Expression of cytokeratin 19, HBME-1 and galectin-3 in neoplastic and nonneoplastic thyroid lesions

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In this study, 105 cases of thyroid lesions were evaluated to assess the role of HBME-1, cytokeratin-19 (CK-19), galectin-3 in distinguishing benign from malignant thyroid lesions. Thirty-seven papillary, 10 follicular, 6 medullary, 1 mixed medullary follicular cell carcinoma, 3 poorly differentiated carcinoma, 18 adenomatous nodular hyperplasia, 30 follicular adenoma cases were included in the study. Immunohistochemical staining was performed with HBME-1, CK-19, galectin-3 on cross-sections derived from selected paraffin blocks. Benign and malignant lesions were compared in terms of intensity, percentage and type of staining with CK-19, HBME-1 and galectin-3, and a statistically significant difference ($p < 0.05$) was found. The percentage and intensity of staining was higher in malignant lesions. Especially, strong and diffuse expressions of CK19, HBME-1 and galectin-3 were observed in papillary carcinomas. Membranous (luminal) staining was seen more frequently in malignant lesions; cytoplasmic staining in benign lesions. It was concluded that these markers could assist in the diagnosis of thyroid lesions with cellular properties suspicious for the diagnosis of papillary carcinoma and without capsule and vessel invasion. They may be used especially in cases where the follicular variant of papillary carcinoma, follicular adenoma and follicular carcinoma are confused with each other and follicular adenoma cannot be differentiated from follicular carcinoma.

Key words: thyroid, malignancy, benign lesions, cytokeratin 19, HBME-1, galectin-3, immunohistochemistry.

Introduction

Primary benign thyroid tumors or adenomatous nodules resembling tumors are encountered frequently. It has been shown that more than 50% of clinically evident single nodules are multinodular goitre or thyroiditis [1]. Primary thyroid cancers constitute 1% of all malignant tumors arising from all organs. However, thyroid carcinomas arising from follicular epithelium are the most common among endocrine system malignancies. There are many factors affecting the prognosis of thyroid cancer including age, gender, distant metastasis, lymph node metastasis, histological subtype, dimension of primary tumor and multicentricity. Marked differences are found in cancers arising from follicular thyroid cells in terms of morphological phenotype, clinical course and genotype [2].

As in many other organ lesions, the immunohistochemical method is used for the evaluation of thyroid lesions, especially thyroid tumors for diagnosis and differential diagnosis. Immunohistochemical markers supporting the diagnosis of thyroid cancer can be divided into two classes: thyroglobulin, TTF-1 (thyroid transcription factor-1) is related to cell type. The second group is related to a pathological type: cytokeratin-19 (CK-19) is primarily directed for papillary carcinomas, and high molecular weight cytokeratin (HMWCK), S100, HBME-1, galectin-3 (Gal-3), CITED-1, fibronectin, p27, calcitonin, bcl-2 and N-myc are reported to be markers having a prognostic value for medullary carcinoma. In practice, markers related to the cell type are more useful than markers related to the pathological type [3].

Cytokeratin-19 is a low molecular weight cytokeratin in a group of intermediate filaments. It is expressed on neoplastic epithelium. However, focal reactivity has been reported in benign follicular lesions and areas of degeneration in some studies [4-6]. The HBME-1 is a mesothelial marker. It has been shown to be useful as a marker for malignant tumors arising from follicular epithelium [7, 8]. Galectin-3 is β-galactosidase binding lectin consisting of amino acids. Although it is more prominent in the cytoplasm, it is also found in the nucleus, epithelium and on immunized cell surfaces. Its exact role is not known, but it is related to biological and pathological states including cell development, cell adhesion, inflammation and apoptosis [9, 10].

In this study, benign and malignant thyroid lesions are compared in terms of intensity, percentage and type of staining with CK-19, HBME-1 and galectin-3.

