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Expression of b-HCG in Breast Tumors

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Abstract

Background: Human chorionic gonadotropin (HCG) is a glycoprotein hormone, which consists of two polypeptide subunits (alpha and beta), produced by syncytial trophoblast cells of the placenta during pregnancy. Ectopic HCG production occurs in many tumors including breast tumor.

Objectives: The objective of the study is to investigate the expression of β–HCG in breast tumor and its correlation with pathological prognostic factors (age, tumor type, site, size, histological grade, lymphocytic infiltration, vascular invasion and lymph node involvement).

Methods: A total of 44 breast tumors were selected, consisting of eight benign lesions (Fibrocystic disease in four cases and fibroadenoma in the rest) and 36 malignant breast tumors (invasive ductal carcinoma (21 cases) all of not-otherwise-specified type (NOS), in situ ductal carcinoma (6 cases), invasive lobular carcinoma (6 cases) and in situ lobular carcinoma (3 cases).

Results: β-HCG expression was found in 6 of 36 malignant breast tumors (16.7%). None of the benign breast lesions showed β-HCG expression. High expression of β-HCG is seen more frequently in infiltrative ductal carcinoma with higher-grade tumor and in old age group (≥50 years).

Conclusion: It was concluded that high expression of β-HCG is seen more frequently in infiltrative ductal carcinoma with higher grade. There was a high β-HCG expression in tumors more than or equal to 5-cm diameter.

Key words: Breast tumors, β-HCG

Introduction

Breast cancer is the most common cancer among women world wide, and is the second most common after lung cancer for both genders, according to the World Health Organization [(1)].

Human Chorionic Gonadotropin (HCG) is a glycoprotein hormone, which consists of two polypeptide subunits (alpha and beta), produced by syncytial trophoblast cells of the placenta during pregnancy [(2,3)]. The β-subunit of glycoprotein hormone is unique, giving the biological and immunological specificity of the HCG hormone [(4)]. Ectopic HCG production occurs in many tumors including breast [(5)]. Several reports have shown that the production of this hormone by a neoplasm is associated with a more aggressive behavior [(6)].

A number of studies using peripheral blood of breast cancer patients, showed a wide variety in the frequency of raised levels of β-HCG [(7,8)].

The ectopic production of HCG by nontrophoblastic tumors is well documented. Adenocarcinoma arising in the mammary gland

has been shown to stain positively for the Beta subunit of HCG [5].

All tumors found by radioimmunoassay to contain β-HCG were also found to be immunohistochemically positive in formalin fixed tissue whereas those not containing measurable HCG did not stain significantly [9].

The presence of increased serum levels of HCG and its metabolites is generally agreed to be a sign of poor prognosis [10,11].

Methods

This is a retrospective study of forty-four cases of surgical lesions (total mastectomy and excisional biopsies). The cases were consist of eight benign lesions (Fibrocystic disease (four cases) and fibroadenoma (four cases)) and 36 malignant breast tumors (invasive ductal carcinoma (21 cases) all of not-otherwise-specified type (NOS), in situ ductal carcinoma (six cases), invasive lobular carcinoma (six cases) and in situ lobular carcinoma (three cases)). These cases were retrieved from Al-Kadhemia Teaching Hospital Laboratory and Medical City Hospital Laboratory for the period June, 2003 to June, 2005. For each case representative sections were stained with haematoxylin and eosin (H & E) and others were stained immunohistochemically for β-HCG from the available formalin fixed paraffin embedded tissues.

Haematoxylin and eosin stained sections were examined for the type of tumor, histological grading (WHO and Bloom-Rechardson grading system), also for identifying vascular invasion and lymphocytic infiltration.

Statistical analysis of the data was performed using Chi square test (contingency table). The results were considered statistically significant when the alfa level of significance (p) was equal or less than 0.05.

