Role of CD10 Marker in Differentiating Malignant Thyroid Neoplasms from Benign Thyroid Lesions (Immunohistochemical & Histopathological Study)

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Abstract

BACKGROUND: CD10 was initially recognised as a cell–surface antigen expressed by acute lymphoblastic leukaemias, and hence it's early designation as Common Acute Lymphoblastic Leukemia Antigen (CALLA). Also, it has been proven to be reactive in various non-lymphoid cells and tissue and different types of neoplasms.

AIM: To evaluate the immunohistochemical expression of CD10 in malignant thyroid neoplasms and different benign lesions and to assess whether CD10 can be used as a malignancy marker in thyroid pathology or not.

MATERIAL AND METHODS: A total of 83 archived, formalin fixed, paraffin embedded tissue blocks of 83 cases of malignant thyroid neoplasms and different benign lesions. The samples were immunohistochemically analysed for CD10 expression. A p-value of less than 0.05 was considered statistically significant.

RESULTS: CD10 was expressed in 91% of the studied malignant thyroid neoplasms and 58% of benign thyroid lesions. It was expressed in 26 of 28 (92.9%) conventional papillary carcinomas, ten of 10 (100%) follicular variants of papillary carcinoma, seven of nine (77.8%) minimally invasive follicular carcinomas, two of three (66.7%) widely invasive follicular carcinomas, and seven of 7 (100%) undifferentiated carcinomas, seven of 11 (66.7%) adenomatous nodules and eight of 15 (53.3%) follicular adenomas. No statistically significant correlations were detected between CD10 expression and patients' age, sex, lymph node metastasis, tumour stage and capsular invasion.

CONCLUSION: CD10 shows strong sensitivity (91.2%) and moderate specificity (42.3%) in the diagnosis of malignancy overall and shows strong sensitivity (86.4%) and moderate specificity (42.3%) in the diagnosis of malignancy in the follicular-patterned lesions. So, CD10 might be useful in differentiating malignant from benign thyroid lesions (good positive test) and in the diagnosis of follicular variant of papillary carcinoma.

Introduction

Thyroid cancer represented the most common endocrine malignancy [1]. Thyroid carcinoma accounts for about 1% of all cancers, and its incidence has notable geographic variation [2]. Papillary thyroid carcinoma (PTC) is the commonest form of malignant thyroid tumour accounting for 75% to 85% of all thyroid cancer cases [3].

There are two main obstacles to the diagnosis of thyroid lesions especially the follicular-patterned ones which encompass four entities: adenomatous nodule, follicular adenoma (FA), follicular carcinoma (FC), and follicular variant of papillary thyroid carcinoma (FVPTC) [4]; the discrimination of minimally invasive follicular carcinoma from follicular adenoma or adenomatous nodule and the correct diagnosis of follicular carcinoma [5], [6], [7]. FC is differentiated from FA when there is a capsular, vascular, or extra-thyroid invasion or if there are nodal or distant metastases [8]. Furthermore, the differential diagnosis of follicular cell-derived hyperplastic and neoplastic lesions may be very problematic, and the matter is rarely solved by immunohistochemistry [9].

Moreover, some of the encapsulated thyroid nodules showing follicular morphology may exhibit diffuse or focally intermediate nuclear features of

papillary carcinoma. Thus, it may become another source of controversy [10]. As long as the lesion shows capsular and/or vascular invasion, it is possible to make a diagnosis of well-differentiated carcinoma without further subtyping. On the contrary, if there is no invasion, follicular adenoma (FA) and papillary carcinoma follicular variant (PCFV) should be considered in the diagnosis. This crucial issue cannot be solved by morphology only and even immunohistochemically for some nodules. In this situation, these cases are stated as 'well-differentiated tumour of uncertain malignant potential' (WDTUMP) [10].

Several immunohistochemical markers such as HBME1, CK19 and galectin 3 have been used to overcome this problem [10], [11]. These antibodies can be valuable, especially when used together, but all display some disadvantages and limitations [10], [11], [12], [13], [14], [15]. So, more reliable markers are still required to differentiate between benign and malignant thyroid neoplasms.

