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Prognostic value of HER2/neu expression in papillary thyroid carcinoma

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Abstract

Thyroid carcinomas are the most common endocrine tumors account for 1–2% of all malignancies. Papillary thyroid carcinoma is the most frequent type, representing more than 70% of thyroid malignancies. Although PTC has a favorable prognosis overall. However, there is a minor fraction of patients with a dismal course of disease. Proto-oncogene HER-2/neu (C-erbB2) amplification or overexpression plays an important part in tumor development, progression and aggressiveness, through direct effects on the cell cycle, angiogenesis, cellular motility and apoptosis. To study the prevalence and clinical significance of HER2 overexpression and its association with clinicopathological featuresof papillary thyroid carcinoma (PTC)in Tobruk-Libya The study group included 142 selected cases of papillary thyroid carcinoma, diagnosed at Pathology department of Tobruk Medical Center, Libya, between 2016 and 2019. All patients were surgically treated and underwent total thyroidectomy. Other clinicopathological data (gender, age, tumor size and lymph node metastasis) were extracted from medical files. All cases are stained with Hematoxylin and eosin stains and immunohistochemistry for Her2/neu. The details of 142 patients selected for analyses are as follows. The mean age of the patients at initial surgery was 36.4 years (range, 26–58 years), and 34 were (23.9%) males and 108 (76.1%) were females. 103 cases of the tumours were conventional papillary carcinomas (72.5%); 23 cases were papillary microcarcinoma (16.2%) and 16 cases were the follicular variant of papillary thyroid carcinoma (11.3%). Tumor size ranged between 2 and 42 mm, with a mean of 16.34 mm. Multifocality was present in 36 cases (25.4%) while 106 cases (74.6%) were unifocal. Lymph nodes metastasis were present in 61 cases (43%) and 81 cases (57%) shows no lymph nodes metastasis. Immunohistochemical analysis of HER2 expression was shown in all cases. While 118 cancers (83.1%) showed negative HER2 staining (score 0 and 1), there were 92 with score 0 and 26 with 1+. 22 cases showed positive HER2 immunostaining (15.5%) with 2+ and 2 (1.4%) with 3+. Total number of cases which demonstrated overexpression of 2+/3+ were 24 (16.9%). HER-2/neu can be used as prognostic marker useful for papillary thyroid carcinoma with the well-known clinicopathological prognostic factors.

Keywords: Immunohistochemistry (IHC); HER2/neu; Papillary thyroid carcinoma

Introduction

Thyroid carcinomas, originating from the follicular cells, are the most common endocrine tumors. They account for 1–2% of all malignancies [1], and more than 90% are differentiated forms, classified according to the histopathological criteria in two main groups: papillary thyroid carcinomas (PTCs) and follicular thyroid carcinomas (FTCs) [2]. PTC is the most frequent type, representing more than 70% of thyroid malignancies [3]. Although PTC has a favorable prognosis overall, with an average 10-year survival rate of over 90% [4]. However, there is a minor fraction of patients with a dismal course of disease. Tumor recurrence occurs in approximately 5% of PTC and the mortality rate is 1–2% [5].

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Therefore, the identification of new, complementary prognostic factors can be regarded as a challenging issue in thyroid pathology [6]. Aggressive malignant behavior is strongly related to various clinicopathological variables, including tall cell variant, advanced stage, vascular invasion and nodal or distant metastasis. These parameters are statistically powerful but still not sufficient to predict unfavorable disease course in all patients [5].

As our knowledge on the molecular mechanisms involved in thyroid cancer development and progression continuously increase, it can be hoped, that molecular information will eventually contribute to a better initial assessment of tumor's aggressiveness. Proto-oncogene HER-2/neu (C-erbB2), also known as CD340, is located on the 17q chromosome and it codifies the transmembrane tyrosine kinase receptor for the epidermal growth factor (EGF) [7]. Its amplification or overexpression plays an important part in tumor development, progression and aggressiveness, through direct effects on the cell cycle, angiogenesis, cellular motility and apoptosis [8].

