The application of Hector Battifora Mesothelial-1, CITED-1 and Fibronectin-1 in differential diagnosis of thyroid follicular neoplasms.

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Abstract: Background: The differentiation of benign from malignant follicular thyroid neoplasms remains difficult and some controversial results have been reported for the immunohistochemical markers of malignancy proposed so far. Nodular tumors exhibiting a predominantly follicular architecture are the most common presenting and confusing pattern of thyroid neoplasms. They can be benign as follicular adenoma (FA) or malignant as papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy. **Material and methods:** This study was carried out on 176 thyroid specimens received as paraffin blocks (84 FA, 50 PTC and 42 FTC) using three markers HBME-1, CITED-1 and FN-1. **Results:** All three markers combined were positive in 23 malignant cases with no combined positivity in the benign cases. CITED-1 was positively expressed in 65 malignant thyroid lesions (50 PTC and 15 FTC). HBME-1 was positive in 58 malignant cases (46 PTC and 12 FTC). FN-1 was positive in 52 malignant cases (46 PTC and 6 FTC). At least for 2 positive markers, regardless of which two, the sensitivity for the detection of malignancy was 58.7% with 100% specificity while single marker immunoreactivity increased sensitivity but markedly reduced specificity. CITED-1, HBME-1 and FN-1 expression was statistically significant in PTC cases than their expression in FTC. **Conclusions:** A panel of HBME-1, CITED-1 and FN-1 can be a useful tool for differentiation between benign and malignant follicular thyroid neoplasms and probable distinguishing of PTC from FTC.
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1. Introduction:

Thyroid nodules are common condition, few of them turn out to be malignant. Their prognosis and management depends on the diagnosis. The current diagnostic gold standard is pathologic evaluation using routine hematoxylin and eosin (H&E) stains. However, the distinction by conventional histopathology between benign and malignant neoplastic lesions is often difficult as morphologic similarities are frequent, and follicular and papillary architectures may be seen in both benign and malignant lesions. Several critical features of malignancy, for example, pale nuclei for papillary thyroid carcinoma are open to subjective interpretations, and interobserver disagreements among pathologists are well documented [1].

Nodular tumors exhibiting a predominantly follicular architecture are the most common type of lesion of the thyroid. These nodular lesions can be benign as follicular adenoma (FA) or malignant as papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy. However, the follicular variant of PTC (PTCFV) often poses a diagnostic challenge in which the differential diagnosis includes other follicular patterned lesions such as follicular adenoma (FA) and follicular carcinoma. The distinction between these lesions is important because prognosis and management differ. Because PTCFV is diagnosed almost solely based on subjective cytologic criteria (nuclear grooves, nuclear clearing, nuclear overlap, and intranuclear pseudoinclusions) [2], it is not surprising that disagreements in the diagnosis of PTC have underscored the interobserver variability in the evaluation of these lesions [3]. As the diagnostic decision favouring one or another has clinical consequences and implies different modalities of treatment, many studies have focused on the identification of protein markers to improve the differential diagnosis of thyroid lesions using immunohistochemistery [4-7].

Hector battifora mesothelial-1 (HBME1) is a monoclonal antibody to an unelucidated membrane antigen found in the microvilli of mesothelial cells, normal tracheal epithelium, and adenocarcinoma of the lung, pancreas, and breast [8]. Its usefulness as a marker of thyroid malignancy in fine-needle aspiration and tissue specimens has been demonstrated in several studies, showing diffuse strong staining in the majority of PTCs [9-12]. However these results still controversial and in need of more studies to assess its diagnostic usefulness and accuracy.

CITED-1 protein belongs to a family of nuclear proteins presumably involved in the regulation of transcription factors [3]. Of the limited studies designed to address the diagnostic usefulness of this protein, CITED1 was shown to be promising in the distinction of PTC from benign thyroid lesions. However, the results of these studies have been suboptimal [1,13].

Fibronectin-1 (FN-1) is an antibody against multifunctional adhesive glycoproteins found in the extracellular matrix and body fluids. They have affinity for collagen, fibrin, heparin, and cell surfaces and are involved in various biologic processes including cell adhesion, migration, and tumor progression. It appears to play diverse biological roles in cellular adhesion, cellular morphology, cell spreading, cell migration, phagocytosis, oncogenic transformation and probably others. In neoplastic tissues, the function of FN has been increasingly implicated in cellular adhesion and metastasis [14]. Fibronectin emerged as a potential marker of thyroid carcinoma in microarray studies in which it was reported to be up-regulated compared with normal tissue [15,16]. Therefore, the identification of markers to unequivocally differentiate between benign and malignant tumors is critical to avoid unnecessary surgery.

