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Evaluation of the Diagnostic Value of the Cluster of Differentiation 10 in the Diagnosis of Follicular Thyroid Carcinoma

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Abstract

Objectives: Few studies have so far focused on the role of the cluster of differentiation 10 (CD10) in the prognosis of papillary thyroid carcinoma in Iran. Accordingly, this study aimed at evaluating the diagnostic value of CD10 in follicular thyroid carcinoma.

Materials and Methods: This cross-sectional study was performed on 89 patients with thyroid carcinoma at Imam Reza Hospital (Tabriz Medical Sciences) during 2016-2017. The diagnostic value of the CD10 test was evaluated for the accurate diagnosis of papillary thyroid carcinoma. Finally, data were analyzed using Mann-Whitney, chi-square, and Pearson correlation tests.

Results: Among the studied samples by the CD10 method, it was found that 41 (46.06%) and 48 (53.94%) were positive and negative, respectively. There was a significant correlation between CD10 expression and tumor size ($P=0.0001$), as well as lymph node involvement ($P=0.031$) and capsular invasion ($P=0.008$).

Conclusions: In general, the CD10 biomarker could be an accessory diagnostic tool in addition to basic methods in the diagnosis of the follicular variant of papillary carcinoma although its diagnostic value in follicular carcinoma is not sufficiently high.

Keywords: Follicular Adenocarcinoma, Papillary Carcinoma, CD10

Introduction

Distant metastasis in thyroid cancers is not a common phenomenon, and follicular thyroid carcinoma (FTC) is found among well-differentiated carcinomas (1,2). From the point of immunohistochemistry, follicular carcinoma is positive for thyroglobulin and low molecular weight keratin and epithelial membrane antigen while negative for calcitonin (3, 4). Lungs and bones are the most common metastasis sites (4-6). The prevalence of bone metastases has been reported in 28%-40% of studies. On the other hand, the FTC rarely appears as distant metastasis, especially as a single lesion (7-9). Most reported metastases in the FTC have been associated with the invasion of blood vessels, but the FTC has had capsular invasion in less than 1% of cases and there has been no evidence of vascular involvement (10,11). Although the morphological features of thyroid lesions can be found in the pathology type, various studies have suggested that differentiating the FTC from benign lesions by morphology is often problematic. This important issue among pathologists is also a major challenge. To overcome this problem, various cytological, immunohistochemical (ICH), and molecular studies have been carried out while focusing on different biomarkers in surgical and fine-needle biopsy samples to increase diagnostic accuracy (12,13). CD10 is a metalloproteinase attached to the membrane, which was initially used in the diagnosis and categorization of lymphoma and leukemia. Recently, the diagnostic use of CD10 has been investigated in various non-hepatocellular lesions such as breast, liver, and uterus malignancies. This biomarker is found in many benign and malignant tissues and plays an important role in homeostasis, neoplastic changes, and tumor progression. It is also an essential prognostic factor in cancer, thus its expression indicates an increase in the growth rate (14, 15). Given that the use of the CD10 biomarker has not been able to accurately confirm the diagnosis of cancer in different tissues and there are inconsistent results in our studies, this biomarker seems to be a specific biomarker for a specific tissue type. Therefore, the purpose of this study was to evaluate the diagnostic value of CD10 in the diagnosis of FTC in order to determine whether this biomarker can be effective in the diagnosis of FTC.

Materials and Methods

This cross-sectional study was conducted during 2016-2017 with the participation of 89 patients who met the inclusion and exclusion criteria in Imam Reza Hospital affiliated to Tabriz University of Medical Sciences. The minimum sample size based on several similar studies (14-16) was considered to be 80 individuals, and given that the sample size in this study was of census type, more people

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Key Messages

- Accurate diagnosis of follicular thyroid carcinoma is essential to increase the survival of these patients.
- Biomarker CD10 is one of the strongest biomarkers in cancer diagnosis.
- CD10 biocarps can be effective in the early diagnosis of follicular thyroid carcinoma.

entered the study to increase the power of the results, the final sample size in this study was 89 people.

