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Original Article

# Utility of immunohistochemical markers in differential diagnosis of follicular cell-derived thyroid lesions

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ABSTRACT

*Background:* Differentiating the different follicular derived lesions from each other can be challenging. Although immunohistochemistry is generally accepted as a useful ancillary technique in the diagnosis, controversy exists regarding the best marker or combination of markers to distinguish each lesion from its mimics. In this study, we aimed at evaluating multiple markers to compare their sensitivity and usefulness, and to find out if a combination of the evaluated markers can be of additional value in discriminating thyroid lesions.
*Methods:* The study included two groups of follicular derived thyroid lesions. Immunohistochemical evaluation of CD56, HBME-1, Gaectin-3 and CK19 was done for the two groups. The sensitivity and the specificity for each marker and their combination in the diagnosis were calculated.
*Results:* Each studied marker was sensitive and specific for certain thyroid lesion but the sensitivity and the specificity were increased when two or more markers from the panel were used together.
*Conclusions:* Although no single immunohistochemical marker by itself is completely sensitive and specific for follicular thyroid lesions, the combination of CD56, HBME-1, Gaectin-3 and CK19 attains high sensitivity and specificity in differentiating follicular derived thyroid lesions.


## 1. Introduction

Follicular derived thyroid disease refers to the presence of a benign or malignant solid nodule, a multinodular gland, Grave's disease, or thyroiditis. The microscopic distinction by conventional histology between benign and malignant lesions may be difficult [1,2]. Most of the discovered nodules are benign. More than 80% of the malignancies present in palpable thyroid nodules are papillary thyroid carcinoma (PTC) followed by follicular carcinoma (FC) [3–5].

The "gold standard" in diagnosis of thyroid nodules is pathologic evaluation using routine hematoxylin and eosin (H&E) staining. However, morphologic overlap between follicular lesions especially the follicular variant of papillary carcinoma (FVPC) is common which is characterized by an almost exclusive follicular growth pattern and a set of nuclear features identical to those of the classic type of PTC [6,7]. Diagnostic dilemma may arise when an encapsulated nodule with a follicular pattern of growth exhibits clear nuclei with grooves and so distinguishing

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follicular adenoma (FA) from encapsulated FVPTC becomes difficult. There are several other thyroid lesions that may contain papillary processes with nuclear features, which pose diagnostic difficulties with PTC [8]. Multinodular goiter (MNG) with delicate papillary budding and focal nuclear clearing may be confused with PTC [9,10]. Also a new category emerged that was named Follicular Neoplasm/atypical cells of undetermined significance (AUS). This category accounts for 10–25% of all cases and represents a therapeutic problem because of the low risk of malignancy [2].

A growing number of some promising immunohistochemical (IHC) markers for the differential diagnosis of thyroid lesions have emerged, including CD56, Hector Battifora mesothelial (HBME-1), galectin-3 (Gal-3) and CK19 but till now none of them are conclusive [5,7].

CD56 is a neural cell adhesion molecule. Its expression may affect the migratory capability of tumor cells. Hence it is not surprising that loss of CD56 correlates with metastatic potentials and poor prognostic outcome in some malignancies [7]. It has been reported to be expressed in normal thyroid follicular cells with frequent low expression in malignant thyroid tumors especially PTC [10].

HBME-1 is an antigen on the surface of mesothelial cells. In thyroid neoplasms, Husain et al. [11] study showed that HBME-1 was positive in PTC and FC. However, none of them have shown a diagnostic accuracy sufficient for using a single antibody in the diagnosis of malignant thyroid neoplasms. Besides, no studies have been performed to determine whether HBME-1 is a useful diagnostic tool for distinguishing FA or Follicular Neoplasm/atypical cells of undetermined significance (AUS) [12].

