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Original Article

Differential diagnosis of papillary thyroid carcinoma: Immunocytochemical study of 112 cases

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Abstract. Papillary carcinoma is diagnosed mainly by its classical papillary structures and nuclear changes. However similar structural and cytological features may also be seen in other lesions of thyroid. Immunohistochemical staining methods help in these circumstances that cytological features do not suffice for differential diagnosis. In this study we stained 112 parafin-embedded blocks with thyroidal lesions (60 papillary carcinoma and 52 other benign or malignant thyroidal lesions) with HBME-1, CK-19, S-100 and EMA. Papillary carcinomas were stained 8.3% weakly, 90% moderately and strongly with HBME-1; 11.7% weakly, 88.3% moderately and strongly with CK-19; 50% weakly, 50% moderately and strongly with EMA; 26.6% weakly, 48.4% moderately and strongly with S-100. Other thyroid lesions were stained 36.5% weakly, 5.8% moderately with CK-19; 26.6% weakly, 15.4% moderately with EMA; 7.7% weakly, 1.9% moderately with S-100. None of the thyroid lesions, but papillary carcinoma, were stained with HBME-1. Papillary carcinoma cases had significantly higher staining with all four markers. However, HBME-1 and CK-19 were considered more valuable in differential diagnosis for papillary carcinomas, since they showed moderate and strong staining. Also high sensitivity and specificity of HBME-1 makes it a good marker for the diagnosis of papillary thyroid cancer.

Keywords: Papillary thyroid carcinoma, HBME-1, CK-19, S-100, EMA

1. Introduction

Papillary carcinoma is diagnosed mainly by its classical papillary structures and nuclear changes. However many other pathologies share similar structural changes. Immunohistochemical staining methods help in these circumstances that cytological features do not suffice for differential diagnosis. In this study we utilized immunohistochemistry with HBME-1, CK-19, S-100 and EMA in the diagnosis of papillary cancer.

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2. Materials and methods

Parafin-embedded blocks of pathological specimens of papillary cancer (n=60) or other benign or malignant thyroidal lesions (n=52) dating between 1994 to 2002 were retrieved from the archieves of Department of Pathology of Yuzuncu Yil University Faculty of Medicine, Van, Turkiye. Sections were taken from appropriate blocks and stained with CK-19, HBME-1, S-100 and EMA primary antibodies (DAKO PAP) with avidin-biotin peroxidase method. Positive controls were prepared with appropriate tissue sections for each marker.

The slides were inspected under light microscope.

Staining patterns were ranked as negative, weak (+), moderate (++) or strong (+++).

Statistical analysis was made with Pearson chi-square test. $P < 0.05$ was accepted as significant.

Table 1

The staining rates in the papillary carcinoma and other pathologies

		The staining rates															
		CK-19				HBME-1				EMA				S-100			
		-	+	++	+++	-	+	++	+++	-	+	++	+++	-	+	++	+++
Diagnosis	n	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
PCa (Total)	60	-	7 (11.7)	18 (30)	35 (58.3)	1 (1.7)	5 (8.3)	34 (56.7)	20 (33.3)	-	30 (50)	20 (33.3)	10 (16.7)	15 (25)	16 (26.6)	19 (31.7)	10 (16.7)
PCa PV	37	-	-	5 (13.5)	32 (86.5)	-	4 (10.8)	21 (56.7)	12 (32.5)	-	14 (37.8)	14 (37.8)	9 (24.4)	7 (18.9)	12 (32.5)	11 (29.7)	7 (18.9)
PCaFV	23	-	7 (30.5)	13 (56.5)	3 (13)	1 (4.3)	1 (4.3)	13 (56.6)	8 (34.8)	-	16 (69.6)	6 (26.1)	1 (4.3)	8 (34.8)	4 (17.4)	8 (34.8)	3 (13)
FCa	5	2 (40)	2 (40)	1 (20)	-	5 (100)	-	-	-	3 (60)	2 (40)	-	-	4 (80)	-	1 (20)	-
Nodular hyperplasia	25	15 (60)	10 (40)	-	-	25 (100)	-	-	-	16 (64)	4 (16)	5 (20)	-	22 (88)	3 (12)	-	-
Follicular adenoma	12	8 (66.7)	4 (33.3)	-	-	12 (100)	-	-	-	6 (50)	6 (50)	-	-	11 (91.6)	1 (8.4)	-	-
Graves disease	6	4 (66.6)	1 (16.7)	1 (16.7)	-	6 (100)	-	-	-	5 (83.3)	-	1 (16.7)	-	6 (100)	-	-	-
Hashimoto thyroiditis	4	1 (25)	2 (25)	1 (25)	-	4 (100)	-	-	-	-	2 (50)	2 (50)	-	4 (100)	-	-	-
Specificity		94.2%				100%				84.6%				98,1%			