In view of this, our study offered a combined approach using a panel of HBME-1, CITED-1 and FN1 to investigate their diagnostic usefulness in differential diagnosis of benign and malignant thyroid neoplasms.

2. Material and methods:

We studied 176 thyroid specimens diagnosed by two pathologists as follows: 84benign thyroid nodules diagnosed as follicular adenomas (FA) and 92 malignant nodules (50 PTC and 42 FTC). Samples were collected as formalin-fixed, paraffin-embedded tissue blocks, with H&E stained slides from the archive of the pathology department of faculty of medicine, Tanta university and private labs. Immunohistochemistry was performed using the immunoperxoidase method on 4-m-thick sections from formalin-fixed, paraffin-embedded blocks. Pretreated sections were incubated with mouse monoclonal HBME-1 antibody (1:50, Thermo Scientific, Egypt). HBME-1 staining pattern is cytoplasmic and membranous. [17]. CITED-1 rabbit polyclonal antibody (1.0 µg/mL., Thermo Scientific, Egypt) was also applied to the sections. CITED-1 staining pattern is cytoplasmic and nuclear [1]. In addition, FN-1 a mouse polyclonal antibody (Thermo Scientific, Egypt) is applied to the same sections. Staining of FN-1 is cytoplasmic [18]. The degree of immunostaining for all three antibodies was scored according to the proportion of positively stained tumor cells and the intensity of staining. Tumor cell proportion was classified as follows: 0% (negative), 5-29% (weak), 30-69% (moderate), and 70-100% (strong) HBME-1 -positive tumor cells. Staining intensity was classified as none (0), weak (1), moderate (2) and strong staining (3). For all antibodies, the antigen retrieval (PBS buffer; pH 7.4) was done for all sections and were incubated with the primary antibody for 2 h at room temperature. The sections were incubated with secondary antibody (HRP-Rabbit/Mouse) for 15 min at room temperature. A case of PTC positive for all 3 antibodies served as the positive control, and appropriate negative control procedure also was run in parallel, a section was processed in which the primary antibody was changed by PBS. Immunohistochemical staining was evaluated independently by two pathologists.

Data were described as number and percentage. Sensitivity was calculated as the proportion of affected biopsies resulting in positive tests. Specificity was calculated as the proportion of unaffected biopsies resulting in negative tests. Positive predictive value was calculated as the proportion of positive tests that correctly identified affected biopsies. Negative predictive value was calculated as the proportion of negative tests that correctly identified unaffected biopsies. Accuracy was calculated as the proportion of correctly identified biopsies on the total of biopsies. Calculations were performed with Stata 10. Two-sided Fisher's exact test was used to determine statistical significance with level set at 0.05.

3. Results:

All three markers combined were positive in 23 malignant cases with no combined positivity in the benign cases. CITED-1 was positively expressed in 65 malignant thyroid lesions (50 PTC and 15 FTC) (Fig. 1,2,3). HBME-1 was positive in 58 malignant cases (46 PTC and 12 FTC) (Fig. 4,5). FN-1 was positive in 52 malignant cases (46 PTC and 6 FTC) (Fig. 6,7). At least 2 immunoreactive markers (+ + −), regardless of which two, were seen in 0/84 benign cases, in 54/92 malignant cases. The diagnostic accuracy of the panel is summarized in Table (1). When considering at least 2 positive markers (+ + −), regardless of which two, the sensitivity for the detection of malignancy was 58.7% with 100% specificity while, as expected, single marker immunoreactivity (+ − −) increased sensitivity (93.5%) but markedly reduced specificity (85.7%). When comparing the expression of the three studied markers in PTC and FTC, CITED-1, HBME-1 and FN-1 expression was statistically significant in PTC cases than their expression in FTC ($P<0.001$, $P<0.01$ and $P<0.001$ respectively) (Table 2).

Table (1): Immunohistochemical staining results of all three markers in benign and malignant thyroid cases and their diagnostic accuracy.