Structurally, CD10 is known as a single-chain, 90-110-kDa cell surface zinc-dependent metalloprotease that inactivates many bioactive neuropeptides [16]. Lately, it has been established to be reactive in various non-lymphoid cells and tissues and different types of neoplasms [17]. In thyroid pathology, it was positive in thyroid marginal zone non-Hodgkin lymphoma [18]. The utility of CD10 marker in differentiating different benign and malignant thyroid lesions has been demonstrated in some reports [17], [19].

Material and Methods

This cross-sectional study included 83 cases with different benign and malignant thyroid lesions obtained through the collection of archived paraffin blocks, from the Department of Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt, during the period from June 2016 till September 2017. Cases with deficient clinical data, tiny biopsies or poorly fixed specimens were not included in the study. The medical records which included clinical and histopathological data such as age, gender, site and size of the tumours were revised.

Each paraffin block was re-cut by rotator microtome at 5 μ thickness then mounted on glass slides to be stained by Haematoxylin and Eosin (H&E) for histopathological re-evaluation by two pathologists. Histopathologic examination of H&E stained slides was performed under low power than high power for confirming the diagnosis. Histological classification for thyroid tumours was done according to WHO classification 2004 [20].

Cases included 11 adenomatous nodules, 15 follicular adenomas, 12 follicular carcinomas, 38 papillary carcinomas and 7 undifferentiated carcinomas.

Paraffin blocks were cut at 5 μ thickness then mounted on charged slides and stained manually for immunohistochemistry. The sections were deparaffinized in xylene, for 10 min, then dehydrated in descending series of ethanol (100%, 96%, 70%), followed by washes in TBS (0.05 mmol/L Tris-buffer physiological saline, pH 7.4-7.6), for 5 min.

Antigen retrieval was achieved by heating the samples without boiling in 10 mmol/L sodium citrate buffer, pH 6.0 (200 mL) in a microwave oven. This treatment was conducted twice for 7 min. The sections were washed in TBS buffer for 30 min.

The endogenous peroxide was blocked by 0.3% hydrogen peroxide in methanol for 5 min. The sections were washed in TBS for 15 minutes. To inhibit non-specific background staining; the samples were incubated in a superblock for 5-10 minutes at room temperature.

The primary antibody was monoclonal mouse CD10 antibody clone GM003 (Genemed, South San Francisco, CA, USA) was purchased from SNF medical Company, LOT NO.L 60125051, at 1:50 dilution for one hour at room temperature. The dilution was based on dilution experiments. The antibody was diluted with 20 mmol/L TBS, pH 7.4 (10 mmol/L $CaCl_2$, 0.1% NaN_3 and 1% BSA). The sections were incubated in the diluted antibody. The incubation took place in incubation boxes overnight. The secondary antibody (4.5 μL biotinylated anti-mouse antibody in 1 mL of 1% BSA) was pipetted onto the sections and incubated in the moist box for 30 min. The secondary antibody was washed in TBS buffer for 15 min.

The final staining was done in diaminobenzidine tetrahydrochloride (DAB) solution (49 mL TBS-buffer, 34 mg imidazole, 17 μL 30% hydrogen peroxide and 1 mL 30% DAB), for 5-15 min. The slides were washed with distilled water, 70% ethanol for 1 min, then in distilled water. The nuclei were stained with Mayer's hematoxylin for 30 seconds as a counterstain. The extra stain was washed with tap water. The slides were then transferred through ascending ethanol series, and xylene before mounting.