HER-2/neu is considered a new prognostic factor in numerous types of cancer. It is involved in tumor biology, with a key role in the uncontrolled cell growth. HER-2/neu overexpression, firstly demonstrated in breast and ovary cancer [9] and later confirmed in gastric, colon, lung and bladder cancer [10] is associated with poorly differentiated phenotype, high metastasis capacity and poor overall survival [11]. Moreover, HER-2/neu becomes a therapeutic target in the breast and gastric cancer [12].

HER-2/neu overexpression in PTC has been identified in the aggressive forms with an increased potential of metastasis, allowing the supplementary Herceptin therapy for these patients, similar to breast cancer [9]. However, data on HER-2/neu involvement in PTC are controversial. HER-2/neu overexpression is reported in a wide range of values, varying from 0% to 79% [13].

Due to increased incidence of papillary thyroid cancer in Tobruk, Libya, we were able to collect a cohort of 142 papillary thyroid cancer with follow up information. In this project we utilized this patient collection to investigate prevalence and clinical significance of HER2 overexpression in papillary thyroid cancer.

Material and Methods

The present study is a retrospective study.

The study group included 142 selected cases of papillary thyroid carcinoma, diagnosed at Pathology department of Tobruk Medical Center, Libya, between 2016 and 2019. All patients were surgically treated and underwent total thyroidectomy. The selection process was based on the histological criteria for diagnosis of papillary thyroid carcinoma.

Other clinicopathological data (gender, age, tumor size, focality and lymph node metastasis) were extracted from medical files.

Five tissue specimen of normal thyroid tissue and other five tissue specimen of thyroid hyperplasia were added in the study to compare HER2/neu expression.

Processing Procedures

For each case, a representative paraffin-embedded tissue was chosen.

The paraffin wax sections were cut at 4 microns and stained by:

- Hematoxylin and eosin stain for routine histopathological examination.
- Immunohistochemical staining by HER2/neu monoclonal antibodies.

Each case of papillary thyroid carcinoma was studied for histopathological diagnosis.

Each section obtained from the blocks was placed on positive charge slides, dewaxed in xylene, rehydrated in consecutive descending concentrations of ethanol (100%, 90%, 80%, and 70%), and rinsed in distillated water.

For antigen retrieval, slides were placed in a plastic container filled with sufficient citrate buffer pH 6 and heated in a microwave oven at 100ºC for three successive times, five minutes each. The amount of fluid in the container was checked and was added if necessary to prevent slides from drying out.

The slides were immersed in 3% hydrogen peroxide for 10 minutes to block endogenous peroxidase, and incubated with the primary antibody for HER-2/neu (rabbit monoclonal, Thermo Scientific), at 1:100 dilution, overnight, at 40C. Chromogen application by using DAB (3,3-diaminobenzidine tetrahydrochloride). The counterstaining of the sections was done with

Mayer's Hematoxylin. Positive and negative controls have been simultaneously run in order to verify the accuracy of the technique.

The evaluation of HER-2/neu expression was based on an adapted semiquantitative score proposed for thyroid carcinomas [14], that assess not only membranous, but also cytoplasmic immunopositivity.

Briefly, tumors were categorized into four groups based on intensity score (0, 1+, 2+, 3+). Intensity score 2+ and 3+ was taken as positive

Statistical Analysis

The collected data were coded then entered and analyzed using the SPSS version 22 (Statistical package for social science). Descriptive statistics was done for categorical variables by frequency and percentage, and for numerical variables in the form of mean and standard deviation (mean ± SD). Suitable statistical tests of significance were used: Chi-Square ($\chi 2$) test for categorical data & P-values equal to or less than 0.05 were considered statistically significant.