	Benign (n=84)	Malignant (n=92)	Sensitivity	Specificity	PPV	NPV	Accuracy
All 3 positive	0	23	25%	100%	100%	54.9%	60.8%
At least 2 positive	0	54	58.7%	100%	100%	68.9%	78.4%
At least 1 positive	12	86	93.5%	85.7%	87.7%	92.3%	89.8%
HBME1+CITED1	0	34	36.9%	100%	100%	59.2%	67%
HBME1+FN1	0	29	31.5%	100%	100%	57.1%	64.2%
CITED1+FN1	0	37	40.2%	100%	100%	60.4%	68.7%
CITED1 +	5	65	70.7%	94%	92.8%	74.5%	81.8%
HBME1 +	5	58	63%	93%	89.8%	62.2%	69.9%
FN1 +	2	52	56.5%	97.6%	96.4%	68.3%	77.3%

Table (2): Immunohistochemical expression of the three markers in PTC and FTC cases.

Protein	PTC (n=50)	FTC (n=42)	P-value
CITED-1	50 (100%)	15 (35.7%)	< 0.001
HBME-1	46 (92%)	12 (28.6%)	< 0.01
FN-1	46 (92%)	6 (14.3%)	<0.001

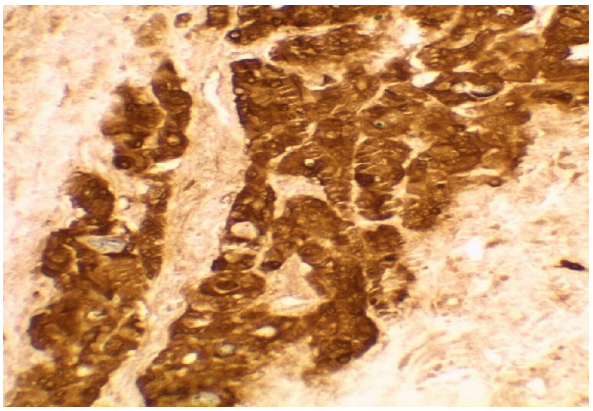

Fig.(1): Papillary thyroid carcinoma with strong cytoplasmic and nuclear expression of CITED-1 (X400).

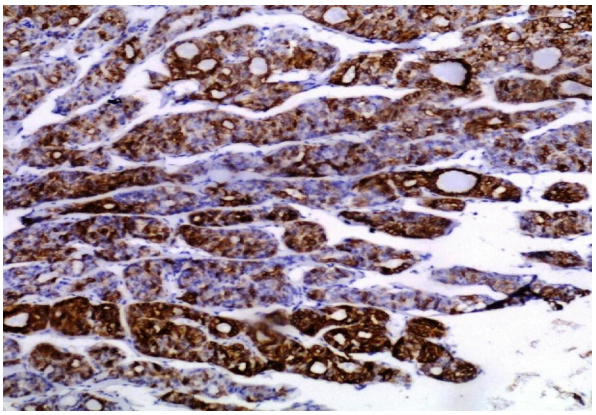

Fig.(3): Follicular thyroid carcinoma showing moderate cytoplasmic and nuclear expression for CITED-1 (X200)

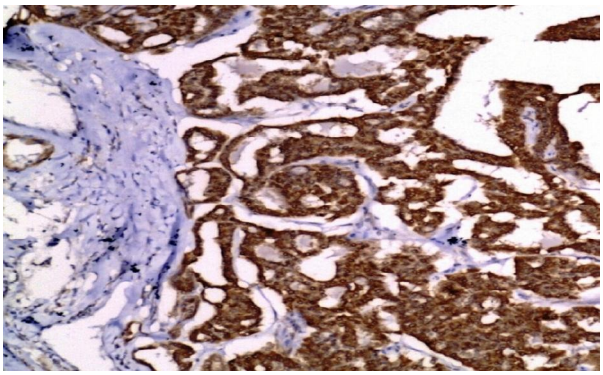

Fig. (2): Follicular variant of papillary thyroid carcinoma showing moderate positive cytoplasmic and nuclear expression of CITED-1 (X100).

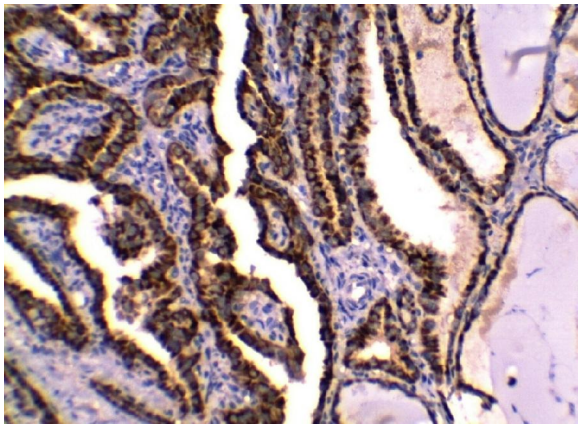

Fig. (4): Papillary thyroid carcinoma showing positive strong cytoplasmic immunoexpression of HBME-1 (X400).