Material and methods

Pathological reports and slides stained with hematoxylin-eosin of 105 materials reported between 2003 and 2007 were evaluated retrospectively with all prognostic parameters. The diagnoses of these materials were distributed as follows: 37 papillary carcinoma, 10 follicular carcinoma, 6 medullary carcinoma, 1 mixed medullary follicular cell carcinoma, 3 poorly differentiated carcinoma, 18 adenomatous nodular hyperplasia and 30 follicular adenoma cases. Slides which represent the lesions and are appropriate for immunohistochemical study were selected. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded 5 μm-thick tissue sections. Negative controls were used to rule out nonspecific staining. CK-19 (Neomarkers, monoclonal, 1 : 20 diluted), HBME-1 (Neomarkers, monoclonal, 1 : 20 diluted), galectin-3 (Neomarkers, monoclonal, 1 : 20 diluted) antibodies were applied. The sections were deparaffinized, rehydrated in graded alcohols, and processed using the Neomarkers kit. Antigen retrieval was performed in a microwave oven for 15 minutes in 10 mM citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked with a 3% H_2O_2-methanol solution, and the slides were incubated in 10% normal goat serum for 30 minutes to prevent non-specific staining. They were then incubated for 2 hours at room temperature with an appropriately diluted primary antibody. The following mouse monoclonal antibodies were used: CK-19, HBME-1, galectin-3. Thereafter, the sections were incubated with biotinylated goat anti-polyvalent (Labvision) for 15 minutes and streptavidin peroxidase, (Labvision) for 15 minutes. 3-amino-9-ethyl carbazole-AEC (Labvision) was used as a chromogen, and the sections were counterstained with Mayer's hematoxylin.

The preparations were evaluated under light microscope by a semiquantitative method.

The percentage of staining for CK-19, HBME-1 and galectin-3 was scored as follows:

- 0; no staining in the area of the lesion – score 0,
- 1+; 5-29% staining in the area of the lesion – score 1,
- 2+; 30-69% staining in the area of the lesion – score 2,
- 3+; 70-100% staining in the area of the lesion – score 3.

The intensity of staining for CK-19, HBME-1 and galectin-3 was scored as follows:

- 0; no staining in the area of the lesion – score 0,
- 1+; poor staining in the area of the lesion – score 1,
- 2+; moderate staining in the area of the lesion – score 2,
- 3+; strong staining in the area of the lesion – score 3.

The staining pattern of HBME-1 was evaluated as follows:

- Membranous staining; lined or fringed staining is present on the cytoplasmic membrane at the luminal side.
- Cytoplasmic staining; staining is present in the follicular cell cytoplasm.
- Mixed staining; both membranous and cytoplasmic staining is present.

Statistical Package for Social Sciences 11.0 was used for statistical analysis. Student t test and Mann-Whitney U test were used for paired group comparisons. Value of $p < 0.05$ was considered to be significant.

Results

When malignant and benign lesions were compared in terms of percentage of staining with CK-19, +3 staining was found in 49.1% of malignant lesions and +1 staining in 45.8% of benign lesions. Student t test revealed a statistically significant difference ($p = 0.001$ vs. $p = 0.05$) (Table I).

Malignant and benign lesions were compared in terms of intensity of staining with CK-19, and +3 staining was found in 66.7% of malignant lesions and +3 staining in 41.7% of benign lesions. Student t test revealed a statistically significant difference between malignant and benign lesions ($p = 0.044$ vs. $p = 0.05$) (Table II, Fig. 1).

When these lesions were compared in terms of percentage of staining with HBME-1, +3 staining was found in 38.6% of malignant lesions and +1 staining in 50% of benign lesions. Student t test revealed a statistically significant difference between malignant and benign lesions ($p = 0.001$ vs. $p = 0.05$) (Table III, Fig. 2).

