithelia and basal cell layers of stratified epithelium. Thyroperoxidase (TPO) has a key role in the iodine metabolism, being essential for the thyroid function. HBME-1 is a monoclonal antibody generated against a membrane antigen of mesothelial cells [3]. It was originally found in malignant mesothelioma; several investigators showed that HBME-1 play an important role in diagnosis of papillary thyroid carcinoma.

GAL3 polypeptide 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 available to distinguish the malignant thyroid nodules from the benign ones [4].

In spite that the positive expression of CK19, HBME-1, GAL3 and negative expression of TPO have been found in papillary thyroid cancer, the roles of these biomarkers in the aggressive behavior of PTCs are still controversial [5, 6]. The aim of present study was to investigate the relationship between the expression of CK19, TPO, HBME-1 and Galectin-3 and the aggressive behavior of PTCs by correlating immunohistochemical results with the clinical features.

Materials and methods

Patients

Patients with histologically confirmed papillary carcinoma treated between December 2011

Table 1. Summary of clinicopathological traits

Parameter	% (NO. of cases)
Age (yr) (mean [range]: 48.43 19-79)	
≤ 45	31.0 (52/168)
> 45	69.0 (116/168)
Gender	
F	82.7 (139/168)
M	17.3 (29/168)
Total tumor diameter	
≤ 1 cm	76.2 (125/164)
> 1 cm	23.8 (39/164)
Capsular invasion	
Present	15.5 (25/161)
Absent	84.5 (136/161)
LNM	
Present	30.5 (29/95)
Absent	69.5 (66/95)

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

Parameter		Ck19		Total	*P*
		positive	negative		
Gender	F	125	5	130	0.161
	M	26	3	29	
Age	≤ 45 y	48	2	50	1.000
	> 45 y	102	6	108	
Total tumor diameter	≤ 1 cm	116	3	119	0.017
	> 1 cm	31	5	36	
Capsular invasion	Present	19	3	22	0.09
	Absent	126	5	131	
LNM	Present	27	0	27	0.171
	Absent	55	6	61	

and January 2014 were identified from the Department of General Surgery, Affiliated Union Hospital. All patients had undergone total resection of primary thyroid carcinoma [7, 8]. The study was approved by the ethics committees of union hospital.

Clinical and pathological data

All available clinical and pathological data were reviewed for 168 papillary thyroid cancer patients. Informations included the gender, age, total tumor diameter [9, 10], capsular invasion, lymph node metastases and the expression of cytokeratin 19, TPO, HBME-1, and Galectin-3 (weakly and strongly expression both consider as positive expression).

Statistical analysis

EpiData Software v3.1 (EpiData Association, Odense, Denmark) was used for initial clinical and pathological data entry. Continuous variables were presented as mean ± standard deviation (SD). Discrete variables were reported as proportions and analyzed by the chi-square test or Fisher's exact test. And statistical significance was set at a two-tailed *P* value of < 0.05. Univariate analyses between covariates (such as age, gender, total tumor size, capsular invasion and lymph node metastases) and expression of biomarker were performed by Fisher's exact test or the chi-square test. More than one significant variables of the univariant analysis were assessed in multivariate analysis by a binary logistic regression. Statistical analyses were performed by SPSS software (version 13.0, Chicago, IL, USA).

Results

In the 168 patients (**Table 1**), the female: male ratio was 4.8:1 with a mean age of 48.43 yr (range: 19-79 yr). seventy-two percent (125/164) of cases had total tumor diameter less than 1 cm, and only fifteen percent of tumors showed capsular invasion. LN metastasis was found in 30.5% (29/95) of cases.

The results are summarized from **Tables 2** to **5**. For each of the tested criteria, all patients with PTCs were divided into positive and negative expression groups.

According to our results (**Table 2**), positive expression of the CK19 was correlated significantly with the total tumor diameter ($P < 0.05$). This indicated that the larger volume of the TTD is more likely to express CK19. On the other hand, the expression of the CK19 had no relationship with the other clinical characteristics, including gender, age, capsular invasion and LNM. The multivariate analysis wasn't conducted owning to less than two significant variables of the univariant analysis for CK19.

Negative expression of TPO was correlated significantly with total tumor diameter ($P < 0.05$), suggesting that the smaller volume of the TTD tended to express TPO more frequently (**Table**

Table 3. Prediction of some clinicopathological characteristics of PTC based on immunohistochemical expression of TPO

Parameter		TPO		Total	*P*
		positive	negative		
Gender	F	17	111	128	0.479
	M	5	22	27	
Age	≤ 45 y	6	42	48	0.670
	> 45 y	16	90	106	
Tumor Size	≤ 1 cm	11	106	117	0.03
	> 1 cm	10	24	34	
Capsular invasion	Present	5	15	20	0.132
	Absent	16	113	129	
LNM	Present	6	20	26	0.197
	Absent	7	51	58	