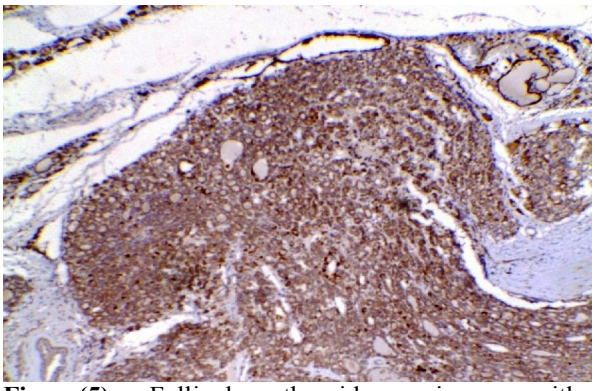

Fig. (5): Follicular thyroid carcinoma with mushroom capsular invasion showing HBME-1 positive immunostaining (X40).

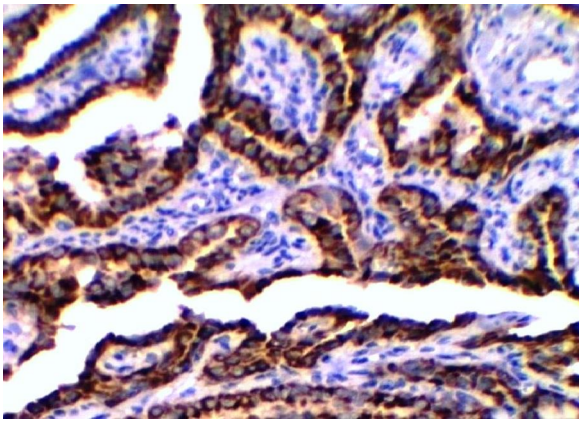

Fig.(6): Papillary thyroid carcinoma showing positive cytoplasmic FN-1 expression (X400)

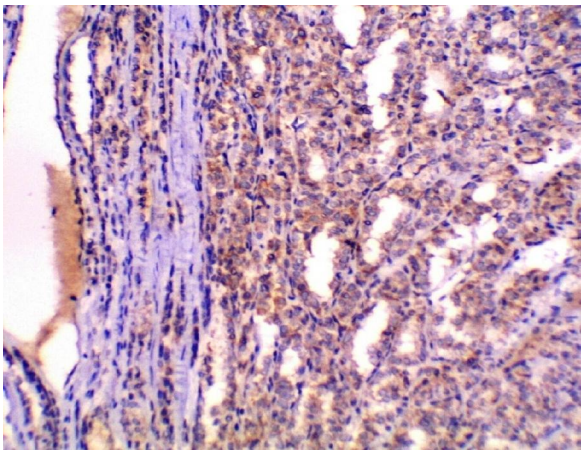

Fig.(7): Follicular thyroid carcinoma with capsular invasion showing strong cytoplasmic expression of FN-1 (X200).

4. Discussion:

In our study, we reported CITED-1, HBME-1 and FN-1 immunohistochemical expression in benign and malignant thyroid neoplasms. All three markers showed high sensitivity, specificity and diagnostic accuracy especially with combination of two markers. There were significant difference in expression between the studied PTC and FTC cases.

In approval with our results, Prasad *et al.*, found that the expression of FN-1, CITED1 and HBME1 in malignant tumors was diffuse, while in benign tumors and non-neoplastic thyroid tissues, there was no expression or focal expression, usually in less than a third of the tumor cells [1]. In 2008, Liu *et al.* also found that malignant tumors showed overexpression of FN-1 (all carcinomas), HBME-1 (mostly PTC and FTC). The most prominent differences were observed in PTC in comparison with benign lesions and adjacent normal thyroid tissues. PTC showed high expression levels of FN-1, HBME-1 and CITED-1. In the comparison between FTC and PTCFV, the only differentially expressed protein was HBME-1. PTCFV differed from FA for FN-1 and HBME-1 [18].

Scognamiglio *et al.,* also stated that positive immunostaining was observed in a higher percentage of PTCs than in FAs for HBME-1 and CITED-1 [3]. Also in 2006, Barroeta *et al.,* confirmed that HBME-1 was the most specific marker for thyroid malignancy as HMBE-1 was expressed in 70% of malignant and 10% of benign follicular derived lesions of thyroid (*P* value: <0.0001) [19]. This was the same results reached by Park *et al.,* in 2007. The overexpression of HBME-1 was significantly associated with differentiated thyroid carcinomas ($P<0.001$) and all the benign cases showed no expression of HBME-1 [20].

