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Original contribution

Galectin-3 is highly expressed in nonencapsulated papillary thyroid carcinoma but weakly expressed in encapsulated type; comparison with Hector Battifora mesothelial cell 1 immunoreactivity

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Summary The histologic diagnosis of the follicular variant of papillary thyroid carcinoma (FVPTC) may be troublesome, especially in its encapsulated form. We evaluated the expression of galectin-3 (gal-3) and Hector Battifora mesothelial cell (HBME-1) in 200 formalin-fixed thyroid tissues with diagnosis of classical variant of papillary thyroid carcinoma or FVPTC, encapsulated or with infiltrative growth, with or without lymph node metastasis. All cases of classical variant of papillary thyroid carcinoma were consistently positive for gal-3; similar results have been obtained by using HBME-1. Interestingly, the invasive type of FVPTC, with or without metastasis, was strongly positive for gal-3 (78.2% and 96%, respectively), whereas only 46.8% of encapsulated FVPTCs without metastasis showed immunostaining for this marker. In the latter group, the HBME-1 expression achieved a significantly higher percentage of positivity (87%). Surprisingly, gal-3 immunodetection showed negative results in 4 encapsulated FVPTCs, despite the strong immunoreactivity in corresponding metastasis. Our data suggest that gal-3 immunodetection alone is not able to support the diagnosis of encapsulated FVPTCs.

1. Introduction

The follicular variant of papillary thyroid carcinoma (FVPTC) is a distinctive variant of well-differentiated papillary thyroid carcinoma (PTC) characterized by follicular architecture and a distinctive set of cytological findings classically associated with papillary carcinoma (ie, ground glass nuclei, nuclear overlapping, nuclear enlargement, irregularity of the nuclear contours, including nuclear pseudoinclusions and nuclear grooves) [1-4]. Supportive features for the diagnosis may be the presence of an invasive pattern of growth and desmoplastic response at

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invasive areas, whereas psammoma bodies are seen occasionally [2,3]. Two distinct entities of FVPTC include the diffuse type, with invasive behavior, and the encapsulated type, characterized by the presence of a distinctive capsule around the lesion [5]. The incidence of FVPTC is difficult to determine by reason of its variable morphologic spectrum. Some of these carcinomas may be underdiagnosed as benign follicular nodule if the characteristic nuclear features are not widely spread throughout the lesion, or misdiagnosed as follicular carcinoma, in presence of capsular and/or vascular invasion [6,7]. This may lead to problems in the management of patients with these lesions [8]. Recently, some authors have proposed the label of "well differentiated tumor of uncertain malignant potential" in presence of questionable papillary-type nuclear features and questionable capsular and/or vascular penetration [9]. The presence of cytological atypia may raise the possibility of papillary carcinoma, but this alone is not enough to formulate an unequivocal diagnosis. In such cases, ancillary supports may be very helpful [10,11]. Several immunohistochemical markers of malignancy have been claimed to be useful to differentiate between malignant and benign thyroid lesions, such as galectin-3 (gal-3) and Hector Battifora mesothelial cell (HBME-1) [12-20]. Gal-3, a nonintegrin β-galactoside–binding lectin, seems to carry out multiple functions, including cell-cell and cell-matrix adhesion, cell growth regulation, apoptosis, cell repair processes, malignant transformation, and progression in certain types of tissues and cells [21]. This protein is also expressed by macrophages, mast cells, and Langherans cells [22]. Various reports in the literature have discussed how some types of invasive neoplasms (ie, colorectal carcinoma) show an enhanced expression of gal-3 when compared with their counterparts at earlier stages [23]. This may suggest that gal-3 expression has a strong connection with malignant phenotype. This marker was also considered as a potential tool in the differential diagnosis of the follicular-patterned lesions of the thyroid [12,14]. HBME-1 is a monoclonal antibody obtained using a suspension of cells from an epithelial mesothelioma as immunogen [24]. The antibody recognizes an undetermined antigen, abundant on the surface of normal and neoplastic mesothelial cells [25]. Immunostaining often shows a characteristic "thick brush border," a pattern which correlates with the presence of long and abundant microvilli [18,25]. Using HBME-1, Miettinen and Karkkainen [25] reported that thyroid papillary and follicular carcinomas have strong and uniform immunoreactivity, whereas normal thyroid, nodular goiter, and follicular adenoma do not, or show only weak and focal staining. The authors suggested that HBME-1 could be useful in the evaluation of thyroid lesions.

The present study was designed to evaluate the expression of gal-3 and HBME-1 in a series of well-differentiated PTCs with a follicular or classical architecture, encapsulated or not encapsulated, with or without lymph node metastasis.

2. Materials and methods

2.1. Tissue specimens

Ten percent of formalin-fixed, paraffin-embedded blocks, routinely prepared from surgical specimens of 200 cases of thyroid papillary carcinomas, were selected for this study. Normal thyroid parenchyma was observed at the periphery of the tumor in all cases. One hundred thirty-eight thyroid lesions were diagnosed as FVPTC, consisting of 62 encapsulated without metastasis and 46 with neither capsule nor metastasis, whereas the FVPTCs with lymph node metastasis consisted of 26 without capsule and only 4 encapsulated (Fig. 1A and B). The 62 cases diagnosed as classical variant of PTC (CVPTC) consisted of 17 encapsulated without metastasis, 19 without capsule nor metastasis, 22 without capsule but with lymph node metastasis, and only 4 encapsulated with lymph node metastasis.

2.2. Immunohistochemistry

Tissue sections 5 μm thick were deparaffinized in xylene and rehydrated in a graded ethanol series. Slides were stained using a diaminobenzidine detection system preceded, only for gal-3, by heat-induced epitope retrieval involving immersion of tissue sections in a prewarmed buffer solution (Target Retrieval Solution, DakoCytomation, Carpinteria, CA) and maintaining heat in a steamer at 98°C for 50 minutes. To reduce nonspecific staining caused by endogenous biotin, the Endogenous Biotin Blocking Kit (Ventana Medical Systems, SA, Illkirch, Cedex, France) was used. Immunostaining for gal-3 and HBME-1 was performed using monoclonal antibodies, diluted 1:100, provided by Novocastra (Newcastle, UK)

Notes to Fig. 1 Histology and gal-3 and HBME-1 expression in a case of encapsulated follicular variant of PTC and its corresponding lymph node metastasis. A, Low-power view showing a distinctly fibrous capsule around the neoplastic lesion (H&E, original magnification ×1.5). Inset, high-power view showing the nuclear features of papillary carcinoma (H&E, original magnification ×40). B, Low-power magnification of a regional lymph node metastasis by the same case of follicular variant of papillary carcinoma (H&E, original magnification ×1.5). C, Absence of gal-3 immunoreactivity in the neoplastic cells. There are some gal-3–positive macrophages and fibroblasts (hematoxylin counterstain, original magnification ×20). D, In the lymph node, all metastatic papillary carcinoma cells strongly expressed gal-3 in the cytoplasm. Some macrophages in a germinal center and a few endothelial cells showed gal-3 expression (hematoxylin counterstain, original magnification ×20). E, Diffuse and strong cell membrane immunoreactivity to HBME-1 in the primary tumor (hematoxylin counterstain, original magnification ×20). F, Diffuse and strong HBME-1 positivity in the metastatic neoplastic cells (hematoxylin counterstain, original magnification ×20). Abbreviation: H&E, hematoxylin and eosin.