Galectin-3 is a component of the β-galactoside binding lectins whose function is still unclear. It appears to be involved in the cell–cell and cell–matrix modulation. Therefore, it could play a role in the malignant transformation of thyroid cells and it is expressed in a high proportion of carcinomas, especially of the papillary type [11]. Recently, galectin-3 is initially shown to have utility in the differential diagnosis between benign and malignant thyroid lesions [2]. But some recent studies suggest that it is not reliable [4,9,12].

Cytokeratin 19 (CK19) is a type I intermediate filament protein and is widely present in simple epithelial cells [7]. Several studies demonstrated strong and diffuse positivity in malignant thyroid tumors; however, it is not specific to malignancy [3,11]. Several studies have shown conflicting results regarding the usefulness of CK19 as a diagnostic marker in thyroid lesions [7,13].

Most studies have evaluated the single expression of markers in various thyroid lesions and a few reports have studied the combined expression of markers [14,15]. Therefore, in this study, we evaluated the usefulness of using a panel of four markers (CD56, Gal-3, HBME-1, and CK-19) individually and in combination and their diagnostic value, in various follicular derived thyroid lesions. Our aim was to identify the diagnostic role of these markers in the follicular morphological mimics to determine their sensitivity and specificity in differential diagnosis of thyroid nodules.

**Table 1**
The distribution of the studied cases.

| | | |
|---|---|---|
| Studied cases | | |
| Normal ($n=10$) | | |
| Lesions ($n=70$) | First group ($n=20$) | Grave's disease ($n=4$) |
| | | MNG ($n=5$) |
| | | Hashimoto's thyroiditis ($n=4$) |
| | | FA ($n=7$) |
| | Second group ($n=50$) | PTC ($n=22$) |
| | | FTC ($n=15$) |
| | | WDTs-UMP ($n=7$) |
| | | FT-UMP ($n=6$) |

## 2. Materials and methods

### 2.1. Tissue specimens

Thyroid gland lesions from January 2009 to January 2013 were searched through the database charts at the pathology department of Tanta University Hospital. Demographic information, gender, type of surgery, clinical data, tumor stage, treatment, tumor recurrence and follow up were reviewed. The study included 25 male and 45 female patients with a median age of 32.5 years (range 13–78 years). The material of this retrospective study included 70 specimens of surgically removed, formalin-fixed and paraffin embedded thyroid lesions. Furthermore, another 10 samples of randomly chosen normal thyroid tissue obtained from radical laryngectomies for laryngeal carcinomas were included. This study was approved by the ethical committee of the hospital. The tissue processing and the general histological report were performed as described previously by Ozolins et al. [16]. The diagnosis and typing of thyroid pathology were performed according to the World Health Organization Classification [17].

For simplicity and practical clinical considerations, the 70 selected thyroid lesions were divided into two groups: benign (including nonneoplastic and neoplastic) and malignant. The first benign group (20 cases) included 4 Grave's disease cases; 5 MNG cases; 4 Hashimoto's cases and 7 FA cases, while the malignant group (50 cases) had inclusion criteria as follows: differentiated thyroid cancer originating from follicular epithelial cells except a Hürthle cell variant. This included 22 PTC cases; 15 FTC cases; 7 cases of well differentiated tumors of unknown malignant potential (WDTs-UMP) and 6 cases of follicular tumor of unknown malignant potential (FT-UMP). The 22 PTC cases were further classified into 14 cases of classic PTC and 8 cases of FVPCs (Table 1).

For the diagnosis of FA, they were defined as completely encapsulated follicular tumors with homogeneous architecture and morphology, without capsular and vascular invasion [7]. While for PTC we followed the histological criteria proposed by Chan [18], which are divided into major and minor features. The major features include: (1) nuclei are ovoid; (2) nuclei are crowded; (3) nuclei show a clear chromatin; and (4) psammoma bodies are found. If one of the four features was lacking, four or more of the following features may occur: (1) presence of abortive papillae; (2) irregular shaped follicles; (3) dark colloid; (4)