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Diagnostic Utility of Immunohistochemical Markers Trop2 and CD56 in Differentiating Follicular Derived Thyroid Lesions

Samar M Abdel Raouf[1]*, H Atia[2], Sameh Abdelazeem Soliman[2], Tamer Mohamed Elshahidy[3] and Salem Youssef Mohamed[2]

[1]Department of Pathology, Faculty of Medicine, Zagazig University, Egypt
[2]Department of Internal Medicine, Faculty of Medicine, Zagazig University, Egypt
[3]Department of General surgery, Faculty of Medicine, Zagazig University, Egypt

Abstract

Background: Thyroid cancer is the most common malignant endocrine neoplasm worldwide. Diagnostic conflicts may occur regarding follicular derived thyroid lesions; therefore there is an increasing demand for using markers that help in attaining correct diagnosis. Trop2 is a trans membrane glycoprotein present in various epithelial malignancies. CD56 is a neural cell adhesion molecule that is expressed in the normal follicular epithelium of the thyroid gland.

Aim: To evaluate the diagnostic utility of immunohistochemical markers (Trop2 and CD56) in differentiating follicular derived thyroid lesions in Egyptian patients.

Materials and methods: Expression of Trop2 and CD56 was evaluated immunohistochemically in 71 cases of follicular derived thyroid lesions; 35 benign lesions (10 cases nodular goitre (NG), 5 cases Graves' disease and 20 cases follicular adenoma (FA)), 36 malignant cases (23 classic papillary thyroid carcinoma (PTC), 9 follicular variant papillary carcinoma (FVPC) and 4 cases of follicular carcinoma (FC)).

Results: Expression of Trop2 and CD56 loss revealed 80.5% and 83.3% sensitivity and 97.1% and 91.4% specificity respectively for differentiating malignant from benign follicular derived thyroid lesions while these markers showed 90.6% and 84.4% sensitivity and 97.4% and 84.6% specificity respectively in PTC versus all other studied lesions.

Conclusion: Trop2 and CD56 are valuable in the differentiation between benign and malignant follicular derived thyroid lesions with good sensitivity and specificity, while Trop2 is better in the distinction of PTC from other lesions. All PTC cases revealed either Trop2 positivity or CD56 loss raising the sensitivity to 100%.

Keywords: Thyroid lesions; Follicular lesions; Trop2; CD56; Immunohistochemistry

Correspondence to: Samar M Abdel Raouf, Department of Pathology, Faculty of Medicine, Zagazig University, Zagazig, Egypt, Tel: +20-1091505471; E-mail: samar.foda75@yahoo.com

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Introduction

Thyroid cancer is the commonest endocrine malignancy worldwide and one of the most rapidly increasing cancer in the United States. Nearly 52070 new cases of thyroid cancer were reported in the United States in 2019, this represents 3% of all new cancer cases [1]. In Egypt, thyroid cancer accounts for 2.6% of all malignant neoplasms and 80.3% of endocrine tumors [2]. It represents 3.6% of total female malignancy and is considered the fifth most common cancer in women, according to the National Cancer Registry Program. The approximate number of cancer thyroid in Egypt was 2448 cases in 2015 [3]. Differentiating thyroid lesions may be problematic in some cases due to overlapping morphologic features, also distinguishing follicular lesions by fine-needle aspiration cytology is limited by the possibility of indeterminate cytologic diagnosis [4] Accurate pathological diagnosis is needed to prevent over-treatments and minimize related costs, immunohistochemical markers can help eliminate the conflict and reach a definitive diagnosis

(TROP-2) is a trans membrane glycoprotein, it is the protein product of TACSTD2 (tumor-associated calcium signal transducer gene family), It is involved in various signalling pathways, normally expressed in placenta and is overexpressed in human malignancies [4-6].

CD56 is a neural cell adhesion molecule that mediates cell-cell adhesion; it is expressed in neurons, numerous immune cells, and is constantly expressed in normal follicular epithelial cells of the thyroid gland. Previous studies have reported that the absence of this marker is related to malignant potentiality and metastasis of tumor cells [7,8].

Aim

To evaluate the diagnostic utility of immunohistochemical markers

(Trop2 and CD56) in differentiating follicular derived thyroid lesions in Egyptian patients.

Materials and Methods

Tissue preparation

This work was done in the pathology department in collaboration with the general surgery and internal medicine departments, faculty of medicine Zagazig University.