*PCa = Papillary carcinoma; PCa PV = Papillary carcinoma papillary variant; PCaFV = Papillary carcinoma follicular variant; FCa = Follicular carci noma

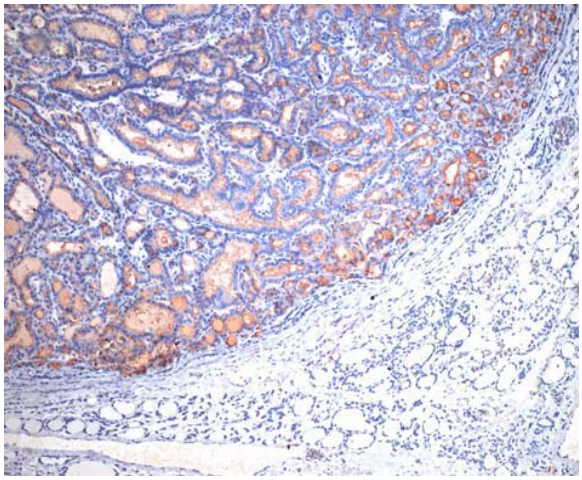

Figure 1. Strong membranous staining in follicular variant of papillary carcinoma with HBME-1.Normal thyroid tissue is not showing staining (Right lower corner). (Avidin-biotin peroxidase x 125)

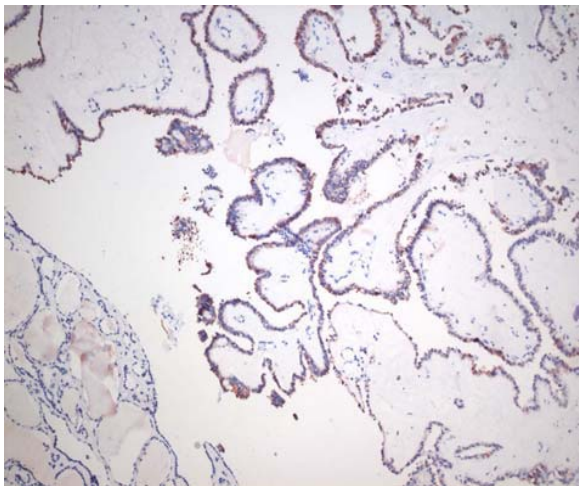

Figure 2. Cytoplasmic staining in papillary variant of papillary carcinoma with CK-19 .Normal thyroid tissue is not showing staining(Left lower corner). (Avidin-biotin peroxidase x 125)

3. Results

Among 60 specimens of papillary cancer, 45 were of women, 15 were of men (mean age: 43, range: 18-70). Thirtyseven were papillary and 23 were follicular variant. The staining pattern was cytoplasmic with CK-19, membranous with HBME-1 and EMA, and cytoplasmic or sometimes nuclear with S-100.

HBME-1 showed strong staining in 12 of 37 papillary variants, moderate staining in 21 and weak staining in four cases. Follicular variants were strongly positive in three out of 27 cases (Figure 1), moderately positive in 13, weakly positive in one and negative in one another.

CK-19 showed strong staining in 32 of the papillary variants (Figure 2), moderate staining in five. Follicular variants were strongly positive in three out of 27 cases, moderately positive in 13, weakly positive in one and negative in one another.

EMA showed strong staining in nine of the papillary variants, moderate staining in 14 and weak staining in 14 cases. Follicular variants were strongly positive in one, moderately positive in six, weakly positive in 16.

S-100 showed strong staining in three of the papillary variants, moderate staining in 11, weak staining in 12 and negative in seven cases. Follicular variants were strongly positive in three cases, moderately positive in eight, weakly positive in four and negative in eight.

