ORIGINAL ARTICLE

Diagnostic value of CD56 and nm23 markers in papillary thyroid carcinoma

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ABSTRACT

Context: Thyroid cancer is the most common malignant endocrine tumor. Nowadays tissue biopsy and pathological assessment are the best diagnostic modalities for thyroid lesions. Differential diagnosis between adenomas and follicular variant of papillary thyroid carcinoma (PTC) is an important issue in pathology. **Aims:** This study is designed to show any association between expressions of CD56 and nm23 and types of thyroid lesions (benign vs. malignant). **Settings and Design:** In this cross-sectional study, 78 paraffin-embedded tissue blocks of thyroid tissue from a tertiary care center were selected, and assessed by using immunohistochemistry for expressions of CD56 and nm23 genes. **Materials and Methods:** we studied 39 benign and 39 malignant thyroid lesions, CD56 and nm23 expressions were determined by immunohistochemical staining, and the results were used for differentiation of benign and malignant lesions of thyroid. **Statistical Analysis:** The obtained results were analyzed and evaluated using SPSS (Version 18). **Results:** CD56 was expressed in 93% of benign specimens and in only 5% of malignant types. The sensitivity and specificity of this test were 94.8% and 92.3, respectively ($P = 0.001$). All malignant specimens and 95% of benign specimens were positive for nm23. The sensitivity and specificity of nm23 were 100% and 5%, respectively. **Conclusion:** Considering high sensitivity and specificity of CD56, it is possible to apply immunohistochemistry for definite diagnosis and differentiation of benign lesions from PTC. We conclude that by using this marker, the diagnostic mistakes in pathologic diagnosis of thyroid cancer *versus* benign lesions like thyroid adenoma will decrease.

KEY WORDS: CD56, nm23, papillary thyroid carcinoma

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INTRODUCTION

Thyroid cancer is the most common malignant tumor among endocrine tumors with the incidence of ≈ 9/100000 per year in the United States. Majority of thyroid cancers present as thyroid nodules and rarely express as cervical lymphadenopathy.[1]

The incidence of thyroid cancer has been increased in recent years due to earlier diagnosis of disease, technological development, and also early diagnosis of micrometastasis.[1] These neoplasms originate from two basic cells: Follicular epithelial cells and parafollicular cells (C cells). Papillary carcinoma and follicular carcinoma originate from follicular epithelial cells and both are usually well differentiated tumors. Medullary thyroid carcinoma (MTC) originates from parafollicular cells.[1]

Papillary thyroid carcinoma (PTC) is more common than follicular carcinoma.[1] Tissue biopsy and routine staining are gold standard in the diagnosis of thyroid nodules, but due to morphologic overlap between follicular lesions and carcinoma, in some cases the definite diagnosis is not possible.[2] Diagnostic criteria for PTC were established more than 50 years ago, but there is still disagreement among expert pathologists.[3,4]

The diagnosis of thyroid tumors in typical cases is relatively easy, but there are frequent cases of malignant tumors in which differential diagnosis from benign lesions is not easy. In such cases, diagnosis by a histopathologic study may be impossible even for expert pathologists and reproducibility of the diagnosis may not be acceptable among various pathologists. Thus, it is so critical to find appropriate markers to differentiate among thyroid neoplasms, especially malignant tumors and benign lesions, since incorrect diagnosis can lead to total thyroidectomy and lifelong dependency for medical treatment.[5]

Ancillary methods, like immunohistochemistry (IHC), may be helpful in such cases. Some markers including CK19, Galectin-3, CD56, CD44, and nm23 have been introduced to facilitate in the diagnosis of these cases.[6,7]

CD56 is a neural cell adhesion molecule and its expression affects the ability of immigration of tumoral cells and its deficiency is associated with metastasis through blood and lymph vessels.[6]

Nm23 is one of the suppressor genes of metastasis. A significant association has been found between low expression of the nm23 gene and the metastatic potential of tumoral cells in breast cancer, melanoma, hepatoma, and ovarian cancer. However, conversely in hematologic malignancies and prostate cancer, the high expression of nm23 had been associated with poorer prognosis.[8] Since the expression of this protein is an essential biologic event in the pathogenesis of human malignancies, this study is designed to find appropriate, accessible, and reliable markers to differentiate PTC from other thyroid lesions.

MATERIALS AND METHODS

In this study, the paraffin-embedded specimens of thyroid tissue, available in a tertiary care center, between 2008 and 2010, were selected (39 benign and 39 malignant thyroid lesion diagnosed according to present criteria). Then slides from tissue blocks were prepared and stained with hematoxylin and eosin (Hand E) and reevaluated by a pathologist, then appropriate slides were prepared from suitable paraffin blocks for IHC staining using a standard technique (streptavidin biotin–peroxidase technique) with nm23 (Clone 37.6, code NCL-nm23, Novocastra) and CD56 (Clone 123C3, code M7304, Dako) markers.