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

Parameter		HBME-1		Total	P
		positive	negative		
Gender	F	71	16	87	0.187
	M	19	1	20	
Age	≤ 45 y	32	5	37	0.625
	> 45 y	58	12	70	
Tumor Size	≤ 1 cm	66	8	74	0.188
	> 1 cm	23	6	29	
Capsular invasion	Present	14	0	14	0.207
	Absent	74	14	88	
LNM	Present	16	5	21	0.342
	Absent	31	5	36	

Table 5. Prediction of some clinicopathological characteristics of PTC based on immunohistochemical expression of Galectin-1

Parameter		Galectin-1		Total	P
		positive	negative		
Gender	F	15	14	29	0.476
	M	6	3	9	
Age	≤ 45 y	7	3	10	0.460
	> 45 y	14	14	28	
Tumor size	≤ 1 cm	12	10	22	0.488
	> 1 cm	9	4	13	
Capsular invasion	Present	2	2	4	0.627
	Absent	19	11	30	
LNM	Present	7	2	9	0.659
	Absent	8	4	12	

3). However, the expression of TPO was not related to the patients' gender, age, capsular invasion or LNM.

In addition, we found there was no association of the expression of the HBME-1 and Galectin-3 with the clinical features of the PTCs (**Tables 4**, **5**).

Discussion

Papillary thyroid cancer is the most frequently observed malignant tumor in the thyroid, accounting almost for 94% of all thyroid carcinoma. In general, the prognosis of PTC is favorable and ten-year survival rate for PTCs is greater than 90% [11]. However, about 20% of the differentiated thyroid cancer will present with metastasis [12]. So accurate biomarkers which can predict the aggressive behavior of thyroid carcinoma is critical for clinical management [13].

CK19 belongs to the intermediate filaments; it is normally expressed in ductal epithelium such as pancreas, bile ducts and so on, and has been applied to hepatocellular carcinomas, PTCs, squamous carcinomas and colorectal adenocarcinoma [6, 14-16]. CK19 was proved to be an independent prognostic factor for pancreatic neuroendocrine tumors [17]. TPO is one of best-studied and most promising markers that have been proved to be present in normal and in benign nodules; while it was absent or only slightly present in cancers. If more than 80 percent of thyroid cells are positive for TPO, the sample would be considered benign [18]. HBME-1, as well known for its ability to separate mesothelioma from adenocarcinoma, is a monoclonal antibody that was positive to variable degrees in all cases of papillary carcinoma in Casey's studies [19]. Galectin-3 is part of a family of lectins not integrins which regulate growth, intervene in molecular adhesion; it is expressed in thyroid cancer including papillary carcinoma, follicular carcinoma as well as medullary carcinoma. GAL3 could be a important tool for guiding therapeutic decisions in patients with thyroid nodules [18].

The significance of the biomarkers, such as CK19, TPO, HBME-1, GAL3, have been widely explored and debated for the differential diagnosis of thyroid neoplasms [5, 20-25], but the value of these biomarkers as prognostic factors for PTCs is not clear [6]. Thus, in the present study, we attempted to investigate whether the expression of the CK19, TPO, HBME-1 or GAL3 is linked to the aggressive behavior in papillary thyroid carcinoma.

Tijana et al [6] 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.

According to our results, positive expression of the CK19 and negative expression of TPO were both correlated significantly with the total tumor diameter, which was related to the progression of PTC. However, there was no association of the expression of the CK19 and TPO with the gender, age, capsular invasion or LNM; Moreover, the HBME-1 and GAL3 were not associated with the TTD, capsular invasion or LNM.

In short, CK19 and TPO may be useful predictors for the papillary thyroid carcinoma progression because their expression is associated with the total tumor diameter of PTCs. However, more researches are still needed to verify whether the expression of the HBME-1 and GAL3 had value for predicting the aggressive behavior of PTCs.

Disclosure of conflict of interest

None.

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References

[1] Davies L and Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006; 295: 2164-2167.

[2] Jemal A, Siegel R, Xu J and Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010; 60: 277-300.

[3] de Matos PS, Ferreira AP, de Oliveira Facuri F, Assumpcao LV, Metze K and Ward LS. Usefulness of HBME-1, cytokeratin 19 and galectin-3 immunostaining in the diagnosis of thyroid malignancy. Histopathology 2005; 47: 391-401.

[4] Saussez S, Glinoer D, Chantrain G, Pattou F, Carnaille B, Andre S, Gabius HJ and Laurent G. Serum galectin-1 and galectin-3 levels in benign and malignant nodular thyroid disease. Thyroid 2008; 18: 705-712.

[5] Cheng S, Serra S, Mercado M, Ezzat S and Asa SL. A high-throughput proteomic approach provides distinct signatures for thyroid cancer behavior. Clin Cancer Res 2011; 17: 2385-2394.

[6] Isic Dencic T, Cvejic D, Paunovic I, Tatic S, Havelka M and Savin S. Cytokeratin19 expression discriminates papillary thyroid carcinoma from other thyroid lesions and predicts its aggressive behavior. Med Oncol 2013; 30: 362.