The comparison of the lesions according to the degree of staining with HBME-1 showed +3 staining in

Table I. Percentage of staining in malignant and benign lesions with CK-19 (p = 0.001)

			Percentage of staining with CK-19				Total
			0	1	2	3	
Group	Malignant	n	10	5	14	28	57
		%	17.5	8.8	24.6	49.1	100
	Benign	n	10	22	11	5	48
		%	20.8	45.8	22.9	10.4	100
Total		n	20	27	25	33	105
		%	19.0	25.7	23.8	31.4	100

Table II. Intensity of staining in malignant and benign lesions with CK-19 (p = 0.044)

			Intensity of staining with CK-19				Total
			0	1	2	3	
Group	Malignant	n	10	4	5	38	57
		%	17.5	7.0	8.8	66.7	100
	Benign	n	10	5	13	20	48
		%	20.8	10.4	27.1	41.7	100
Total		n	20	9	18	58	105
		%	19.0	8.6	17.1	55.2	100

Table III. Percentage of staining in malignant and benign lesions with HBME-1 (p = 0.001)

			Percentage of staining with HBME-1				Total
			0	1	2	3	
Group	Malignant	n	6	12	17	22	57
		%	10.5	21.1	29.8	38.6	100
	Benign	n	16	24	4	4	48
		%	33.0	50.0	8.3	8.3	100
Total		n	22	36	21	26	105
		%	21.0	34.3	20.0	24.8	100

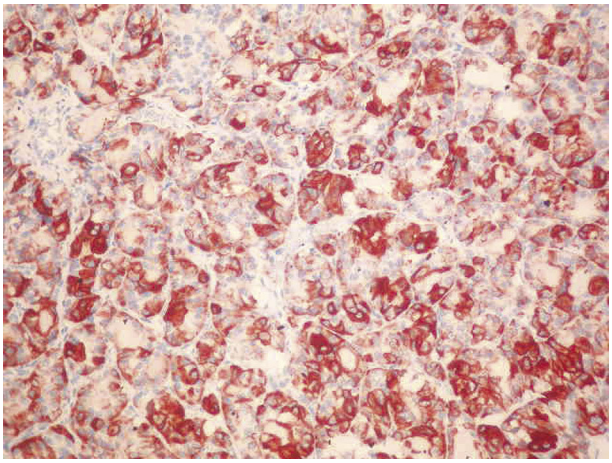

Fig. 1. +3/+3 percentage of staining/intensity of staining in papillary carcinoma with CK-19. Magnification 200×

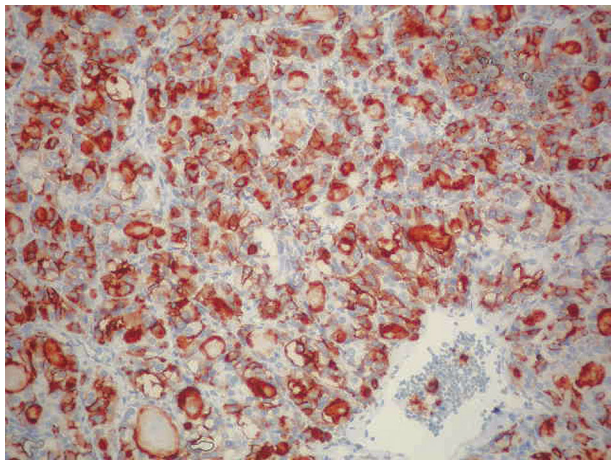

Fig. 2. +3/+3 percentage of staining/intensity of staining in papillary carcinoma with HBME-1. Magnification 200×

Table IV. Intensity of staining in malignant and benign lesions with HBME-1 (p = 0.001)

			INTENSITY OF STAINING WITH HBME-1				TOTAL
			0	1	2	3	
Group	Malignant	n	6	2	5	44	57
		%	10.5	3.5	8.8	77.2	100
	Benign	n	16	13	14	5	48
		%	33.3	27.1	29.2	10.4	100
Total		n	22	15	19	49	105
		%	21.0	14.3	18.1	46.7	100

Table V. Type of staining in malignant and benign lesions with HBME-1

			TYPE OF STAINING WITH HBME-1			TOTAL
			Membranous	Cytoplasmic	Mixed	
Group	Malignant	n	38	5	8	51
		%	74.5	9.8	15.7	100
	Benign	n	11	21	0	32
		%	34.4	65.6	0	100
Total		n	49	26	8	83
		%	59.0	31.3	9.6	100

77.2% of malignant lesions, and no staining was seen in 33.3% of benign lesions. Student t test revealed a statistically significant difference between malignant and benign lesions in terms of intensity of staining with HBME-1 (p = 0.001 vs. p = 0.05) (Table IV).