The inclusion criteria were satisfaction with the study, thyroid cancer, and over 18 years of age while the exclusion criteria included inflammatory thyroid lesions, poorly differentiated and undifferentiated thyroid carcinoma, and poorly preserved specimens. Study participants were those who had been referred to a thoracic surgeon for thyroid problems, and surgical procedures were performed to diagnose their cancer, and specimens were sent to the pathology laboratory. Moreover, all of them were included in the study based on the inclusion and exclusion criteria.

Research Method

Paraffin blocks were cut by microtome in 4-µm slices and stained by hematoxylin and eosin (H&E) staining, and capsular invasion was investigated by a light microscope (Zeiss model). The IHC method was used to determine the expression of the CD10 biomarker in each tissue sample. For this purpose, the prepared paraffin blocks in accordance with the conventional method were provided by microtome 4-µm slices.

IHC staining was performed according to the staining protocol in BioGenex USA Laboratory Kit. This kit is designed to express antigens on a variety of human tissues. The following steps were generally performed according to this protocol:

1. The tissue slices were immersed in water and alcohol solution, as well as hot water baths for a few seconds, and then placed on slides.
2. The obtained slide was heated at 56-60˚C for 30 minutes.
3. Different percentages of methanol solution in water (i.e., 100, 100, 6, and 75%, respectively) were obtained, and then the aforementioned slides were immersed in these solutions at different time intervals (i.e., 3 seconds, 5 minutes, 5 minutes, 3 seconds, respectively) and washed with a 10% phosphate-buffered *saline* (PBS) buffer.
4. The slide was immersed in 30% hydrogen peroxide solution in methanol (one portion of hydrogen peroxide in 9 parts of methanol) for 10 minutes.
5. The slide was then placed in a sodium citrate buffer solution and transferred to an autoclave at 120 ˚C and pressure of 1/2 atm. It was removed and then washed as well.
6. Two drops of the serum blocking solution were added to each slide and placed at room temperature for 10 minutes.
7. The surface of the slide was covered with two drops of primary antibody (CD10 Ab) for 30-60 minutes and washed again.
8. Two drops of biotinylated second antibody were added and then enzyme conjugate was added to the sample, and the samples were kept for 10 minutes.
9. Two drops of the obtained reagent were added to the slide and washed with distilled water for 3-5 minutes.
10. In the contrast phase, 5 drops of hematoxylin solution were added to the slide and washed with ordinary water after 3-1 minutes and then dehydrated in methanol.
11. The slide was incubated in the PBS solution for 10 seconds.
12. For clarification, the slide was placed in the xylene solution for a few minutes.
13. From the Histomount solution, two drops were added to the slide and placed on the lamellar sample.
14. At the end of the slide, a 40-magnification Zeiss microscope was used to determine the presence of the CD10 biomarker under the supervision of a qualified pathologist (a member of the research group), and the percentage of positive tumor cells was determined accordingly.

Data were analyzed by SPSS 20 software using Mann-Whitney and chi-square tests to evaluate the relationship between the percentage of CD10 expression in lymph nodes and capsular invasion, as well as the relationship between CD10 expression status and capsular invasion, respectively. In addition, the *t* test and Pearson correlation coefficient were applied to study the relationship between the CD10 expression status and tumor size, as well as the CD10 expression percentage and tumor size, respectively, and a *P* value of less than 0.05 was considered statistically significant.

Results

In general, 104 patients referred to the mentioned training center during the mentioned period with the involvement of thyroid cancer and 89 of them met the inclusion criteria and were included in this research project. The study started and finished with 89 patients (104 patients were diagnosed with follicular neoplasm in fine-needle aspiration slides). In permanent pathology reports, there were 55, 34, 8, 5, and 2 cases of the follicular variant of papillary carcinoma, FTC, classical papillary carcinoma, conventional papillary carcinoma, and multi-nodular goiter, respectively. A total of 89 follicular carcinoma and follicular variant of papillary carcinomas were studied and the remaining 15 cases were excluded from the investigation.