Results

The expression of β-HCG was positive in 6 of 36 malignant breast lesions (16.7%). None of the benign or insitu breast lesions were positive for β-HCG. Five out of 21 invasive ductal carcinoma (23.8%) were β-HCG positive (Figure 1).

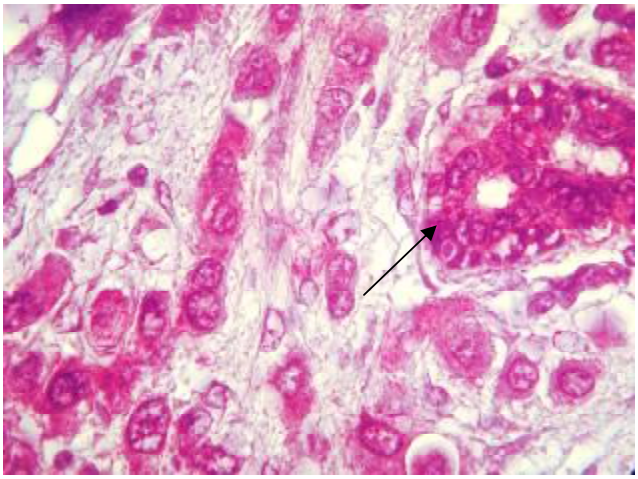

Figure 1. Invasive ductal carcinoma shows positive reactivity for **β**-HCG. Grade **III**. The cytoplasm stains with red color. (X 1000) (Immunohistochemical staining, alkaline phosphatase method).

One out of 6 invasive lobular carcinoma (16.7%) were β-HCG positive (Figure 2).

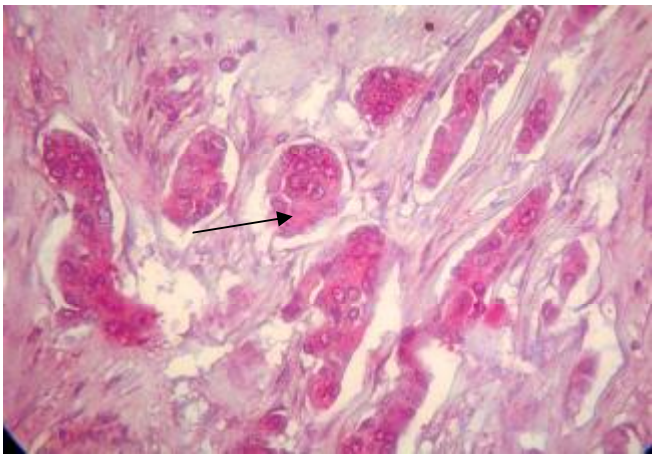

Figure 2. Invasive lobular carcinoma shows positive reactivity for **β**-HCG Grade **II**. The cytoplasm stain with red color (x 400). (Immunohistochemical staining, alkaline phosphatase method).

No statistical difference for both ductal and lobular carcinoma (P= 0.146) and (P=0.427), respectively. In invasive ductal carcinoma 3 out of 5 cases (60%) were focally positive β-HCG. In invasive lobular carcinoma 1 of 1 case (100%) was Focal positive β-HCG. Statistical analysis revealed no significant difference (P=0.836) (Table 1).

Table 1. β-HCG expression in breast carcinoma according to Pattern of staining

Type of malignancy	Pattern of staining		Total
	Focal	Diffuse	
Invasive ductal carcinoma	3 (60%)	2 (40%)	5
Invasive lobular carcinoma	1(100%)	0	1
Total	4	2	6

P = 0.836 (not significant)

Two of the six β-HCG positive cases were for women of less than 50 years old group and the other four cases were for more than 50 years old. Statistical analysis revealed a significant difference (P=0.039) (Table 2).