Positive control for cases stained for CD10 was done using sections obtained from tonsils, which exhibited a strong intensity of CD10 immunostaining and the negative control was obtained by omitting the primary antibody. Tumour tissue sections were examined and scored under LEICA ICC50HD microscope at low power than high power magnification by two independent pathologists who were not informed of the histological diagnosis. The sections were regarded as positive when immunoreactivity was observed in the cytoplasm and

cell membrane. For each case, 10 high power fields were evaluated. Immunoreactivity was graded as 0 (negative) when less than 10% of tumour cells were positive, 1 (weak) when 10-49% of tumour cells were positive and 2 (strong) when 50% or more of tumour cells was positive. The immunoreactivity interpreted based on the percentage of the stained cells irrespective of the intensity of the staining.

Data were collected, coded and analysed using the Statistical Package for Social Science (SPSS version 21.0). Data presented in the form of mean, standard deviation and percentage. For categorical variables, differences were analysed using Chi-square (X^2) test and Fisher's-exact test. Cohen's kappa is used for measurement of the agreement. A p-value of less than 0.05 was considered significant. Sensitivity, specificity, and diagnostic accuracy were assessed. Sensitivity means the true positive rate; specificity means the true negative rate.

Results

Clinicopathological characteristics of the studied cases and their correlation with CD10 expression are summarised in (Table 1).

Table 1: Clinicopathological characteristics of the studied cases and its correlation with CD10 expression

Parameter	Number (%)	CD10 (Negative) expression	CD10 (weak)	CD10 (strong)	P value
Age					
< 45 years	54 (65.1%)	5 (13.9%)	8 (22.2%)	23 (63.9%)	0.197
≥ 45 years	29 (34.9%)	0 (0.0%)	6 (28.6%)	15 (71.4%)	
Gender					
Male	15 (18%)	0 (0.0%)	5 (45.5%)	6 (54.5%)	0.141
Female	68 (82%)	5 (10.9%)	9 (19.6%)	32 (69.6%)	
Category					
Malignant	57 (68.7%)	5 (8.8%)	14 (24.6%)	38 (66.7%)	0.001
Benign	26 (31.3%)	11 (42.3%)	6 (23.1%)	9 (34.6%)	
Pathologic tumour stage (T)					
T1	18 (31.6%)	2 (11.1%)	3 (16.7%)	13 (72.2%)	
T2	20 (35.1%)	2 (10.0%)	2 (10.0%)	16 (80.0%)	0.180
T3	16 (28.1%)	1 (6.3%)	8 (50.0%)	7 (43.8%)	
T4	3 (5.3%)	0 (0.0%)	1 (33.3%)	2 (66.7%)	
Lymph Node (LN) Metastasis					
N0	43 (75%)	5 (11.6%)	9 (20.9%)	29 (67.4%)	0.275
N1	14 (25%)	0 (0.0%)	5 (35.7%)	9 (64.3%)	
Stage					
Stage I	37 (64.9%)	5 (13.5%)	8 (21.6%)	24 (64.9%)	
Stage II	9 (15.8%)	0 (0.0%)	3 (33.3%)	6 (66.7%)	0.778
Stage III	7 (12.3%)	0 (0.0%)	2 (28.6%)	5 (71.4%)	
Stage IV	4 (7.0%)	0 (0.0%)	1 (25.0%)	3 (75.0%)	
Papillary carcinoma cases					
With capsular invasion	17 (44.7%)	0 (0.0%)	7 (41.2%)	10 (58.8%)	0.2
Without capsular invasion	21 (55.3%)	2 (9.5%)	4 (19.0%)	15 (71.5%)	

CD10 immunostaining was identified in 26 of 28 (92.9%) conventional papillary carcinomas, ten of 10 (100%) follicular variants of papillary carcinoma, seven of nine (77.8%) minimally invasive follicular carcinomas, two of three (66.7%) widely invasive follicular carcinomas, seven of seven (100%) undifferentiated carcinomas, eight of 15 (53.3%) follicular adenomas and seven of 11 (63.6%) adenomatous nodules (Table2).

