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Association of CA 15-3 and CEA with Clinicopathological Parameters In Patients With Metastatic Breast Cancer

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Abstract

Background. Breast cancer is the most common cancer and the leading cause of cancer death for women**,** a third of women are diagnosed with breast cancer at a late stage when the disease has a poor prognosis. Serum tumor markers have been widely used as noninvasive tools for measuring treatment response, early diagnosis of recurrence and predicting prognosis. In breast cancer, the most widely used serum tumor markers are cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA). The aim of this study was to investigate the association of serum CA15-3 and CEA levels with clinicopathological parameters in patients diagnosed with metastatic breast cancer (MBC).

Patients and methods. This retrospective study was conducted on 50 patients who had used to predict response to chemotherapy in patients with metastatic breast cancer. The concentration of serum CA15-3 and CEA levels were measured using chemiluminescent enzyme immunoassays (ABBOTT ARCHITECT). The upper limits of normal for CA15-3 and CEA were 31.3 U/ml and 5 ng/ml, respectively.

Result. Of the 50 patients, elevated CA 15-3 and CEA levels at initial diagnosis of recurrence were identified in 37 (74%) and 32 (64%) patients, respectively. Elevated CA 15-3 and CEA levels were significantly associated with breast cancer molecular subtypes (P=0.005 and P=0.008, respectively). Elevated CA 15-3 level was correlated with bone metastasis (P=0.047).

Conclusion. CA 15-3 and CEA level elevation at initial diagnosis of recurrence were found to be associated with breast cancer molecular subtype; these serum tumor markers are frequently increased in the HER2-enriched and triple negative (TN) molecular subtypes of breast cancer.

Introduction

Each year more than one million women are diagnosed with breast cancer worldwide over half of whom will die from the disease (1), regional and distant recurrences remain a major threat to breast cancer patients (2), (3).

CA15-3 and CEA are the markers most widely used for surveillance purposes and monitoring of

treatment response in clinical practice (4).

Aim of the work

The work aims to analyze the association of serum CA 15-3 and CEA levels with clinicopathological parameters in patients with metastatic breast cancer and determined whether the elevation of these two tumor markers is correlated with metastatic site(s).

Patients and methods

This retrospective study was conducted at Clinical Pathology Department, Faculty of Medicine, Sohag University Hospitals on 50 patients who had used to predict response to chemotherapy in patients with metastatic breast cancer (MBC).

For each patient the following was done: I-History taking (including site of first metastasis), II-clinical examination- Routine investigations: 1- Complete blood picture,2- Liver function tests,3- Kidney function tests. IV - special investigations: A- Tumor markers: Cancer antigen 15-3, and CEA (Carcinoembryonic antigen), B- Immunohistochemistry: (Estrogen receptor (ER), Progesterone receptor (PR), Human epidermal growth factor receptor 2(HER2), Ki -67 proliferation index). V- Consent was taken from all patients. Inclusion criteria: All the patients were staged according to the American Joint Committee on Cancer (AJCC, 7th edition) TNM staging system for breast cancer, distant metastasis refers to the presence of breast cancer lesions at sites distant to the primary site. The sites of distant relapse were categorized as follows: bone, brain, liver, lungs, distant lymph nodes and pleura. Exclusion criteria: Breast cancer patients without distant spread excluded. About 5 ml venous blood was withdrawn from patients under aseptic conditions. Samples taken were divided into 2 tubes as follows: 2 ml of blood into K3 EDTA (ethylene- diamine- tetra acetic acid) VACUTAINER tubes for complete blood picture.3 ml blood into a sterile plain vacutainer for other investigations.

Tumor marker analysis: The concentration of serum CA 15-3 and CEA levels were measured using chemiluminescent enzyme immunoassays (ABBOTT ARCHITECT). The upper limits of normal for CA15-3 and CEA were 31.3 U / ml and 5 ng/ml, respectively. In this study, breast cancer was classified into five subtypes based on the expression of ER, PR, HER2 and Ki-67 proliferation index as follows: **1-** Luminal A, ER - and /or PR positive and Ki-67 <14%. **2** Luminal B, ER - and /or PR- positive and Ki-67 >14%. **3-** Luminal / HER2: ER- and/or PR - positive and HER2- positive. **4-** HER2-enriched, ER - and PR - negative and HER2- positive. **5-** Triple- negative (TN) subtype: ER -, PR - and HER2-negative.