[7] Li Z, Liu CP, Shi L and Huang T. [Operation for differentiated thyroid cancer: a experience of 546 cases]. Zhonghua Wai Ke Za Zhi 2008; 46: 375-377.

[8] Udelsman R and Shaha AR. Is total thyroidectomy the best possible surgical management for well-differentiated thyroid cancer? Lancet Oncol 2005; 6: 529-531.

[9] Zhao Q, Ming J, Liu C, Shi L, Xu X, Nie X and Huang T. Multifocality and total tumor diameter predict central neck lymph node metastases in papillary thyroid microcarcinoma. Ann Surg Oncol 2013; 20: 746-752.

[10] RA D. Pathology and genetics of tumours of endocrine organs. Lyon: World Health Organization; 2004.

[11] Liu Z, Xun X, Wang Y, Mei L, He L, Zeng W, Wang CY and Tao H. MRI and ultrasonography detection of cervical lymph node metastases in differentiated thyroid carcinoma before reoperation. Am J Transl Res 2014; 6: 147-154.

[12] Leboulleux S, Bastholt L, Krause T, de la Fouchardiere C, Tennvall J, Awada A, Gomez JM, Bonichon F, Leenhardt L, Soufflet C, Licour M and Schlumberger MJ. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. Lancet Oncol 2012; 13: 897-905.

[13] Vini L and Harmer C. Management of thyroid cancer. Lancet Oncol 2002; 3: 407-414.

[14] Uenishi T, Kubo S, Yamamoto T, Shuto T, Ogawa M, Tanaka H, Tanaka S, Kaneda K and Hirohashi K. Cytokeratin 19 expression in hepatocellular carcinoma predicts early postoperative recurrence. Cancer Sci 2003; 94: 851-857.

[15] Durnez A, Verslype C, Nevens F, Fevery J, Aerts R, Pirenne J, Lesaffre E, Libbrecht L, Desmet V

and Roskams T. The clinicopathological and prognostic relevance of cytokeratin 7 and 19 expression in hepatocellular carcinoma. A possible progenitor cell origin. Histopathology 2006; 49: 138-151.

[16] Bhatavdekar JM, Patel DD, Chikhlikar PR, Shah NG, Vora HH, Ghosh N and Trivedi TI. Molecular markers are predictors of recurrence and survival in patients with Dukes B and Dukes C colorectal adenocarcinoma. Dis Colon Rectum 2001; 44: 523-533.

[17] Jain R, Fischer S, Serra S and Chetty R. The use of Cytokeratin 19 (CK19) immunohistochemistry in lesions of the pancreas, gastrointestinal tract, and liver. Appl Immunohistochem Mol Morphol 2010; 18: 9-15.

[18] Gomez Saez JM. Diagnostic usefulness of tumor markers in the thyroid cytological samples extracted by fine-needle aspiration biopsy. Endocr Metab Immune Disord Drug Targets 2010; 10: 47-56.

[19] Casey MB, Lohse CM and Lloyd RV. Distinction between papillary thyroid hyperplasia and papillary thyroid carcinoma by immunohistochemical staining for cytokeratin 19, galectin-3, and HBME-1. Endocr Pathol 2003; 14: 55-60.

[20] Wang N, Dong CR, Jiang R, Tang C, Yang L, Jiang QF, Chen GG and Liu ZM. Overexpression of HIF-1alpha, metallothionein and SLUG is associated with high TNM stage and lymph node metastasis in papillary thyroid carcinoma. Int J Clin Exp Pathol 2014; 7: 322-330.

[21] Barut F, Onak Kandemir N, Bektas S, Bahadir B, Keser S and Ozdamar SO. Universal markers of thyroid malignancies: galectin-3, HBME-1, and cytokeratin-19. Endocr Pathol 2010; 21: 80-89.

[22] Paunovic I, Isic T, Havelka M, Tatic S, Cvejic D and Savin S. Combined immunohistochemistry for thyroid peroxidase, galectin-3, CK19 and HBME-1 in differential diagnosis of thyroid tumors. APMIS 2012; 120: 368-379.

[23] Zhu X, Sun T, Lu H, Zhou X, Lu Y, Cai X and Zhu X. Diagnostic significance of CK19, RET, galectin-3 and HBME-1 expression for papillary thyroid carcinoma. J Clin Pathol 2010; 63: 786-789.

[24] Wu G, Wang J, Zhou Z, Li T and Tang F. Combined staining for immunohistochemical markers in the diagnosis of papillary thyroid carcinoma: improvement in the sensitivity or specificity? J Int Med Res 2013; 41: 975-983.

[25] Mataraci EA, Ozguven BY and Kabukcuoglu F. Expression of cytokeratin 19, HBME-1 and galectin-3 in neoplastic and nonneoplastic thyroid lesions. Pol J Pathol 2012; 63: 58-64.