This retrospective study was performed in Zagazig University Hospitals during the period between May 2017 and May 2019. The immunohistochemistry was applied to paraffin-embedded thyroid lesions removed by surgical resection from seventy-one Egyptian patients operated in the General Surgery Department, Faculty of Medicine, Zagazig University, Egypt.

The cases were 35 benign lesions, 10 of them diagnosed as nodular goitre (NG), 5 cases of Graves' disease and 20 cases of follicular adenoma (FA). The malignant cases were 36 carcinomas, including 23 classic papillary thyroid carcinoma (PTC), 9 follicular variants papillary carcinoma (FVPC) and 4 cases of follicular carcinoma (FC). Cases with indefinite diagnosis or equivocal features were excluded from the study. Thyroid tumors were classified and evaluated according to 4th edition WHO Classification of tumors of Endocrine Organs in 2017 [9].

Ethical consideration

This study was performed with approval of ethics committee of our institution, (ZU-IRB: No 6029) and in accordance with the Helsinki Declaration of 1975 as revised in 2000 for studies involving humans [10]. Informed consent was obtained from all participants included in the study.

Immunohistochemical staining

The immunohistochemical staining procedure was applied on 4 micrometre thickness representative tissue sections. To remove paraffin-xylene solution absolute ethyl alcohol was used. Then the slides were washed in running water, dried and 1% hydrogen peroxide mixture was added. After 10 min methyl alcohol was put to the solution until reaching the boiling temperature, the slides were autoclaved at 100 C for 15 min then, they were cooled to room temperature. The sections were washed using a wash buffer. After that, tissue sections were incubated for an hour with anti-TROP-2 antibody (sc-376181, monoclonal, clone F-5; Santa Cruz Biotechnology, USA) using 1:40 dilution and anti-CD56-antibody (NCL-CD56-1B6, monoclonal; Novocastra) at dilution of 1: 300. Next, sections were washed twice using a buffer wash. After adding the DAB solution, the slides were washed again in buffer wash. After that, Mayer's hematoxylin was used as a counterstain.

Evaluation of Trop2 immunohistochemical stain

Regarding Trop2 expression, cases with absent staining or staining in less than 5% of cells were categorized as negative. Only membranous staining of more than 5% of the cells was recorded as positive: 1+ (5–25%), 2+ (26–50%), 3+ (51–75%), and 4+ (> 75%) [11].

Evaluation of CD56 immunohistochemical stain

The expression of CD56 was estimated as follows: regarding the percentage of positive tumor cells: 0, if staining in less than 10% of cells; 1+, staining in 10-25% of cells; 2+, staining in 26-50% of cells; 3+, staining in more than 50% of cells. A score of 0 was recorded as negative, and scores of 1- 3 were recorded as positive for CD56 [12].

Positive and negative control

Normal urothelium served as a positive control for Trop2 while CD56 positive control was represented by histocytes and macrophages. For negative control slides, we replaced the primary antibodies with phosphate-buffered saline (PBS).

Statistical analysis

Collected data were represented as number and percentage. A Chi-square test was used to compare the differences for statistical significance. $P<0.05$ was considered significant. For validity assessment of markers, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (DA) was used, considering histological diagnosis as the gold standard. The collected data were computerized and statistically analysed using (SPSS 22.0 for Windows; SPSS Inc. Chicago, Illinois, USA) and MedCalc windows (MedCalc Software bvba 13, Ostend, Belgium).

Results

Non neoplastic Lesions

Regarding Trop2 immunoexpression, none of the five cases of Graves' disease showed positive expression, also all the colloid goitre cases were negative for Trop2 (Table 1, Figures 1 and 2).

CD56 immunoexpression showed a 20% loss (one out of 5 cases), while all cases of colloid goitre showed preserved CD56 staining.

Benign neoplastic Lesions (FA)

As regards Trop2 expression one out of 20 (5% of follicular adenoma cases) showed positive expression while two cases (10%) showed CD56 loss.

Malignant neoplastic Lesions

Regarding Trop2 expression in papillary thyroid carcinoma, 21 cases (91.3% of classic PTC) were positive, and 8 cases (88.9% of FVPC)

Table 1: Immunohistochemical expression of Trop2 and CD56 in follicular derived thyroid lesions.