Statistical analysis

Results were reported as mean ± standard deviation (SD) or median for quantitative variables and percentages for categorical variables. The groups were compared using Student's *t*-test for continuous variables and the Chi-square test (or Fisher's exact test, if required) for categorical variables. *P* values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 18 (SPSS Inc, Chicago, IL, USA) for Windows.

RESULTS

A total number of 78 specimens of thyroid tissue (39 malignant and 39 benign) were selected for the study and subsequent confirmation of the diagnosis. From these, 61 cases (78.2%) were females and 17 (21.8%) were males. Most of the benign lesions (32 cases, 82.1%) were females. Among malignant lesions, 29 (74.4%) and 10 (25.65%) cases were females and males, respectively. The most common benign lesion was nodular goiter (32 cases, 59.0%), followed by follicular adenoma (7 cases, 17.9%), Hashimoto's thyroiditis (4 cases, 10.3%), Hürthle cell adenoma (4 cases, 10.3%), and Graves disease (1 case, 2.46%). All the malignant specimens were PTC including classic PTC (28 cases, 71.7%), follicular variant (5 cases, 12.8%), tall cell variant (3 cases, 7.7%), diffuse sclerosing variant (2 cases, 5.2%), and micropapillary carcinoma (1 case, 2.6%).

Results of CD56 staining

Of total 39 studied benign cases, 36 cases (92.3%) expressed CD56 [Figure 1] and only 3 cases (7.7%) were negative. In malignant specimens, 37 cases (94.9%) were negative for CD56 and only 2 cases had ability to express CD56 [Figure 2]. A significant relationship was found between CD56 staining and PTC ($P = 0.001$).

The sensitivity for expression of CD56 in separating benign thyroid lesions from malignant lesion (PTC) was 94.8%, and its specificity was 92.3%. The positive and negative predictive values of this test were 92.5% and 94.7%, respectively.

Among females, of total of 32 benign specimens, 30 cases (93.8%) were positive for CD56 and only 2 cases (6.35%) were negative, and of total of 29 malignant cases, 28 cases (96.6%) were negative for CD56 and only 1 case (3.4%) was positive. Given these findings, the sensitivity of this marker to differentiate between malignant and benign lesions in female gender was 96.5% and the specificity was 96.7%. The positive and negative predictive values were 93.3% and 96.7%, respectively. There was a significant association between malignant lesions and expression of CD56 ($P = 0.001$).

In male gender, of total of 7 benign thyroid lesions, 6 cases (85.75%) were positive for CD56 and only 1 case (14.3%) was negative, and of total of 10 cases of malignant thyroid lesions, 9 cases (90.0%) did not express CD56, and only 1 case (10.0%) was positive. The sensitivity and specificity of this marker were 90.0% and 85.7%, respectively. The positive and negative predictive values were 90.0% and 85.7%, respectively. A statistically significant relation was detected between CD56 and the type of thyroid lesions (malignant vs. benign) in male gender ($P = 0.002$).

Results of nm23 staining

Among 39 cases of benign thyroid lesions, 37 cases (94.9%) were positive for nm23 [Figure 3a] and only 2 cases (5.1%) were negative. Among 39 cases of malignant thyroid lesions (PTC) all cases (100%) were positive for nm23 [Figure 3b]. A significant association was not found between nm23 expression and types of thyroid lesions ($P = 0.147$).

The sensitivity of this marker was 100%, while its specificity was 5.1%. The positive and negative predictive values were 51.3% and 100%, respectively.

DISCUSSION

Pathologic examination using H and E staining is the gold standard in diagnosis of thyroid nodules. Morphologic overlap between follicular neoplasm and follicular variants of PTC is

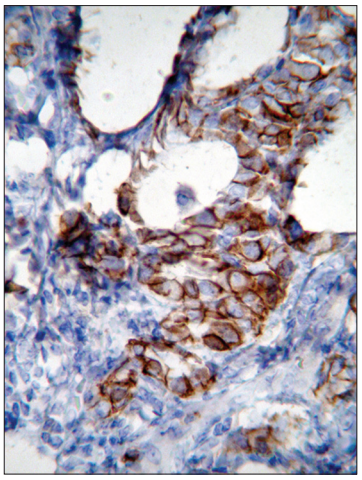

Figure 1: CD56 staining in a benign thyroid lesion (IHC ×400)