Results and Discussion

Clinicopathological Features

The details of 142 patients selected for analyses are as follows. The mean age of the patients at initial surgery was 36.4 years (range, 26–58 years), and 34 were (23.9%) males and 108 (76.1%) were females. 103 cases of the tumours were conventional papillary carcinomas (72.5%); 23 cases were papillary microcarcinoma (16.2%) and 16 cases were the follicular variant of papillary thyroid carcinoma (11.3%). Tumor size ranged between 2 and 42 mm, with a mean of 16.34 mm. Multifocality was present in 36 cases (25.4%) while 106 cases (74.6%) were unifocal. Lymph nodes metastasis were present in 61 cases (43%) and 81 cases (57%) shows no lymph nodes metastasis.

HER2 expression

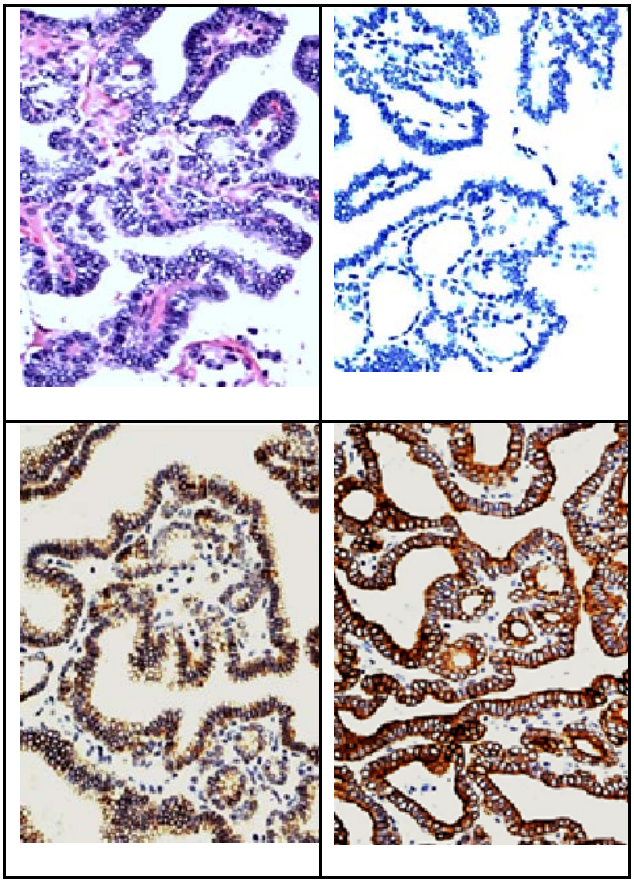
Immunohistochemical analysis of HER2 expression was shown in all cases. While 118 cancers (83.1%) showed negative HER2 staining (score 0 and 1), there were 92 with score 0 and26 with 1+.22 cases showed positive HER2 immunostaining (15.5%) with 2+ and 2 (1.4%) with 3+. Total number of cases which demonstrated overexpression of 2+/3+ were 24 (16.9%) (Figure 1).

HER-2/neu positivity was noticed in 24 (16.9%) cases, from which 17 cases were classified as conventional papillary thyroid carcinoma, 4 cases were classified as papillary microcarcinoma subtypes and 3 cases were classified as follicular variant of papillary thyroid carcinoma subtypes (Table 1).

Immunohistochemical analysis of HER2 expression was negative in normal thyroid follicular cells and also negative in follicular cells of thyroid hyperplasia.

Table 1: HER-2/neu expression in different subtypes of papillary thyroid carcinoma (PTC)

Histological subtypes	HER2/neu expression		Total
	Positive	Negative	
Conventional	17	86	103
Papillary microcarcinoma	4	19	23
Follicular variant	3	13	16
Total	24	118	142