Statistical analysis:

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, standard error, T-test, analysis of variance [ANOVA] test, and chi-square by SPSS V17. All the statistical assessments were two - sided and statistical significance was set at $P<0.05$.

Results

The clinicopathological characteristics of 50 metastatic breast cancer patients were analyzed. The median age of the subjects was 49 years (range, 25 -71 years). Patients are divided according to the level of CA15-3 into two groups: patients with normal level of CA15-3 and patients with elevated level of CA15-3. Also, Patients are divided according to the level of CEA into two groups: patients with normal level of CEA, and patient with elevated level of CEA.

Table (I) shows that serum levels of CA15-3 and CEA have no significant relationship with tumor size, lymph node status, and grade of tumor. **Highly significance difference** was found between normal and elevated CA15-3 as regard to molecular subtypes of breast carcinoma (P value = 0.005), and **highly statistical significance difference** was found between normal and elevated CEA as regard to molecular subtypes of breast carcinoma (P value = 0.008).

Table I. Correlation between serum CA 15-3 and CEA levels at initial diagnosis of recurrence and tumor size, nodal status, grade distribution, and molecular subtypes.

Character	CA 15-3			CEA		
	Normal	Elevated	P value	Normal	Elevated	P value
Tumor size						
T1	5(33%)	10(66.6%)	0.34	7(46.7%)	8(53.3%)	0.45
≥ T2	8(22.8%)	27(77.2%)		11(31.4%)	24(68.6%)	
Lymph node status						
N0	4(36.4%)	7(63.6%)	0.41	4(36.4%)	7(63.6%)	0.30
≥ N1	9(23.1%)	30(76.9%)		15(38.5%)	24(61.5%)	
Grade						
I	3(20%)	12(80%)	0.10	4(30.8%)	9(69.2%)	0.12
II	5(26.9%)	14(73.7%)		5(31.3%)	11(68.7%)	
III	7(43.8%)	9(56.2%)		10(47.6%)	11(52.4%)	
Molecular subtype						
Luminal A	5 (29.4%)	12 (70.6%)	0.005	8 (47.1%)	9 (52.9%)	0.008
Luminal B	4 (28.6%)	10 (71.4%)		5 (35.7%)	9 (64.3%)	
Luminal /HER2	1 (14.3%)	6 (85.7%)		2 (28.6%)	5 (71.4%)	
HER2-enriched	1 (25%)	3 (75%)		1 (25%)	3 (75%)	
Triple Negative	2 (25%)	6 (75%)		2 (25%)	6 (75%)	

Correlation between serum CA 15-3 and CEA levels and number of metastatic site and site of first distant metastasis was summarized in (Table II) No statistical significance was found between normal and elevated CEA as regard to number of metastatic site (P value = 0.45), **Statistical significance difference** was found between normal and elevated CA15-3 as regard to bone metastasis (P value = 0.049).

Table II. Correlation between serum CA 15-3 and CEA levels at initial diagnosis of recurrence and number of metastatic site and site of first distant metastasis.

Number of metastatic site							
Single		8 (34.8%)	15 (65.2%)	0.25	5 (21.7%)	18 (78.3%)	0.45
Multiple		5 (18.5%)	22 (81.5%)		13 (48.2%)	14 (51.8%)	
Metastatic site							
Bone	+	8 (80%)	2 (20%)	.049	5 (50%)	5 (50%)	0.50
	-	10 (77%)	3 (23%)		13 (100%)	0 (0%)	
Brain	+	1 (100%)	0 (0%)	0.39	1 (100%)	0 (0%)	0.45
	-	14 (64%)	8 (36%)		17 (77%)	5 (23%)	
Liver	+	1 (33%)	2 (66%)	0.58	2 (66%)	1 (33%)	0.45
	-	14 (70%)	6 (30%)		16 (80%)	4 (20%)	
Lung	+	2 (50%)	2 (50%)	0.50	2 (50%)	2 (50%)	0.50
	-	13 (68%)	6 (32%)		16 (84%)	3 (16%)	
Distant node	+	3 (100%)	0 (0%)	0.09	3 (100%)	0 (0%)	0.32
	-	12 (60%)	8 (40%)		15 (75%)	5 (25%)	
pleura	+	2 (100%)	0 (0%)	0.26	2 (100%)	0 (0%)	0.39
	-	13 (62%)	8 (38%)		16 (76%)	5 (24%)	

Table (III) shows that there is no correlation between hormonal receptors estrogen and progesterone, HER2 status and Ki-67 proliferation index with both levels of CA15-3 and CEA.