Diagnosis	N	Trop2		CD56	
		Positive	Negative	Loss	Present
Total cases	71	30(42.3%)	41(57.7%)	33(46.5%)	38(53.5%)
Papillary thyroid carcinoma (PTC)	32	29(90.6%)	3(9.3%)	27(84.4%)	5(15.6%)
Classic type (PTC)	23	21(91.3%)	2(8.7%)	20(87%)	3(13%)
(FVPC)	9	8(88.9%)	1(11.1%)	7(77.8%)	2(22.2%)
Follicular carcinoma	4	0(0%)	4(100%)	3(75%)	1(25%)
Follicular adenoma	20	1(5%)	19(95%)	2(10%)	18(90%)
Graves' disease	5	0(0%)	5(100%)	1(20%)	4(80%)
Colloid goitre	10	0(0%)	10(100%)	0 (0%)	10 (100%)

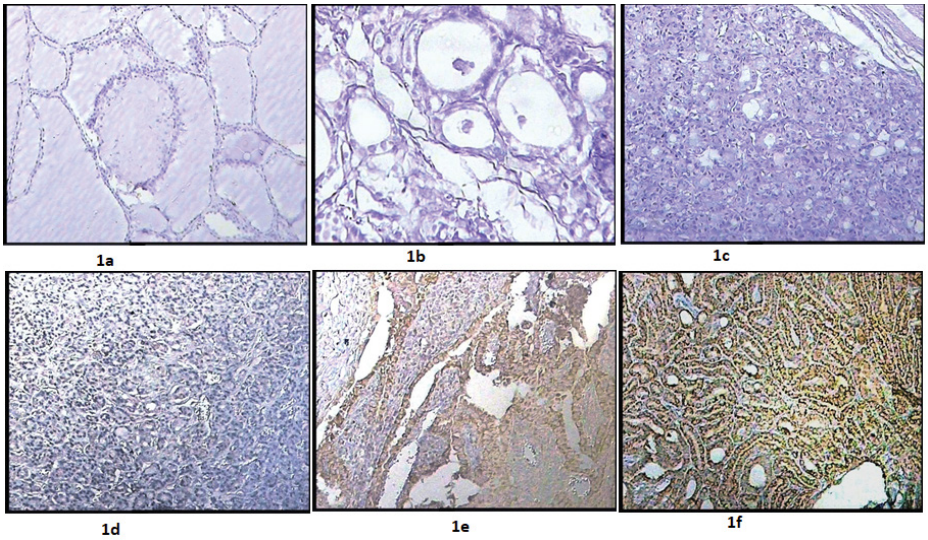

Figure 1: Immunohistochemical staining for Trop2 in follicular derived thyroid lesions; (a) Negative Trop2 expression in colloid goitre; (ABC, DAB chromogen X100) (b) Negative Trop2 expression in Graves' disease; (ABC, DAB chromogen X400) (c) Negative Trop2 expression in follicular adenoma; (ABC, DAB chromogen X100) (d) Negative Trop2 expression in follicular carcinoma; (ABC, DAB chromogen X100) (e) Positive membranous Trop2 expression in PTC; (ABC, DAB chromogen X100) (f) Positive membranous Trop2 expression in FVPC; Magnification of all samples (ABC, DAB chromogen X100).