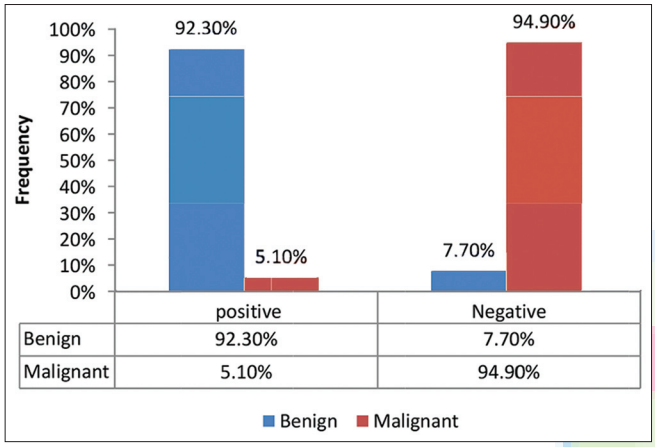

Figure 2: Frequency of CD56 in benign and malignant thyroid lesions

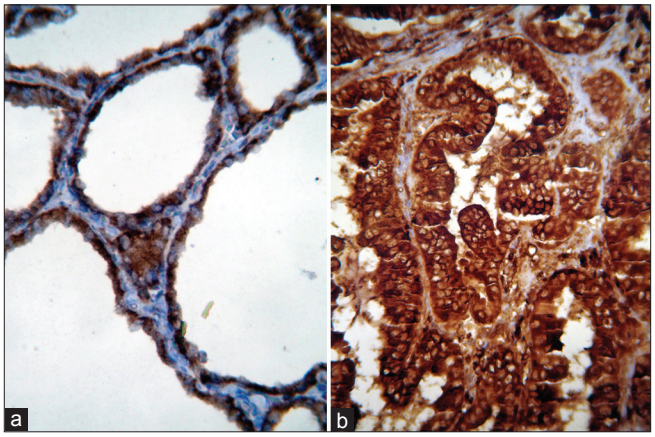

Figure 3: (a) nm23 staining in a benign thyroid lesion (IHC ×100), (b) nm23 staining in papillary thyroid carcinoma (IHC ×400)

common, and it is difficult to reach at definite diagnosis in some cases.[9] Considering this fact that incorrect diagnosis (over- or underdiagnosis) may cause complications and may even lead to patients' death, so, correct diagnosis and subsequently proper treatment are mandatory. Differential diagnosis of these cases may be possible by using IHC. CD56 is expressed in follicular thyroid cells and may be helpful in diagnosis of thyroid lesions.[6] Young park *et al.*[10] showed that CD56 has an important role as a negative diagnostic marker for PTC and differentiation from other malignant and benign lesions. In this study, expression of the CD56 gene in benign lesions was 93%, while it was positive only in 5% of malignant lesions (PTC).

EI Demellawy *et al.*[11] showed diffuse expression of CD56 in neoplastic follicular epithelium except PTC (including follicular variants of PTC). In other words, lack of expression of CD56 in PTC is strongly helpful in differential diagnosis of PTC from other neoplastic lesions with follicular cell origin. They concluded that CD56 is useful to differentiate PTC from benign lesions with sensitivity and specificity of 100%.[6,11] Our findings are consistent with their results. In our study, sensitivity and specificity of CD56 in differentiation of PTC from benign lesions were found to be 94.8% and 92.3%, respectively. Therefore, CD56 had high sensitivity and specificity and is helpful in differentiation of PTC and its follicular variants from other thyroid neoplasms with follicular cells origin. Loss of the expression of CD56, also seems to serve as a good marker of malignancy in cytologic and tissue specimens.[12,13]

In the present study, the CD56 gene was expressed in 93% of all benign lesions, while it was only found in 5% of malignant thyroid lesions (PTC). Because of high sensitivity and specificity of this test, IHC can be used to reach at definite diagnosis and differentiation between benign lesions and PTC, so, it is possible to decrease diagnostic mistakes between PTC and benign lesions.

Nm23 is a suppressor gene for metastasis which is a nucleoside homologous of phosphate kinase.[2] A significant association has been noted between decreased expression of this gene and metastatic behavior of some cancers including breast cancer, melanoma, hepatocellular carcinoma, and ovarian cancer.[9] However, in hematologic neoplasms and prostate cancer, high expression of this gene had been associated with poor prognosis.[8]

Nm23 exists in follicular thyroid cells and since its role in prevention of metastasis of some cancers has been shown, it was applied for the differential diagnosis between benign and malignant thyroid lesions. In this study, all malignant cases expressed nm23 on their cell surfaces and also in 37 out of 39 benign lesions (94.9%). Our results illustrated that the sensitivity of this biomarker is 100%, while its specificity is only 5.1%. Thus, no specific relation was detected between nm23 gene expression and types of thyroid lesions. Our findings were similar to those of Moradi Tabriz *et al.*[7] They assessed expression of nm23 in PTC and follicular neoplasm. No significant difference was found between nm23 expression in follicular adenoma and follicular carcinoma. Moreover, they did not found any significant relation between nm23 and metastatic behavior in PTC and follicular carcinoma. Nm23 was positive in both benign and malignant thyroid lesions and had low positive predictive value, so it is not useful in differential diagnosis of benign from malignant thyroid lesions.

CONCLUSION

Our results showed that CD56, as a biomarker, is helpful in differential diagnosis of PTC from other thyroid lesions, especially in cases with inconclusive results of traditional H and E staining. This marker could be an appropriate guide for physicians to choose the best treatment, decreasing complications and improvement of final prognosis.

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