Malignant and benign lesions were compared in terms of the type of staining with HBME-1, and a higher rate of membranous (luminal) staining was found in malignant lesions and a higher rate of cytoplasmic staining was found in benign lesions. However, the distribution was not appropriate for statistical analysis (Table V, Fig. 3).

When these lesions were compared in terms of percentage of staining with galectin-3, +3 staining was present in 49.1% of malignant lesions and no staining was seen in 41.7% of benign lesions. Student t test revealed a statistically significant difference (p = 0.001 vs. p = 0.05) (Table VI, Fig. 4).

Comparison of the lesions with the intensity of staining with galectin-3 showed +3 staining in 61.4% of malignant lesions and no staining in 41.7% of benign lesions. Student t test revealed a statistically significant difference between malignant and benign lesions (p = 0.001 vs. p = 0.05) (Table VII).

Discussion

Primary thyroid cancers comprise the largest group among malignancies of the endocrine system. 120,000 new cases are added each year [1]. 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, multinodular goitre, 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 [1].

As in many other organ lesions, the immunohistochemical method is used for the diagnosis and differential diagnosis in evaluating thyroid tumors. Studies performed so far show that immunohistochemical stud-

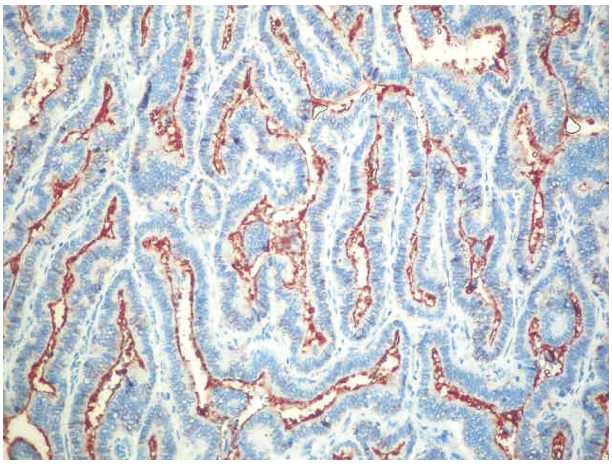

Fig. 3. Membranous (luminal) staining in papillary carcinoma with HBME-1. Magnification 200×

Table VI. Percentage of staining in malignant and benign lesions with galectin-3 (p = 0.001)

			Percentage of staining with galectin-3				Total
			0	1	2	3	
Group	Malignant	n	7	12	10	28	57
		%	12.3	21.1	17.5	49.1	100
	Benign	n	20	14	9	5	48
		%	41.7	29.2	18.8	10.4	100
Total		n	27	26	19	33	105
		%	25.7	24.8	18.1	31.4	100

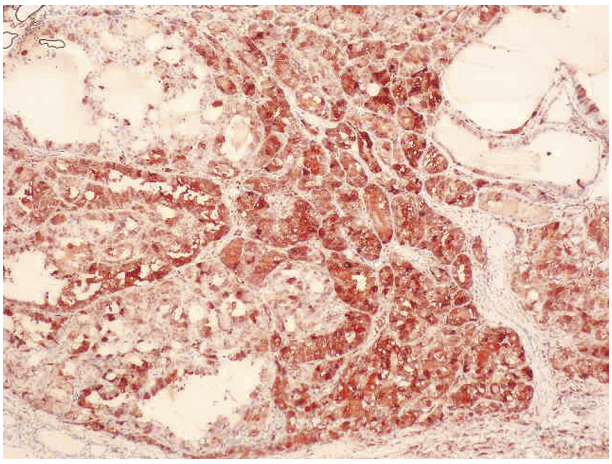

Fig. 4. +3/+3 percentage of staining/intensity of staining in papillary carcinoma with gal-3. Magnification 100×

ies contribute to guidelines of diagnosis for thyroidal lesions [3].