Table 2: Immunoreactivity of CD10 in each diagnostic category

Diagnosis	Total case number	CD10 (Negative) expression	CD10 (weak)	CD10 (strong)
Conventional PC	28	2 (7.1%)	8 (28.6%)	18 (64.3%)
Follicular variant of PC	38	0 (0.0%)	3 (30.0%)	7 (70.0%)
Minimally invasive FC	9	2 (22.2%)	0 (0.0%)	7 (77.8%)
Widely invasive FC	3	1 (33.3%)	2 (66.7%)	0 (0.0%)
Undifferentiated carcinoma	7	0 (0.0%)	1 (14.3%)	6 (85.7%)
Follicular adenoma	15	7 (46.7%)	2 (13.3%)	6 (40.0%)
Adenomatous nodule	11	4 (36.4%)	4 (36.4%)	3 (27.3%)

Studied cases are categorised into two groups (benign and malignant). Ninety-one per cent of malignant cases showed positive CD10 expression and the remaining 9% showed negative CD10 expression, while 58% of benign cases showed positive CD10 expression and the remaining 42% showed negative CD10 expression.

To evaluate the value of CD10 immunostaining in the diagnosis of malignancy, we performed sensitivity, specificity and diagnostic accuracy. CD10 shows strong sensitivity (91.2%), 95% Confidence Interval (95% CI) (80.7 to 97%), moderate specificity (42.3%), 95% CI (23.35% to 63.08%) and diagnostic accuracy (75.9%), 95% CI (65.27% to 84.62%). Cohen's k was run to determine if there was an agreement between CD10 and the diagnostic tool (by H&E). There was moderate agreement k = 4, p < 0.01.

Besides, we separate a subset of 48 thyroid lesions with a follicular growth pattern (15 follicular adenomas, 12 follicular carcinomas, 11 adenomatous nodules and 10 follicular variants of papillary carcinoma). Sensitivity, specificity, and diagnostic accuracy of CD10 for the diagnosis of malignancy in these lesions were 86%, 95% CI (65.09% to 97.09%), 42%, 95%CI (23.35% to 63.08%) , and 62.5%, 95% CI (47.35% to 76.05%) respectively.
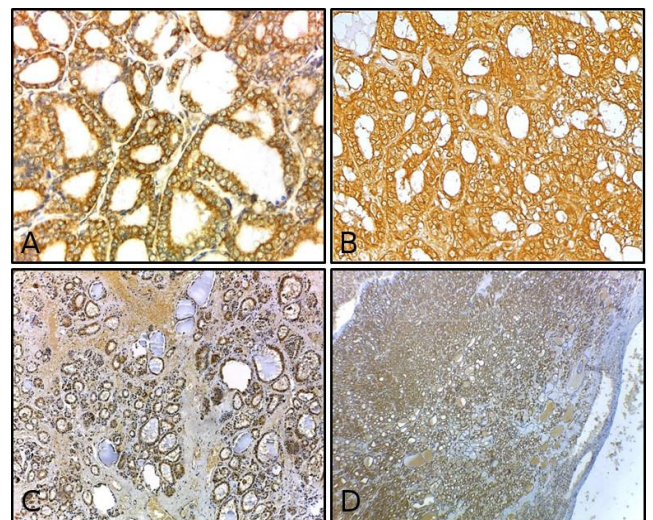

Figure 1: Follicular-patterned lesions; A: Follicular carcinoma showing strong CD10 staining (score 2+) (original magnification X 400); B: Follicular variant of papillary carcinoma showing strong CD10 staining (original magnification X 400); C: Adenomatous nodule showing positive CD10 staining (score 2+) (original magnification X 100); D: Follicular adenoma showing positive CD10 staining (score 2+) (original magnification X 100)

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All the undifferentiated thyroid tumours and 90% of the differentiated tumours showed positive CD10 staining, but there is no statistically significant relationship between CD10 expression and differentiation of thyroid tumours (p = 0.8) (Table 3).

