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Correlation of serum CA 15-3 with histological types of breast cancer

Mahwish Nowshad

IPDM Khyber Medical University, Peshawar

Corresponding author email: moonlight5578@gmail.com

Fozia Rauf

Peshawar Medical College

Naveed Sharif

Khyber Medical University

Ishfaq

Kuwait Teaching Hospital

Ambareen Gul

Mercy Teaching Hospital

Naeemullah

Women and Children Hospital Charsadda

Abstract---Background: The incidence of breast cancer and its fatal effects are constantly on a rise across the globe. Breast cancer is the most common cancer in Pakistan with approximately 1 in every 9 Pakistani women developing breast cancer at some stage of their life. There is a constant search for better screening methods which help in early detection and also reflect upon the prognosis of the tumor. CA 15-3 is a reliable serum marker that also helps in identifying patients who would benefit most from adjuvant therapy. Objective: To determine the correlation of serum CA 15-3 with histological types of breast cancer. Methodology: This prospective cross sectional study was conducted on 51 cases of female carcinoma breast from December 2015 to August 2016. The specimens were collected after mastectomy or lumpectomy and then transported to collection Shaukat Khanum Lab and city lab for chemical analysis and histopathological analysis. All the data was analyzed by using SPSS version 17. Results: In the current study, a total of 51 patients were included. Results of serum CA 15-3 level ranged from 3 to 743.2 U/ml (with mean of 40.62). The upper limit of normal is taken as 32.4 U/ml. 38 (76%) of our cases had serum CA 15-3 level in the range of 0

to 32.4 U/ml while 12(24%) patients had CA 15-3 level more than 32.4U/ml. Non-significant association was observed between histological type and serum CA 15-3. (P=0.383). Conclusion: Our study concludes that females of all ages are affected by carcinoma breast but the prevalence is high in patients in younger age group. Serum CA 15-3 levels were found to be higher in patients with advance disease hence it can prove to be a good prognostic marker and help in follow up of carcinoma breast patients. Non-significant association was observed between histological type and serum CA 15-3.

Keywords---Correlation, serum CA 15-3, histological types, breast cancer.

Introduction

The incidence of breast cancer and its fatal effects are constantly on a rise across the globe¹. Over the past twenty years ratio of breast cancer has increased and WHO in one of its reports has shown double the number of carcinoma breast cases in developing countries by year 2020⁴. Breast cancer is the most common cancer in Pakistani women, with approximately 1 in every 9 Pakistani women developing breast cancer at some stage of their². In females breast cancer is the commonest (20.8%) in Khyber Pakhtunkhwa, followed by skin, ovary, oral carcinoma, esophagus and cervix⁷. Majority of female breast cancer patients in Khyber Pakhtunkhwa presents with advanced disease and hence poor prognosis and outcome⁵. Risk factors of breast carcinoma include female gender, genetic mutations, positive family history, proliferative breast diseases, younger age at menarche, late menopause, 1st pregnancy at age older than 35, nulliparity, radiation exposure, exogenous hormone use, alcohol, high fat diet, sedentary life style and obesity⁶. Breast cancer can be categorized by the microscopic appearance of the cancer cells and the pattern they make in tissue i.e. by histology. This is done because the behavior and prognosis of different histological types of breast cancer varies. WHO classified breast carcinomas into major and minor tumors in 2003⁷. Breast carcinoma is mainly categorized into in situ carcinoma and invasive carcinoma. A large number of tumor markers for diagnosis and prognosis are known for carcinoma breast. These markers also help in selecting appropriate treatment strategy. These include tissue markers like ER, PR and Her2/neu and serum markers like CA 15-3, CA 125, CEA. The serum mucinous markers e.g. CA 15-3 and carcinoembryonic antigen (CEA) are commonly used for breast cancer diagnosis and prognosis⁸. A number of tumor markers give an idea whether the treatment used for patient is effective or not³.

Serum CA 15-3, also called MUC 1 is a glycoprotein residing in the transmembrane region and befits in the family of mucin, this cancer antigen is over expressed in serum of >90% of breast carcinoma patients and cases with metastasis¹⁰ and Studies have shown that an elevated level of serum CA 15-3 predicts early metastasis, frequent recurrences after treatment and bad prognosis¹¹. The sensitivity of serum CA 15-3 is low in early stages of breast cancer and normal tumor serum levels do not exclude the presence of malignancy

however its sensitivity is higher in advanced disease¹². To evaluate the role of serum CA 15-3 as a prognostic marker in different histological types of carcinoma breast more studies are necessary to reach a conclusion.

Research shows ER/PR negative and HER-2/neu positive cases are associated with raised levels of serum CA 15-3¹³. ER, PR negativity and Her-2/ NEU positivity have been found in aggressive tumors with higher tumor grade and size and have poor prognosis¹⁴.

A lot of research is done on the prognostic role of ER, PR and HER-2/ NEU in Pakistan¹⁵ and other parts of the world however only a few studies so far have been done on the prognostic role of serum CA 15-3 in Pakistan^{16, 17} and no such study has been reported from Khyber Pakhtunkhwa province particularly focusing the pushtoon female population. To conduct such study in pushtoon population is further more important due to different genetic makeup and their lifestyle as compared to other races in Pakistan. As different histological types of carcinoma breast also effects the prognosis of the disease and no study so far has been reported with respect to correlation of histological types with serum levels of CA 15-3 hence this prognostic parameter is also included in the present study.