Table 2. β-HCG expression in breast carcinoma relation to age groups

Age group (years)	b-HCG expression		Total
	Positive	Negative	
≤ 35 years	0	9 (100%)	9
36-49 years	2 (8.3%)	22 (91.7%)	24
≥ 50 years	4 (36.4%)	7 (63.6%)	11
Total	6	38	44

P = 0.039 (significant difference)

The six β-HCG positive cases were distributed equally between left and right-breast. Statistically there was no significant difference between 2 sites (P =0.821). Two out of 14 cases (14.3%) of tumor size (2-5 cm) were positive β-HCG.

Four out of 20 cases (20%) of tumor size (> 5 cm) showed β-HCG expressions, although statistically there was no significant difference (P=0.511) (Table 3).

Table 3. β-HCG expression in breast carcinoma in relation to size

Tumor size	b-HCG expression		Total
	Positive	Negative	
≤ 2 cm	0	2 (100%)	2
2-5 cm	2 (14.3 %)	12 (85.7%)	14
> 5 cm	4 (20%)	16 (80%)	20
Total	6	30	36

P = 0.511 (not significant).

According to WHO grading system, β-HCG expressions were found in 2 of 8 (25%) of moderate differentiated ductal carcinoma and in 3 of 12 cases (25%) of poorly differentiated ductal carcinoma. Statistically there was no significant difference (P=0.795). However, according to modified Bloom- Richardson grading system of 21 invasive ductal carcinoma, 3 out of 12 cases (25%) of grade II expressed β-HCG, 2 out of 6 cases (33.3%) of grade III showed positive β-HCG expression and none of the grade I express β-HCG, Statistically there was no significant difference (P=0.704). While one out of 3 invasive lobular carcinoma of grade II (33.3%) showed positive β-HCG. Statistically there was no significant difference (P=0.691) (Table 4).

Table 4. β-HCG expression in breast carcinoma relation to grading system

Tumor grade		β-HCG expression		Total
		Positive	Negative	
1. Invasive ductal carcinoma				
1. WHO grading system*	Well differentiated	0	1 (100%)	1
	Moderate differentiated	2 (25%)	6 (75%)	8
	Poor differentiated	3 (25%)	9 (25%)	12
	Total	5	16	21
2. modified Bloom-Richardson** Grading System	Grade I	0	3 (100%)	3
	Grade II	3 (25%)	9 (75%)	12
	Grade III	2 (33.3%)	4 (66.7%)	6
	Total	5	16	21
2. Invasive lobular carcinoma				
1. modified Bloom-Richardson*** Grading system	Grade I	0	2 (100%)	2
	Grade II	1 (33.3%)	2 (66.7%)	3
	Grade III	0	1 (100%)	1
	Total	1	5	6

* P = 0.795 (not significant), ** P = 0.704 (not significant), *** P = 0.691 (not significant).

Discussions

Many studies had varying results, which led to marked discrepancies in the frequency of β-HCG detection in tumor specimens.

In this study β-HCG frequency considerably less than that of Agnantis et al (1992) [5] and higher than that of Nishiyama et al (1980) [12].

There are several explanations for the discrepant results, first sample size, second is the heterogencity of the tumor cells, and the HCG containing cells may be quite rare and sparsely scattered throughout large areas of tumor or in few clusters (Focal). In this study 60% were focally distributed for ductal carcinoma and 100% for lobular carcinoma which is similar to that reported by Nishiyams et al (1980) [12] and Bellet et al (1980) [13]. Thus the more sections are examined for each tumor the higher percentage of positive results would be expected.

A third factor involves differences in the staining methods used. Another factor that may account for some of the discrepancies involves the method of tissue preparation most of the studies have used formalin fixed, paraffin-embedded specimens including the present study while in McManus et al (1976) [14] who found highest rate

of β-HCG detection in tissue specimen studied fresh frozen sections.

Finally, the discordant results among the various studies may have been due, in part to different specificities of the antibodies used to detect β-HCG.

There is a continuing need to derive markers in breast tumors or in the sera of breast cancer patients, which may give a guide as to future prognosis as well as to, monitor the course of the disease.

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