Cytoskeletal proteins have been identified to provide valuable markers in cell typing and hence tumor diagnosis. Cytokeratin 19 is the lowest molecular weight cytokeratin and is to be found on a diverse range of normal epithelia and tumors. Among various cytokeratins, CK-19 has been reported to be useful in the diagnosis of papillary carcinoma, where it has shown diffuse and strong cytoplasmic staining [4-6]. As reported in studies and many other sources, it is seen that a percentage of staining is higher in malignant lesions than benign lesions [1, 2, 4, 11, 12].

The percentage of staining of cytokeratin types in carcinomas was evaluated in a study performed by Lam in 153 thyroid carcinoma cases [12]. Strong and diffuse staining was seen with CK-19 in more than 80% of papillary carcinomas and focal staining was seen in more than 60% of follicular carcinomas. Immunoreactivity showed variability in medullary carcinoma, poorly differentiated carcinoma and anaplastic carcinoma. Although not specific of papillary carcinoma, strong and diffuse CK-19 immunoreactivity was considered to be important for the diagnosis, thus supporting our study results.

When malignant and benign lesions were compared in terms of intensity of staining with CK-19, we found +3 staining in 66.7% of malignant lesions and +3 staining in 41.7% of benign lesions. There was a statistically significant difference between malignant and benign lesions in terms of intensity of staining with CK19.

In a study performed by Scognamiglio *et al.* [13] consisting of 127 follicular adenoma and papillary carcinoma cases, CK-19 was found to have a confirming role in the differentiation of follicular adenoma from follicular variant of papillary carcinoma. Borroeta *et al.* [14] and Nakamura *et al.* [15] reported studies supporting this conclusion.

Miettinen [16], Fonseca [17] and Sahoo [18] underscored that poorer staining was seen with CK-19 in most follicular carcinomas, although strong staining was seen in papillary carcinomas and this finding was important in the differential diagnosis [5]. Many studies reported that although diffuse staining with

Table VII. Intensity of staining in malignant and benign lesions with galectin-3 (p = 0.001)

			Intensity of staining with galectin-3				Total
			0	1	2	3	
Group	Malignant	n	7	6	9	35	57
		%	12.3	10.5	15.8	61.4	100.0
	Benign	n	20	14	6	8	48
		%	41.7	29.2	12.5	16.7	100.0
Total		n	27	20	15	43	105
		%	25.7	19.0	14.3	41.0	100.0

CK-19 was seen in most cases of papillary carcinoma and follicular variant of papillary carcinoma, variable staining of other malignant and benign lesions could provide differential diagnosis.

When we compared malignant and benign lesions in terms of percentage of staining with CK-19 in our study, we found +3 staining in 49.1% of malignant lesions and +1 staining in 45.8% of benign lesions. There was a statistically significant difference between malignant and benign lesions. As reported in studies and many other sources, it is seen that the percentage of staining is higher in malignant lesions than benign lesions [1, 2, 4, 11, 12].

The HBME-1 is a monoclonal antibody generated against an unknown membrane antigen of mesothelial cells. It was also reported to show preferential reactivity with malignant thyroid tumors as HBME-1 is a marker of mesothelial cells. The HBME-1 decorates a significant proportion of malignancies, including papillary carcinomas, both classical and follicular variants, and follicular carcinoma. In some cases of papillary carcinomas, the staining is predominantly luminal. In some lesions, there is diffuse moderate to strong cytoplasmic reactivity [13-17].

There was no HBME-1 staining in a study which included 40 hyperplastic nodules and 35 follicular adenomas with a total of 232 thyroid lesions [7]. The HBME-1 reactivity was present in all types of follicular epithelial malignant lesions. Fifty-five percent of follicular epithelial malignancies showing HBME-1 immunoreactivity were papillary carcinomas. It was concluded that HBME-1 immunoreactivity is a reliable marker for malignant nodules arising from follicular epithelium and malignant properties should be sought in suspicious adenomas or dominant hyperplastic nodules showing HBME-1 reactivity. When malignant and benign lesions were compared in terms of percentage of staining with HBME-1 in our study, +3 staining was found in 38.6% of malignant lesions and +1 staining was found in 50% of benign lesions. There was a statistically significant difference between malignant and benign lesions.