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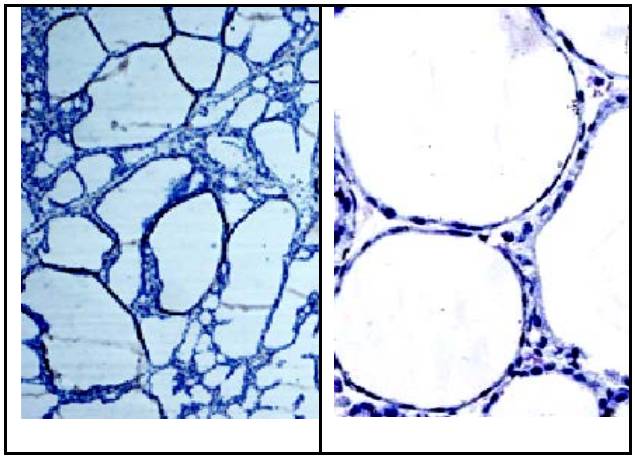

Fig. (1): A- Classic papillary thyroid carcinoma (H&E 40x), B- Negative HER2/neu expression in papillary thyroid carcinoma (HER2/neu 40x), C- Positive HER2/neu expression in papillary thyroid carcinoma (2+) (HER2/neu 40x), D- Positive HER2/neu expression in papillary thyroid carcinoma (3+) (HER2/neu 40x), E- Negative HER2/neu expression in normal thyroid follicles (HER2/neu 40x) and F- Negative HER2/neu expression in follicular cells of thyroid hyperplasia (HER2/neu 40x).

Correlations between HER-2/neu expression and clinicopathological prognostic factors

Univariate analysis revealed significant differences between HER-2/neu expression (positive versus negative) and tumor size (Table 2). No significant correlation was found between HER-2/neu expression and age, gender, histological subtypes, tumor focality, as well as lymph node metastases (Table 2).

Table 2: Relationship between HER-2/neu expression and clinicopathological characteristics.

Clinicopathological characteristics	**HER2/neu expression**		***Chi*-square test**
	Negative 118	**Positive 24**	
Age at initial surgery (median)			
< 33 (71 cases)	61 (85.9%)	10 (14.1%)	*P*=0.371
≥ 33 (71 cases)	57 (80.3%)	14 (19.7%)	
Gender			
Males (34 cases)	29 (85.3%)	5 (14.7%)	*P=0.695*
Females (108 cases)	89 (82.4%)	19 (17.6%)	
Tumor size (median)			
< 12 (71 cases)	65 (91.5%)	6 (8.5%)	*P*=0.007*
≥ 12 (71 cases)	53 (74.6%)	18 (25.4%)	
Histopathological subtype			
Conventional (103 cases)	86 (83.5%)	17 (16.5%)	*P*=0.973
Microcarcinoma (23 cases)	19 (82.6%)	4 (17.4%)	
Follicular variant (16 cases)	13 (81.3%)	3 (18.7%)	
Focality			
Unifocal (106 cases)	91 (85.8%)	15 (14.2%)	*P*=0.133
Multifocal (36 cases)	27 (75%)	9 (25%)	
Lymph node metastasis			
+ve (61 cases)	50 (82%)	11 (18%)	*P*=0.755
-ve (81 cases)	68 (84%)	13 (16%)	

*p-value <0.05 was considered to be statistically significant.

HER2 is a proto-oncogene that has an important role in the development and progression of human cancers, and especially breast cancer [15]. So, it is an essential marker in the molecular classification of breast cancer [16], that it is overexpressed in 15–30% of invasive forms [17].

Many researches demonstrated that HER-2/neu overexpression correlates with the disease stage, number of metastatic axillary lymph nodes, histological type, absence of estrogen and progesterone receptors and recurrence risk [9]. Consequently, the value of HER-2/neu as a therapeutic target reformed the breast cancer

treatment, improving the clinical outcome [18, 19].

Several studies analyzed theHER-2/neu expression in ovary [7], gastric, colonic andesophageal [20], endometrial [21], lung [22], andbladder [23] tumors. These studies sustain that HER-2/neuoverexpression is associated with a more aggressivedisease, incomplete response to primary therapy and worseoverall survival – particularly in ovarian cancer [24]. Therefore, anti-HER2 therapy, such as trastuzumab, has been applied in breast and gastric cancer patients with HER2 overexpression [15].