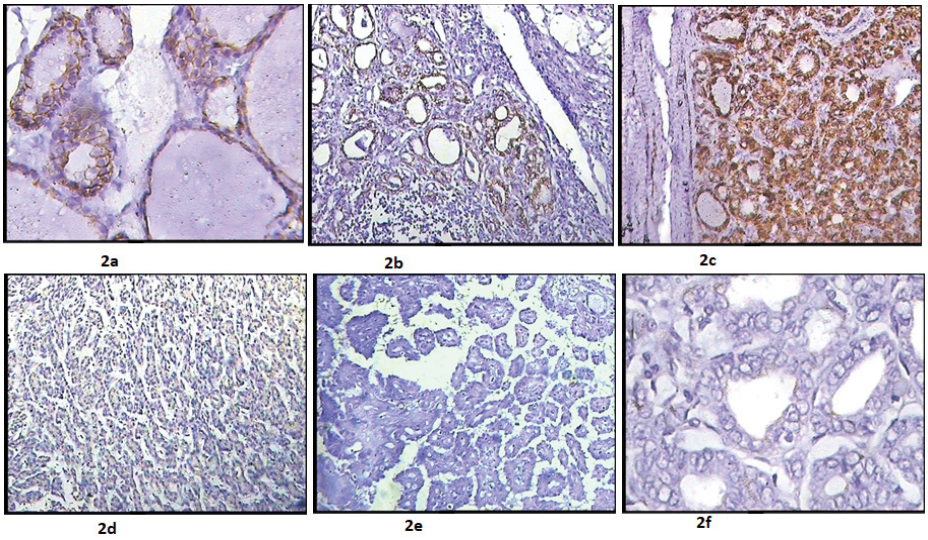

Figure 2: Immunohistochemical staining for CD56 in follicular derived thyroid lesions; (a) Positive membranous CD56 expression in colloid goitre; (ABC, DAB chromogen X400) (b) Positive membranous CD56 expression in Graves' disease; (ABC, DAB chromogen X100) (c) Positive membranous CD56 expression in follicular adenoma; (ABC, DAB chromogen X100) (d) CD56 loss of expression in follicular carcinoma; (ABC, DAB chromogen X100) (e) CD56 loss of expression in PTC; (ABC, DAB chromogen X100) (f) CD56 loss of expression in FVPC; Magnification of all samples (ABC, DAB chromogen X400).

showed positive expression. While none of the follicular carcinoma cases showed positive expression.

There was a highly significant difference in Trop2 expression between (PTC) cases and (FC) cases, p <0.001. The difference in expression of Trop2 between FVPC and FA was highly significant p<0.001 while non-significant statistical difference (p=0.64) was found between FC and FA cases.

CD56 loss of expression in papillary thyroid carcinoma was as follows: 20 cases out of 23 classic PTC (87% loss), 7 cases (77.8%) in FVPC, while 3 cases (75%) of FC cases showed CD56 loss.

No significant difference was recorded between (PTC) cases and (FC) cases regarding CD56 expression, p=0.635.

The relation between all benign versus all malignant follicular derived thyroid lesions in the expression of markers (Table 2)

The sensitivity of differentiating benign from malignant studied cases was good for Trop2 and CD56 (80.5% and 83.3%, respectively), while the specificity was high (97.1% for Trop2) and (91.4% for CD56).

The relationship between (PTC)cases versus all other follicular derived thyroid lesions in the expression of markers (Table 3)

The sensitivity and specificity in differentiating PTC from other studied lesions were high for Trop2 (90.6% and 97.4%, respectively) whereas they were moderate for CD56 expression (84.4% and 84.6% respectively).

Table 2: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (DA) of the immunohistochemical markers in all malignant versus all benign follicular derived thyroid lesions.

Expression of markers	Sensitivity	Specificity	PPV	NPV	DA
Trop2 (+)	80.5	97.1	96.7	82.9	88.7
CD56 loss	83.3	91.4	90.9	84.2	87.3
Trop2 (+) or CD56 (loss)	97.2	100	89.7	74.5	98.6
Trop2 (+) and CD56 (loss)	66.7	88.5	100	96.8	77.4

CD56 loss of expression showed a highly significant difference between FVPC and FA cases, also between FC and FA cases ($p < 0.001$ for both).
The difference in expression for both Trop2 and CD56 in malignant lesions versus benign lesions was highly significant ($p<0.001$)

Table 3: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (DA) of the immunohistochemical markers in PTC versus all other follicular derived thyroid lesions.

Expression of markers	Sensitivity	Specificity	PPV	NPV	DA
Trop2 (+)	90.6	97.4	96.7	92.7	94.4
CD56 loss	84.4	84.6	81.8	86.8	84.5
Trop2 (+) or CD56 (loss)	100	97.4	97	100	98.6
Trop2 (+) and CD56 (loss)	75	82	77.4	80	78.9

The difference in expression for both Trop2 and CD56 in malignant lesions versus benign lesions was highly significant ($p<0.001$)

Combined Expression of Markers

Examining the combined expression of Trop2 and CD56 revealed increasing the sensitivity to 100% in differentiating PTC from other follicular derived thyroid lesions as well as increasing specificity to 100% in the distinction between all benign from all malignant studied cases when either Trop2 or CD56 was expressed. While expression of both markers increased NPV to 100% in differentiating benign from malignant follicular derived thyroid lesions (Tables 2 and 3).

Discussion

Thyroid lesions are common clinical findings, the diagnosis of which is usually settled by histopathology, however, distinguishing problematic cases of follicular derived thyroid lesions may be challenging, immunohistochemical markers can be helpful in the diagnosis of such cases and differentiating benign from malignant lesions [4]. Trop2 is a transmembrane glycoprotein that is up regulated in various types of solid malignancies [11]. CD56 is a membrane glycoprotein. It is an adhesion molecule; hence its loss is associated with tumor invasion and poor prognosis [13].

Our study examined the immunohistochemical expression of Trop2 and CD56 in follicular derived thyroid lesions to validate the possibility of using these markers on a local cohort of patients at our institute.