Another study done by Mataraci *et al.,* reported a statistically significant difference ($P < 0.05$) between malignant and benign lesions according to percentage of staining and intensity of staining with HBME-1. The percentage and intensity of staining were higher in malignant lesions. Diffuse and strong staining was observed in papillary carcinoma. HBME-1 in combination with other immunohistochemical markers as galectin-3 and CK19 were found to be useful for differentiation of the follicular variant of papillary carcinoma from follicular adenoma and follicular carcinoma, and in the differentiation of follicular adenoma from follicular carcinoma [17].

In the same year, Paunovic *et al.,* Suggested that Galectin-3 and HBME-1 could be used as single discriminators between follicular thyroid adenoma and carcinoma, but HBME-1 is the better choice. As a single test, all analyzed tumor markers had

sufficient power to predict differentiated thyroid cancer, with sensitivities ranging from 66.5% to 82.2%. The sensitivity was improved by using combinations of some proposed markers. Only two antigens, HBME-1 and Thyroid peroxidase (TPO), had distinct predictive values for different diagnostic alternatives i.e. a sequential combination improved diagnostic accuracy between follicular thyroid adenoma and the follicular variant of papillary thyroid carcinoma to 92.6% and consequently, between overall benign and malignant thyroid tumors to 89.1%. HBME-1 is the most accurate ancillary stain in discriminating well-differentiated thyroid carcinomas from benign tumors, although the addition of TPO did improve accuracy and served as a useful confirmatory marker [21].

Wu *et al.,* supported the previous studies as they found that the percentages of samples from PTC specimens with cells that demonstrated weak to strong staining for HBME-1 with other markers were significantly higher than the percentages that demonstrated such staining from patients with benign thyroid nodules (all P<001). When considered individually, HBME-1 was the most specific (97.9%) [22]. In 2014, Atik *et al.,* observed that papillary carcinoma demonstrates more intense and diffuse positive staining for HBME-1 which could help for differential diagnosis of these lesions, while there was negativity in FVTPCs (25%) as well as in follicular adenomas (75%) for FN-1. Even those cases that were positive for FN-1 demonstrated weak and focal staining, there was significant background staining which impairs the diagnostic utility of fibronectin [23].

Recently, Liu & Lin reported that in normal thyroid tissue, there was virtually no expression of HBME-1. Overexpression of HBME-1 was demonstrated in malignant thyroid neoplasms, especially PTCs. The overall sensitivity of HBME-1 was 78.8% for thyroid malignancy, 87.3% for PTC, and 65.2% for FTC. The specificity was 82.1%. Expression of HBME-1 was also noted in benign thyroid lesions such as FA but usually in a focal staining fashion, with a reported overall positive rate of 26% [8]. Many other studies have emphasized on the great practical value of overexpression of HBME-1, solely or in combination with other markers, in malignant thyroid tumors when compared to benign ones [24-26].

Interestingly, Barut *et al.,* showed different results as they found that focal HBME-1 expression may be encountered in benign lesions and diffuse positive reaction is characteristic of malignant lesions. They concluded that HBME-1 alone and its combinations with other markers were more sensitive in accurate diagnosis of follicular carcinoma than the other combinations [27].

On the other hand, several studies have focused on determining the efficacy of CITED-1 in the differential diagnosis of benign and malignant thyroid follicular neoplasms. The results of one study done by Huang *et al.,* suggested a remarkable PTC specificity in that the CITED-1 protein was found in 39/42 PTC, 0/6 follicular thyroid carcinoma [15]. Aldred *et al.,* as well, found that CITED-1 which was previously found to be overexpressed in PTCs compared with normal thyroid, was also called present in two or three of the nine tested FTCs [16]. Later in 2011, Lloyd *et al.,* stated that CITED1 can assist in separating some difficult cases of follicular variants of papillary thyroid carcinomas from follicular adenomas [28].

Regarding studies concerned with FN-1 immunoexpression, Wasenius *et al.,* reported that FN-1 was expressed in 81% of the studied cases. All samples consisting of histologically normal thyroid tissue stained only weakly or not at all [4]. These results were in agreement with the results of our study and other studies as well [1,18].

Conclusion:

A panel of HBME-1, CITED-1 and FN-1 can be a useful tool for accurate diagnosis and differentiation between benign and malignant follicular thyroid neoplasms and probable distinguishing of PTC especially the follicular variant from FTC. More studies are needed for the confirmation of the usefulness and accuracy of these markers.

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