Table III. Correlation between serum CA 15-3 and CEA levels at initial diagnosis of recurrence and number

Character		CA 15-3			CEA		
		Normal	Elevated	P value	Normal	Elevated	P value
ER	Negative	6 (33.3%)	7 (21.9%)	0.38	10 (32.3%)	3 (15.8%)	0.19
	Positive	12 (66.7%)	25 (78.1%)		21 (67.7%)	16 (84.2%)	
PR	Negative	5 (27.8%)	9 (28.1%)	0.98	10 (32.3%)	4 (21.1%)	0.37
	Positive	13 (72.2%)	23 (71.9%)		21 (67.7%)	15 (78.9%)	
HER-2	Negative	16 (88.9%)	23 (71.9%)	0.15	25 (80.6%)	14 (73.7%)	0.57
	Positive	2 (11.1%)	9 (28.1%)		6 (19.4%)	5 (26.3%)	
Ki 67	<14%	8 (44.4%)	13 (40.6%)	0.79	14 (45.2%)	7 (36.8%)	0.56
	>14%	10 (55.6%)	19 (59.4%)		17 (54.8%)	12 (63.2%)	

Discussion

The present study was established to analyze the association of serum CA15-3 and CEA levels with clinicopathological parameters in patients with metastatic breast cancer and determined whether the elevation of these two tumor markers is correlated with metastatic site(s).

In our study, we found that no significant difference between tumour size and marker levels (p=0.34) in CA15-3 and (p=0.45) in CEA, this coincides with **Geng et al., 2015** who studied 284 metastatic breast cancer patients and found that there was no significant difference (p=0.45 in CA153) and (p=0.11 in CEA).

However, conflicting **Shao et al., 2015** and **Wu et al.,2014** they found that highly significant difference (P<0.001) in CA15-3 and CEA as regard difference between tumour size and marker levels.

As regard lymph node status, we found that no significant difference between nodal status and marker levels (p=0.41) in CA15-3 and (p=0.30) in CEA they agreed with **Geng et al., 2015** who reported that no significant difference between nodal status and marker levels (p=0.15 in CA15-3) and (p=0.43 in CEA)

Nevertheless, conflicting **Wu et al., 2014** and **Shao et al., 2015** who found that there was significant difference between nodal status and marker levels (P <0.001) in CA15-3 and CEA. (P =0.005) in CA15-3 and (P =0.019) in CEA respectively, while **Hosseni et al.,2015** found that there was significant difference between nodal status and CA15-3 (P <0.001) but no significant difference between nodal status and CEA (P =0.15).

Regarding grade and marker levels there was no significant difference in this study (p=0.11 in CA15-3) and (p=0.12 in CEA), this coincides with **Hosseini et al., 2015** who found that there was no significant difference between grade and marker levels (p= 0.60 in CA15-3) and (p= 0.49 in CEA).

In this study we found that there was significant difference between molecular subtypes and marker levels (p=0.005 in CA15-3), (p=0.008 in CEA) these results are in agreement with **Geng et al., 2015** who found that there was significant difference between molecular subtypes and marker levels (p <0.001 in CA15-3), (p= 0.032 in CEA).

On the other hand, **Wu et al., 2014** found that there was no significant difference between molecular subtypes and CA15-3 (p = 0.51) while there was significant

difference between molecular subtypes and CEA (p= 0.002).