In a study performed by Prasad *et al.* [18] 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%. When we compared malignant and benign lesions in terms of the intensity of staining with HBME-1 in our study, we found +3 staining in 77.2% of malignant lesions and no staining was seen in 33.3% of benign lesions. There was a statistically significant difference between malignant and benign lesions.

The HBME-1 was considered to be a marker with 96% specificity in the diagnosis of suspicious papillary carcinoma. A higher rate of membranous (luminal) staining was found in malignant lesions in accordance with studies performed in cases of malignant lesions and a higher rate of cytoplasmic staining was found in benign lesions [7, 8, 18]. We investigated malignant and benign lesions in terms of the type of staining with HBME-1. However, the distribution was not appropriate for statistical analysis due to low number.

Galectin-3 is a member of a growing family of galactoside- binding animal lectins, involved in the regulation of cell-cell and cell-matrix interaction, cell growth, neoplastic transformation, and apoptosis. Many studies have shown that galectin-3 expression is of value in discriminating benign and malignant thyroid nodules. Galectin-3 is expressed predominantly in the cytoplasm but also in the nucleus and at the cell surface of both epithelial and immune cells. Several studies have demonstrated its utility as a marker of malignant thyroid tumors [20]. In a study performed by Saggiorato *et al.* [9], minimal invasive follicular carcinoma and follicular adenoma were evaluated histopathologically and strong galectin-3 reactivity was found in the case previously diagnosed as follicular adenoma. Thereupon, serial cross-sections were performed and vascular invasion was seen. Conclusively, cytoplasmic (+) staining of galectin-3 should always be a warning and a great number of sampling should be made for malignancy criteria. When we compared malignant and benign lesions with percentage of staining with galectin-3, we found +3 staining in 49.1% of malignant lesions and no staining was seen in 41.7% of benign lesions. There was a statistically significant difference between malignant and benign lesions in terms of percentage of staining with galectin-3. In Barroeta's *et al.* study [14], staining with galectin-3 was present in 70-73% of malignant lesions and 34% of benign lesions. In a study performed by Pisani *et al.* [21], 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 and galectin-3 was concluded as a marker of malignancy. In another study, cytoplasmic and nuclear staining with galectin-3 was seen in malignant neoplasms and no staining with galectin-3 was observed in benign thyroid lesions [22]. When we compared malignant and benign lesions in terms of intensity of staining with galectin-3, we found +3 staining in 61.4% of malignant lesions and no staining was seen in 41.7% of benign lesions. There was a statistically significant difference between malignant and benign lesions.

When we compared malignant and benign lesions according to percentage of staining and intensity of staining with CK-19, HBME-1 and galectin-3, we found a statistically significant difference ($p < 0.05$). The percentage and intensity of staining were higher in malignant lesions. Diffuse and strong staining was

observed in papillary carcinoma with CK19, HBME-1 and galectin-3. Immunohistochemical markers CK-19, HBME-1 and galectin-3 were found to be useful for the diagnosis of papillary carcinoma in thyroid lesions with cell properties suspicious for the diagnosis of papillary carcinoma with no capsule or vessel invasion. It was concluded that these markers could be used especially in the differentiation of the follicular variant of papillary carcinoma from follicular adenoma and follicular carcinoma, and in the differentiation of follicular adenoma from follicular carcinoma.