Among 52 control cases, 25 were nodular hyperplasia, 12 were follicular adenoma, six were Graves, four were Hashimoto thyroiditis and five were follicular carcinoma.

In CK-19 staining, 10 of 25 cases of nodular hyperplasia showed weak staining. EMA was weakly positive in four and moderately positive in five. With S-100, three cases were weakly positive. HBME-1 was negative in all of 25 cases of nodular hyperplasia.

CK-19 staining of 12 cases of follicular adenoma revealed weakly positive in four. With EMA, weak staining was present in six. S-100 was weakly positive in one, while none of 12 cases of follicular adenoma was stained with HBME-1.

Among six cases of Graves disease, two showed weak or moderate staining with EMA. S-100 and HBME-1 were negative in all cases. Among four cases of Hashimoto thyroditis, two were weakly and one moderately stained for CK-19. S-100 and HBME were negative for all four cases.

There were five cases of follicular carcinoma, two of which were weak and one was moderately stained for CK-19. EMA was weakly positive in two. S-100 was moderately stained in one. HBME was negative in all cases.

The staining rates of all cases were given in Table 1.

Staining rates of HBME-1, CK-19, EMA and S-100 were significantly higher in either papillary or follicular variants of papillary thyroid cancer compared to other pathologies (P <0.001 for all).

4. Discussion

Papillary carcinoma is diagnosed mainly by its histopathological features including typical papillary structures and more importantly nuclear changes like clear appearance with a marked nuclear membrane, nuclear grooving, intranuclear inclusions and nuclear overlapping. Psammoma bodies and hyaline bodies are other features of papillary carcinoma. However malignant or benign pathologies (e.g. follicular neoplasia, oncocytic neoplasia, hyperplastic nodules, autoimmune thyroid diseases) may mimic these morphologic changes (1-6).

Another diagnostic challenge is the absence of typical nuclear changes in some papillary carcinomas. Cystic variant of papillary carcinoma shows large edematous papillary structures lined by cells having nuclei with dispersed chromatin and flattened surface. Rarely clear appearance of nuclei may also diminish (1,7,8). Immunohistochemical techniques are uncommonly utilized in the differential diagnosis of papillary thyroid cancer. Strong EMA staining was suggested to be useful in differentiating papillary carcinoma from other lesions (1,9-11). In some studies, EMA positivity was correlated with the presence of metastasis (12).

In our study, moderate to strong staining was present in 50% of papillary cancer whereas it was only moderately positive in 14 of 52 control cases. The difference was significant (P <0.001) and it seems that EMA is a useful marker for the diagnosis of papillary thyroid carcinoma.

S-100 protein is expressed in follicular cells during thyroglobulin synthesis and the levels increase in case of hyperfunctioning (13). Several studies demonstrated usefulness of S-100 staining in thyroid papillary cancer, staining rates increasing as differentiation improves (1,9-11,13). Although positivity rate for S-100 was lower in our study compared to previous ones, it was still significantly higher in papillary carcinoma compared to other pathologies.

CK-19 staining was reported to be a good marker for papillary cancer, especially in papillary variants (14,15). However one study demonstrated strong positivity in follicular carcinomas and denied the value of CK-19 in papillary carcinoma. In our study CK-19 was positive in all cases of papillary carcinoma, mostly in moderate or strong degree (88.3%). Only three (%5.7) cases were stained moderately with CK-19; the difference being significant (P <0.001).

HBME-1 is a mesothelial cell marker which was shown to be present in thyroid tumors of follicular cell origin. Positivity rates differ from 45% to 100% in previous series (15,16). In our study, almost all cases stained positive with HBME-1, mostly being moderate to strong (90%).

The moderate to strong staining with the markers were ranked as 90% with HBME-1, 88.3% with CK-19, 50% with EMA and 48.4% with S-100. Specificities of the markers for papillary cancer were ranked as 100% with HBME-1, 98.1% with S-100, 94.2% for CK-19, 84.6% with EMA when moderate to strong staining was considered. High sensitivity and specificity of HBME-1 makes it a good marker for the diagnosis of papillary thyroid cancer.

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