As regards Trop2 expression, the current study showed positive membranous expression in 90.6% of papillary carcinoma (91.3% in classic type and 88.9% in FVPC), these results are following previous studies in which the expression of Trop2 ranged from 93% to 96% [6,11,14]. Other investigators found lower Trop2 expression in PTC [5,15] while Simms A, et al. (2016) recorded 95% Trop2 expression in classic PTC and 70% expression in FVPC of the studied 137 thyroids fine needle aspiration cytology whereas tissue sections in Tissue Micro Array (TMA) showed Trop2 expression in 90% of classic PTC and 18.8% of FVPC [16]. This discrepancy in results may be attributed to the difference in the number of cases, scoring systems or cut off points. On the opposite side, in this work, none of FC cases showed positive Trop2 expression, this is consistent with previous studies on FC who showed similar results [5,6,16]. Regarding follicular adenoma, this work found positive Trop2 expression in only one case (5%) this is near to previous studies that recorded negative Trop2 expression in the studied FA cases [5,6,15,16], other studies that used another Trop2 clone revealed 12.5% and 37.5% positive expression [11,14]. In our study all non-neoplastic lesions showed negative Trop2 expression, this is following previous studies [11,15,17]. This work showed that Trop2 is useful in distinguishing benign from malignant follicular derived thyroid lesions, with sensitivity 80.5% and specificity 97.1%, these values rise when comparing PTC with all other studied thyroid lesions, with sensitivity 90.6% and specificity 97.4%. Several investigators examined the role of Trop2 in differentiating PTC from its mimickers and reported high sensitivity ranged from 86%and 96% and specificity reaching up to 100% [4,11,14]. Murtezaoglu and Gucer H (2017) stated that Trop2 was rather specific than a sensitive marker in the diagnosis of PTC with sensitivity 50% and specificity 100% this lowered sensitivity was explained by negative Trop2 expression in most of FVPC cases in contrast to strong expression in classic PTC cases [15].

Regarding CD56 immunoexpression, the current work revealed negative membranous expression in 84.4% of PTC (87% of classic PTC and 77.8% of FVPC), and these results agrees with several studies in which CD56 loss of expression ranged from 66.7% to 100% [14,18-24]. On the other hand, this study found 75% loss of CD56 expression in FC cases, this is similar to some previous studies [25,26]. While other studies showed a high expression of CD56 [8,20,23], this may be due to different scoring methods. As regards FA cases, this work found positive CD56 expression in 90% of them, this is near to the results reported by previous studies [14,20,24]. In the current study, concerning benign non-neoplastic lesions, 100% of colloid goitre and 80% of Graves' disease showed positive CD56 expression, also El Demellawy D, et al. (2008) and Erdogan-Durmus S, et al. (2016) reported that all benign lesions strongly express CD56 [18,22]. This work showed that CD56 expression can help in the differential diagnosis of malignant and benign follicular derived thyroid lesions with 83.3% sensitivity and 91.4% specificity, similar findings were reported by Alshenawy HA, et al. (2014), with 80% sensitivity and 90% specificity [25]. Also, previous studies showed a significant difference between benign and malignant cases [14,24]. In distinguishing PTC from other studied lesions, this work showed 84.4% sensitivity and 84.6% specificity for CD56 loss of expression, these results agree with previous studies which found that CD56 expression in PTC cases was extremely low [20,21], similarly, several studies recorded sensitivity ranged from 82% to 95% and specificity ranged from 72.7% to 93.1% [8,14,19,20], while one study stated that all PTC cases showed negative CD56 expression [18] supporting the role of CD56 immunostaining in differentiating PTC from other lesions.

The current study revealed that the specificity for distinguishing malignant from benign follicular derived thyroid lesions raised to 100% with either staining by Trop2 or CD56, therefore discriminating positive benign lesions from true positive malignant lesions. The combined use of markers showed 100% PPV.

Also, we found that all PTC lesions were either positive to Trop2 or CD56, this increased the sensitivity to 100%. Yang X, et al. (2018) reported 100% sensitivity and NPV for the combined use of these markers in distinguishing PTC from FA cases [14].

Our finding revealed that Trop2 and CD56 are valuable in the differentiation between benign and malignant follicular derived thyroid lesions with good sensitivity and specificity, moreover, staining of either marker raises the specificity to 100%, while Trop2 is better than CD56 in the distinction of PTC from other lesions and the sensitivity may reach 100% with staining of either of these markers. So, we recommend using Trop2 and CD56 in a panel of immunohistochemical markers to help in reaching an optimum diagnosis in equivocal cases. Further studies on a larger number of people are also recommended to verify the current result.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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