The elevation of CA15-3 and CEA levels were significantly greater in HER2-enriched tumours (75%) and triple- negative tumours (75%) than in patients with luminal subtypes, with CA15-3 was (70.6%) Luminal A and (71.4%) Luminal B, while with CEA was (52.9%) Luminal A, (64.3%) Luminal B, this result coincides with **Shao et al., 2015** who found that the elevation of CA15-3 was significantly greater in HER2-enriched tumours (27.3%) and triple-negative tumours (18.9%) than in patients with luminal subtypes: (8.8%) Luminal A and, while this is against **Shao et al., 2015** who found elevated CEA was significantly greater in Luminal B (14.6%) and HER2-enriched tumours (9.1%) than Luminal A (5.9%) and triple- negative tumours (2.7%), also Wu et al., 2014 reported that the elevation of CA15-3 and CEA levels were significantly greater in HER2- enriched tumours (15.1%) and Luminal B(15.3%) in CA15-3 , (12.5%) in CEA than triple-negative tumours (14.3%) in CA15-3, (1.6%) in CEA and in patients with Luminal A and (10.3%) in CA15-3, (5%)in CEA .

As regard number of metastatic site (single or multiple), no significant difference was detected with marker levels (p=0.25 in CA15-3), (p=0.45 in CEA) this coincides with **Hosseini et al., 2015** who found that there was no significant difference between number of metastatic site and marker levels (p=0.82 in CA15-3), (p=0.21 in CEA)

However, **Geng et al., 2015** reported that there was no significant difference between number of metastatic site and marker levels with elevated CEA (p=0.72) while elevated CA 15-3 was significantly more common in metastatic breast cancer with multiple metastatic sites (p<0.001) compared to metastatic breast cancer with single metastasis (p= 0.716).

Our study revealed that there was no significant difference regarding all sites of first distant metastasis and levels of CA 15-3 and CEA (p>0.05 in CA15-3 and CEA) except elevated CA15-3 in bone metastasis (P=0.049) , this coincides with **Geng et al., 2015** who found that there was no significant difference regarding all sites of first distant metastasis and levels of CA 15-3 and CEA except elevated CA15-3 in bone metastasis (P=0.017).

In our research elevation of CA15-3 and CEA did not correlate with hormonal receptors, HER2 and Ki-67 proliferation index; no statistical significance was found regarding estrogen receptor status and levels of CA15-3 and CEA (p=0.38 in CA15-3), (p=0.19 in CEA), regarding progesterone receptor status ,no statistical significance was found between progesterone receptor status and levels of CA15-3 and CEA (p=0.98 in CA15-3), (p=0.37 in CEA), regarding HER2 receptor status ,no statistical significance was found between HER2 receptor status and levels of CA15-3 and CEA (p=0.15in CA15-3), (p=0.57 in CEA),and regarding Ki-67 proliferation index, no statistical significance was found between Ki-67 proliferation index and levels of CA15-3 and CEA (p=0.79 in CA15-3), (p=0.56 in CEA), this coincides with **Hosseini et al., 2015** who found that there was no significant difference between hormonal receptors and HER2 status with marker levels; no statistical significance was found regarding estrogen receptor status and levels of CA15-3 and CEA (p=0.22 in CA15-3), (p=0.31 in CEA), regarding progesterone receptor status ,no statistical significance was found between progesterone receptor status and levels of CA15-3 and CEA (p=0.21 in CA15-3), (p=0.67 in CEA), and regarding HER2 receptor status ,no statistical significance was found between HER2 receptor status

and levels of CA15-3 and CEA (p=0.43in CA15-3), (p=0.36 in CEA), but this is against **Shao et al., 2015** who found that estrogen receptor was significantly associated with elevated level of CA153 (p=0.001), while no statistical significance was found between estrogen receptor status and elevated level of CEA, regarding progesterone receptor status , no statistical significance was found between progesterone receptor status and elevated level of CA15-3 (p=0.32),while progesterone receptor was significantly associated with elevated level of CEA (p=0.03), regarding HER2 receptor status no statistical significance was found between HER2 receptor status and elevated level of CA15-3(p=0.54) ,while HER2 receptor status was significantly associated with elevated level of CEA (p=0.003), and regarding Ki-67 proliferation index, no statistical significance was found between Ki-67
proliferation index and both levels of CA15-3 and CEA (p=0.28 in CA15-3), (p=0.09 in CEA).

Conclusion

CA15-3 and CEA level elevation at initial diagnosis of recurrence were found to be associated with breast cancer molecular subtype; these serum tumor markers are frequently increased in the HER2-enriched and TN molecular subtypes of breast cancer.

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