Of 89 patients under study, 13 (14.6%) and 76 (85.4%) cases were males and females, respectively. The maximum and minimum age range were 84 and 27

Table 1. CD10 Results in Study Participants

Count		Results of CD10 Test		Total
		Positive	Negative	
Pathological diagnosis	Follicular variant of papillary carcinoma	36	19	55
	Follicular carcinoma	5	29	34
Total		41	48	89

Note. CD10: cluster of differentiation 10.

years, respectively, and the mean (± standard deviation) age of participants was 44.53 ± 1.29 years. Based on the measurements, the mean ± SD of the tumor size was 3.12 ± 1.25 cm and the smallest and largest sizes were 0.5 cm and 12 cm, respectively. According to Table 1, CD10 was positive in 5 out of 34 patients with follicular carcinoma while it was negative in 29 cases. Among patients with the follicular subtype of papillary carcinoma (55 cases), CD10 was positive and negative in 36 and 19 cases, respectively. Immunohistochemistry was performed and according to previous studies, the expression was less than 10%, negative, and expression was greater and equal to 10%. Among the studied samples, 41 (46.06%) and 48 (53.94%) were positive and negative, respectively.

The results of the Pearson correlation test showed a significant correlation between CD10 expression percentage and tumor size ($P=0.0001$), Indicating an increase in the size of the tumor. Based on the results of the Mann-Whitney test, a significant relationship was found between the percentage of CD10 expression in lymph nodes ($P=0.007$). Using this test, there was a significant relationship between the percentage of CD10 expression and capsular invasion ($P=0.006$). However, no significant relationship was observed between age (Pearson correlation test) and gender (Mann-Whitney test) with the CD10 expression ($P>0.05$).

In the qualitative analysis of data (Table 2), positive and negative expressions of the CD10 expression were observed, and there was a significant relationship between CD10 expression status and tumor size by *t* test ($P=0.006$).

Table 2. Frequency Distribution of CD10 Expression Status and Tumor Size

	No. (%)	Tumor Weight Mean ± SD
CD10 negative	48 (53.94%)	2.25 ± 1.03
CD10 positive	41 (46.06%)	6.43 ± 1.59

Note. CD10: cluster of differentiation 10; SD: Standard deviation.

On the other hand, the results of the chi-square test (Table 3) indicated a significant relationship was detected between the CD10 expression status and lymph node involvement ($P=0.031$).

The results related to the Chi-square test revealed a significant relationship between CD10 expression status and capsular invasion ($P=0.008$) so that CD10 positivity was correlated with capsular invasion (Table 4).

Discussion

In the present study, the increased expression of CD10 was associated with the tumor size, lymph node involvement, and capsular invasion although no significant relationship was found between the expression of this biomarker and the age and gender of patients with papillary thyroid carcinoma. CD10 is a metalloproteinase located at the cell surface. It is a biomarker in hematopoietic and non-hematopoietic tissues that regulates the biological activities of the peptide substrate by decreasing the local concentration available for receptor binding and signal transduction. Positive samples have also shown poor therapeutic response to chemotherapy in positive samples. The expression level of CD10 in the present study was lower than that of the study by Mokhtari and Ameri (17). In this study, the percentage of CD10 expression in thyroid carcinoma specimens was 29.9%. This inconsistency is probably because the samples of our study were evaluated in two groups (N = 134) of benign thyroid lesions and papillary thyroid carcinoma. Taghizadeh-Kermani et al (18) examined the incidence of invasive ductal carcinoma and fibroadenoma and reported that the expression of CD10 was 28%. This difference may also be due to the fact that the study has been performed on the specimens of breast carcinoma and fibroadenoma and there is a possible difference in the pathogenesis of CD10 between the two different tumors.