The mechanism underlying the specific role ofHER-2/neu in the thyroid carcinogenesis is still unknown.A large heterogeneity in HER-2/neu expression, varyingbetween 0% and 79%, is reported [13].

There are differences in HER2/neu expression in thyroid carcinomas resulting from the great variability of the size and general characteristics of the studied groups and from the discrepancies in the methods used for the HER-2/neu scoring, including the subjectivity of evaluation [25, 26].

Ruggeri et al. show a significantly higher HER-2/neuexpression rate in the follicular thyroid carcinoma compared to papillary thyroid carcinoma [27], whereasMdah et al. [14] and Utrilla et al. [28] report that HER-2/neupositivity in 6.9%, respectively 52% of the analyzed papillary thyroid carcinomacases, but no expression in follicular thyroid carcinoma.

We described the degree of HER2/neu staining according to criteria for breast cancer [27, 29], as there are no established criteria for this parameter in thyroid cancer [13]. Cytoplasmic staining isfrequently considered as positive immunoreaction in theHER-2/neu assessment [25, 28, 30, 31]. However, thecytoplasmic immunoreactivity of HER-2/neu, possible dueto the presence of a distinct protein in the mitochondrialcristae [7].

Caria et al. show a relationship betweenHER-2/neu and BRAFV600E mutation in familial PTCwith aggressive behavior [32], and sustain the HER-2/neuoverexpression even in the absence of the gene amplification[13].

The present work focused on the HER-2/neu expressionin available different histological subtypes of papillary thyroid carcinoma and its relationshipwith classical clinicopathological prognostic factors. Inour series, we obtained HER-2/neu positivity in 16.9%,similar to the results reported in other previous papers;Delia et al., 20.8% [7], Siraj et al., 19.7% [13], Ruggeri et al., 18% [27] andSugishita et al., 23% [33].

In our study, HER-2/neu positivity was noticed in 17 cases (16.5%) of conventional papillary thyroid carcinoma, 4 cases (17.4%) of papillary microcarcinoma subtypes and 3 cases (18.7%) of follicular variant of papillary thyroid carcinoma subtypes. These subtypes are considered as non-aggressive. This is in agree with Delia et al. study that found HER-2/neu overexpression was found mainly in non-aggressive histological subtypes of papillary thyroid carcinoma in comparison with the aggressive ones. This observation withstands the association between HER-2/neu and histological subtypes with good prognosis [7].

The clinicopathological characteristics and HER-2/neu expression relationship in our results shows no significant association with age, gender, histopathological subtypes, focality and lymph node metastasis. However, there is significant association with tumor size. Most of these results are similar with several different studies that reportthat is no HER-2/neu association with age, gender, tumor size[14, 27], tumor stage [13, 25,33], lymph node metastasis[13, 14,27, 34], histological type [25, 35], and patient survival [13]. However Delia et al.studydemonstrated that HER-2/neu overexpression correlateswith the histological subtypes with a better clinical course and tumor focality [7]. Unfortunately, there is no much studies to discuss with their results.

Limitations of the study

Our study has some limitations. First, a small sample size was used to identify the value of HER2/neu expression in papillary thyroid carcinoma because of the short study period. Second, we described the degree of HER2 staining according to criteria for breast cancer, as there are no established criteria for this parameter in thyroid cancer. Third, there is no follow-up of the patients. Patients with papillary thyroid cancer rarely die of their disease, and this study is designed and performed recently.

Conclusion

Our results show the potential of HER-2/neu as supplementary marker useful for papillary thyroid

carcinoma in low-risk histological groups, with the well-known clinicopathological prognostic factors.

Definitely, we are attentive that further, larger researches are compulsory to validate HER-2/neu as independent prognostic or predictive factor in papillary thyroid carcinoma. A long-term follow-up study will be necessary to identify the clinical value of HER2/neu expression in papillary thyroid carcinoma.

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