Table 3: Correlation of CD10 immunohistochemical expression with the differentiation of thyroid tumours

Category	CD10			Total	P value
	Negative	Weak	Strong		
Differentiated thyroid carcinoma	5 (10%)	13 (26%)	32 (64%)	50 (100.0%)	0.8
Undifferentiated thyroid carcinoma	0 (0.0%)	1 (14.3%)	6 (85.7%)	7 (100.0%)	

Moreover, we assess the correlation of CD10 expression with some prognostic factors as lymph node metastasis, tumour stage and capsular invasion. No statistically significant relationships were observed between the previously mentioned parameters and CD10 expression (P-value = 0.27, 0.77, 0.2 respectively) (Table1).
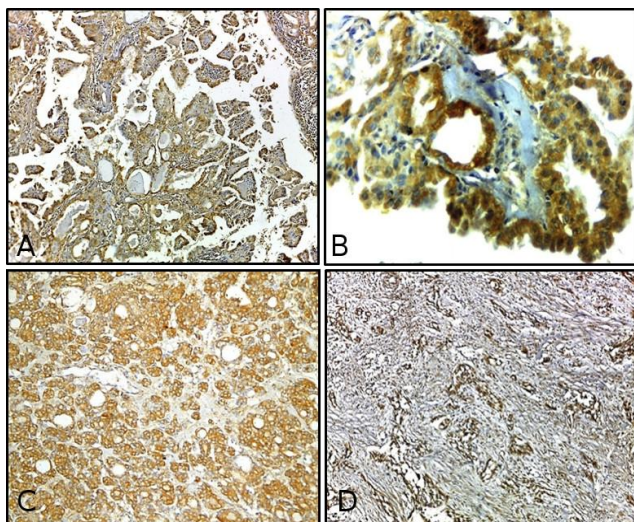

Figure 2: Both differentiated (papillary and follicular carcinomas) and undifferentiated carcinomas showing positive CD10 staining (score 2+); A: Conventional papillary carcinoma (original magnification X 100); B: High power of A (original magnification X 400); C: Follicular carcinoma (original magnification X 100); D: Undifferentiated carcinoma (original magnification X 100)

Discussion

In this study, we aimed to assess the value of CD10 in differentiating benign and malignant tumours of the thyroid especially the follicular patterned thyroid nodules.

The distinction between benign and malignant follicular tumours may be occasionally problematic as it relies mainly on the presence of capsular and/or vascular invasion. If the focus of invasion is small or not evident, right diagnosis becomes difficult.

Furthermore, benign follicular tumours are sometimes misdiagnosed as follicular variants of papillary carcinoma. Lloyd and his colleagues assessed the observer variation in the diagnosis of follicular variant of papillary carcinoma; all ten skilled thyroid pathologists agreed in the diagnosis in only 39% of cases [21].

In order to overcome the previous limitations, several markers of malignancy such as CK19, HBME1, and galectin 3 have been studied in thyroid specimens, but unfortunately, all present some disadvantages and limitations [10], [11]. Also, a marker of malignancy may be used as a preoperative diagnostic tool for suspicious lesions. Thus the extent of surgery and the complementary treatments could be planned before thyroid operations.

Originally, CD10 was thought to be a tumour-specific antigen [22], but studies have shown that it is expressed by a variety of cell types including bronchial epithelial cells, renal proximal tubular epithelial cells, cultured fibroblasts, bone marrow stromal cells, breast myoepithelium, biliary canaliculi, fetal intestine, and certain solid tumours [17], [23], [24].

Tomoda *et al.,* 2003 was the first report on the expression of CD10 marker in thyroid neoplasms. They evaluated CD10 expression in 70 thyroid neoplasms and reported that CD10 was negative in benign lesions and pure papillary carcinomas but was positive in 80% and 77% of follicular carcinomas and follicular variant of PTC, respectively. They deduced that CD10 immunostaining could be a useful marker of follicular carcinoma to distinguish it from follicular adenoma and benign hyperplastic nodules and in diagnosing follicular variants of papillary thyroid carcinoma [17].