References

1. Delellis RA, Williams ED. Tumours of the thyroid and parathyroid. In: The WHO classification of tumours of endocrine organs. Delellis RA, Lloyd RV, Heitz PU, Eng C (eds). IARC Press, Lyon 2004; 50-133.
2. Rosai J. Thyroid gland. In: Rosai J. Rosai and Ackerman's surgical pathology. 9th ed. Mosby Company 2004; 515-568.
3. Rosai J. Immunohistochemical markers of thyroid tumors significance and diagnostic applications. Tumori 2003; 89: 517-519.
4. Beesley MF, Mclaren KM. Cytokeratin 19 and galectin-3 immunohistochemistry in the differential diagnosis of solitary thyroid nodules. Histopathology 2002; 41: 236-243.
5. Cameron BR, Berean KW. Cytokeratin subtypes in thyroid tumors: immunohistochemical study with emphasis on the follicular variant of papillary carcinoma. J Otolaryngol 2003; 32: 319-322.
6. Miettinen M, Kovatich AJ. Keratin subset in papillary and follicular thyroid lesions. Virch Arch 1997; 431: 407-413.
7. Cheung CC, Ezzat S, Freeman JL, et al. Immunohistochemical diagnosis of papillary thyroid carcinoma. Mod Pathol 2001; 14: 338-342.
8. Volante M, Bozzalla-Cassione F, Depompa R, et al. Galectin-3 and HBME-1 expression in oncocytic cell tumors of the thyroid. Virch Arch 2004; 445: 183-188.
9. Saggiorato E, Cappia S, Giuli PD, et al. Galectin-3 as a presurgical immunocytodiagnostic marker of minimally invasive follicular thyroid carcinoma. J Clin Endocrinol Metab 2001; 86: 5152-5158.
10. Hermann ME, Livolsi VA, Pasha TL, et al. Immunohistochemical expression of galectin-3 in benign and malignant thyroid lesions. Arch Pathol Lab Med 2002; 126: 710-713.
11. Goossens A, Heimann R. CK19 is present in fetal thyroid tissue. Am J Clin Pathol 1989; 92: 654-658.
12. Lam KY, Lui MC, Lo CY. Cytokeratin expression profiles in thyroid carcinomas. Eur J Surg Oncol 2001; 27: 631-635.
13. Scognamiglio T, Hyjek E, Kao J, Chen YT. Diagnostic usefulness of HBME-1, galectin-3, CK19 and CITED1 and evaluation of their expression in encapsulated lesions with questionable features of papillary thyroid carcinoma. Am J Clin Pathol 2006; 126: 700-708.
14. Barroeta JE, Baloch ZW, Lal P, et al. Diagnostic value of differential expression of CK19, galectin-3, HBME-1, erk, ret and p16 in benign and malignant follicular-derived lesions of the thyroid: an immunohistochemical tissue microarray analysis. Endocr Pathol 2006; 17: 225-234.
15. Nakamura N, Erickson LA, Jin L, et al. Immunohistochemical separation of follicular variant of papillary thyroid carcinoma from follicular adenoma. Endocr Pathol 2006; 17: 213-223.
16. Casey MB, Lohse CM, 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.
17. de Matos PS, Ferreira AP, de Oliveira Facuri F, et al. Usefulness of HBME-1, cytokeratin 19 and galectin-3 immunostaining in the diagnosis of thyroid malinancy. Histopathology 2005; 47: 391-401.
18. Prasad ML, Pellegata NS, Huang Y, et al. Galectin-3, fibronectin-1, CITED-1, HBME-1 and cytokeratin-19 immunohistochemistry is useful for the differential diagnosis of thyroid tumors. Mod Pathol 2005; 18: 48-57.
19. Erickson LA, Lloyd RV. Utility of a panel of immunohistochemical markers in the diagnosis of follicular variant of papillary thyroid carcinoma. Adv Anat Pathol 2008; 15: 1.
20. Park YJ, Kwak SH, Kim DC, et al. Diagnostic value of galectin-3, HBME-1, cytokeratin 19, high molecular weight cytokeratin, cyclin D1 and p27kip1 in the differential diagnosis of thyroid nodules. J Korean Med Sci 2007; 22: 621-628.
21. Pisani T, Vecchione A, Giovagnoli MR. Galectin-3 immunodetection may improve cytological diagnosis of occult papillary thyroid carcinoma. Anticancer Res 2004; 24: 1111-1112.
22. Weinberger PM, Adam BL, Gourin CG, et al. Association of nuclear, cytoplasmic expression of galectin-3 with beta-catenin/Wnt-pathway activation in thyroid carcinoma. Arch Otolaryngol Head Neck Surg 2007; 133: 503-510.

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