Contrary to the results of our study showing that the CD10 biomarker cannot accurately detect papillary

Table 3. Frequency Distribution of the CD10 Expression Status of the Lymph Node Involvement

	With Lymph Node Involvement	Without Lymph Node Involvement	Total (%)
CD10 positive	7 (17.08%)	34 (82.92%)	41 (46.06%)
CD10 negative	11 (22.91%)	37 (77.09%)	48 (53.94%)
Total	18 (20.22%)	71 (79.78%)	89 (100%)

Note. CD10: cluster of differentiation 10.

Table 4. Frequency Distribution of Capsular Invasion CD10 Expression Status

	With Capsular Invasion	Without Capsular Invasion	Total (%)
CD10 positive	5 (12.19%)	36 (878.81%)	41 (46.06%)
CD10 negative	10 (20.84%)	38 (79.16%)	48 (53.94%)
Total	15 (20.22%)	74 (79.78%)	89 (100%)

Note. CD10: cluster of differentiation 10.

thyroid cancer, Nakazawa et al (19) demonstrated that this biomarker is highly expressed in primary cancers. It was reported that the expression of this biomarker could be useful in the prognosis of metastatic FTC cancers.

Overall, CD10 expression is associated with poor prognosis in patients with thyroid foot carcinoma. As reported by Taghizadeh-Kermani et al (18), CD10 expression in invasive ductal carcinoma was associated with increased tumor size, increased histologic grade, and lymphatic metastasis. In the study of Bilalovic et al (20), CD10 expression in metastatic specimens was higher compared to primary specimens. Mishra et al (21) found the positive effects of the CD10 biomarker on the diagnosis and progression of non-cancerous cancers, which contradicts the results of our study. It is highly expressed and thus can be used in the early detection of cancer.

Similarly, Tariq et al (22) focused on a type of breast neoplasm and represented that 83.3% of samples had a positive CD10 recurrence. Therefore, according to this article, the positive expression of CD10 samples is associated with the decreased survival of patients. In their study, Abdel-Aziz et al (23) found a significant relationship between the CD10 expression and local recurrence of ameloblastoma tumors. However, Shafaei et al reported no correlation between the expression of CD10 and the invasive potency of the basal cell carcinoma tumor (24).

In line with our results, Yegen et al concluded that, unlike previous studies, CD10 was not effective in differentiating benign from malignant lesions although there was a strong association between CD10 and PTC expressions (25). Tariq et al (22) also addressed the role of CD10 in reducing survival and found that CD10 is associated with prognosis, which has a significant relationship with the prognostic factors affecting the progression of the disease in most cases. In a similar study, Lam et al (26) examined the role of biomarkers in the timely diagnosis and progression of thyroid cancer. It is highly expressed in cell proliferation and gene modifications, therefore, it has been identified as a diagnostic biomarker in thyroid cancer.

Limitations

The low sample size and the high cost of laboratory kits made it difficult to verify the higher sample size.

Suggestion

It is suggested that the role of CD10 in the prognosis of patients with papillary thyroid carcinoma be investigated with the features of treatment response, recurrence, metastasis while including more specimens and longer follow-ups. Nonetheless, the researchers do not recommend the use of this biomarker for the diagnosis of thyroid cancer due to its high cost and low accuracy and suggest avoiding the use of this biomarker for thyroid cancer. However, we recommend that this biomarker be screened for other cancers to be used if applicable.

Conclusions

CD10 can be used as an auxiliary tool for the detection of the follicular subtype of papillary carcinoma in addition to standard methods although it is not highly sensitive to differentiating follicular carcinoma from follicular adenoma.

Authors' Contribution

AZR: Study design, intervention; MH: biomarker review; NS: Study design, intervention, article submission; SM: follow-up.

Conflict of Interests

None declared.

Ethical Issues

The research project was approved by the Ethics Committee of Tabriz University of Medical Sciences (ethics no. IR.TBZMED.REC.1397.185). Individual and clear explanations regarding the research project were given to each individual patient.

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