Another research was done by Yegen *et al.*, who have investigated the staining pattern of CD10 in different benign (*n* = 14) and malignant (*n* = 61) thyroid lesions. They reported their results as follows: CD10 was negative in adenomatous nodules, minimally invasive follicular carcinomas and well-differentiated carcinomas. It was positive in conventional papillary carcinomas (64.2%), follicular variants of papillary carcinoma (16.6%), papillary microcarcinomas (50%), widely invasive follicular carcinomas (11.1%) and follicular adenomas (30%). They concluded that, despite CD10 strong positivity in conventional papillary carcinoma, it could not be used as a useful marker for differentiating benign and malignant thyroid lesion [19].

Mokhtari and Ameri, 2014 reported a significant correlation between CD10 expression and both benign and malignant thyroid lesions (P < 0.001) as they found CD10 positivity in 29.9% of PTC cases, but in none of the thyroid benign lesions (0%) [25].

Chu and Arber have investigated CD10 expression in 505 non-hematopoietic neoplasms

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including 55 thyroid tumors [follicular adenoma (n = 24), papillary carcinoma (n = 10), medullary carcinoma (n = 16) and follicular carcinoma (n = 5)] by IHC. They detected that CD10 expression was negative in all the examined thyroid tumours [22].

In like manner, Yasuda et al., have studied the availability of CD10, as a histopathological marker, in different non-hematopoietic neoplasms including thyroid tumours. They reported that CD10 was not present in thyroid tumours and showed no diagnostic value for this group of non-hematopoietic neoplasms [27].

In contrast with the previously mentioned studies, we observed CD10 expression in benign lesions both in FA and adenomatous nodules as well as in carcinomas. Malignant tumours and benign lesions showed 91% and 58% positivity overall respectively. CD10 was identified in 26 of 28 (92.9%) conventional papillary carcinomas, ten of 10 (100%) follicular variants of papillary carcinoma, seven of nine (77.8%) minimally invasive follicular carcinomas, two of three (66.7%) widely invasive follicular carcinomas, seven of seven (100%) undifferentiated carcinomas, eight of 15 (53.3%) follicular adenomas and seven of 11 (63.6%) adenomatous nodules.

Statistically, CD10 shows strong sensitivity (91.2%), 95% CI (80.7 to 97%) and moderate specificity (42.3%), 95% CI (23.35% to 63.08%) in the diagnosis of malignancy overall with diagnostic accuracy (75.9%), 95% CI (65.27% to 84.62%). Furthermore, in the follicular-patterned lesions, it was found that sensitivity, specificity, and diagnostic accuracy of CD10 for the diagnosis of malignancy in these lesions were 86%, 95% CI (65.09% to 97.09%), 42%, 95%CI (23.35% to 63.08%) , and 62.5%, 95% CI (47.35% to 76.05%) respectively.

Our results are not consistent with the results of previous studies. We observed a higher frequency of positivity in both benign and malignant lesions. This discrepancy could be explained by geographic and genetic variability between patients, different sample size, technical variations and different antibodies, clones and brands. A well-known fact in immunohistochemistry is that the specificity and sensitivity of the antibodies may show variations with different clones and brands. Moreover, some studies did not evaluate different malignant thyroid lesions and did not perform CD10 sensitivity and specificity. The strengths of our data are the great variability of the thyroid lesions analysed by IHC using CD10 expression, as well as performing its sensitivity and specificity in the diagnosis of thyroid lesions.

In conclusion, CD10 is highly expressed in malignant tumours (95% of papillary carcinoma, 75% of follicular carcinomas and 100% of undifferentiated carcinoma. CD10 showed strong sensitivity (91.2%) and moderate specificity (42.3%) in the diagnosis of malignancy overall and showed strong sensitivity (86.4%) and moderate specificity (42.3%) in the

diagnosis of malignancy in the follicular-patterned lesions. So, CD10 might be useful in differentiating malignant from benign thyroid lesions (good positive test) and in the diagnosis of follicular variant of papillary carcinoma being observed in 100% of these tumours.

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