Materials and Methods

This prospective cross sectional study was conducted on 51 cases of female carcinoma breast belonging to pushtoon race visiting Peshawar Medical College (PMC) and Khyber Medical College (KMC) teaching hospitals. The study was carried out from December 2015 to August 2016. The study approval was taken from the IERB of the hospital. The overall sample size based on WHO sample size calculator was 51 patients.

Inclusion criteria

Female patients with breast carcinoma diagnosed on histopathological basis
Female patients diagnosed as carcinoma breast clinically
Patients who have received chemotherapy before surgery

Exclusion criteria

Male patients with Carcinoma breast
Patients who are not pushtoon

Data collection procedure

The specimens were collected after mastectomy or lumpectomy. They were immersed in 10% buffered formalin in labeled wide-mouthed transparent plastic container after thorough wash with tap water. It was then transported to collection Shaukat Khanum Lab and city lab for histopathological analysis. For chemical analysis, after taking consent from patient 5cc blood samples of the selected patients were obtained following the standard aseptic technique. Blood was collected to clot at room temperature and then serum was separated by centrifugation at 1000xq for 5-10 minutes and aspirated to serum preserving cups. Samples were stored frozen till analyzed for CA 15-3 using chemiluminescent technology (ADVIA Centaur XP model, 2015; Siemens Medical

Solutions Diagnostics, Tarrytown, NY, USA). The kit used was Ca 15-3 assay; model 2015. The upper limits of normal for serum CA 15-3 were taken as 32.4 U/ml.

Statistical analysis

All the data was analyzed by using SPSS version 17. Frequencies, percentages were determined for variables like histologic type and grade of tumor while means and standard deviation were calculated for variables like age. Correlation between categorical variables was established through Chi-square test. P-value of < 0.05 was taken as significant.

Results

In the current study, a total of 51 patients were included. Age distribution of patients included in the study ranged between 20 and 75 years with mean age of 45 years and Standard deviation of 12.45. In our series of cases, maximum cases (33%) cases were in the age group 41-50 years followed by 23.5% in 31-40 years. The frequency of cases in the age group 20-30 and 51-60 was same as 17.6%. Out of total 51 cases 52.9% (n=27) cases were from left breast and remaining 47.1% (n=24) cases were from right breast.

Out of total 51 cases majority were invasive ductal carcinoma (82.4%, n=42) followed by ductal carcinoma in situ (9.8%, n=5) and invasive lobular carcinoma (7.8%, n=4). Out of 51 cases 66.7% (n=34) cases were of grade II and remaining 33.3% (n=17) were of grade III. Tumor size ranged from 0.4 to 15cm (with mean of 3.678cm). Majority of the cases were more than 2cm (62.74%, n=32) and the remaining were 2cm or below (37.3%, n=19). Out of the tumors that were more than 2cm were divided into 2 to 5cm which had 16(31.4%) cases and 16(31.4%) cases were of more than 5cm. Out of 51 cases 11.8% (n=6) cases showed lymph node metastasis and remaining 88.2% (n=45) cases were negative for lymph node metastasis.

NPI was calculated by using this formula $0.2 \times S+L+G$ and were categorized into 2-4, 5-7 and > 7. Maximum no of cases that is 58.8% (n=30) were in group 2-4 followed by 35.29% (n=18) in group 5-7 and 5.88% (n=3) were in group > than 7. Out of 51 cases 7.8% (n=4) cases belong to stage 0, 31.4% (n=16) belong to stage 1, 39.2% (n=20) belong to stage 2, 15.7% (n=8) belong to stage 3 and 5.9% (n=3) belong to stage 4. (Table 1)

Results of serum CA 15-3 level ranged from 3 to 743.2 U/ml (with mean of 40.62). The upper limit of normal is taken as 32.4 U/ml. 38 (76%) of our cases had serum CA 15-3 level in the range of 0 to 32.4 U/ml while 12(24%) patients had CA 15-3 level more than 32.4U/ml. (Table 2) Out of 42 cases of invasive ductal carcinoma 12(23.5%) cases had elevated preop CA 15-3 levels while rest 30(58.8%) cases had preop serum level within normal range.

Out of 5(9.8%) cases of ductal carcinoma in situ all had their serum CA 15-3 level within normal range. Only 1(1.96%) out of 4 invasive lobular patients had above normal serum level of CA15-3. The remaining 3(5.88%) patients with invasive

lobular carcinoma had serum Ca15-3 level within normal range. Chi-square test was applied to find comparison between histological type and serum CA 15-3, P value comes out to be 0.383 which is more than 0.05 hence this comparison is not significant. (Table 3)

Table 1

Parameter	Sub category	Frequency	Percentage
Age	20-30	9	17.6
	31-40	12	23.5
	41-50	17	33.3
	51-60	9	17.6
	61-70	3	5.9
	+70	1	2
Tumor laterality	Left	27	52.9
	Right	24	47.1
Histological type	Invasice ductal carcinoma	42	82.4
	Ductal carcinoma in situ	5	9.8
	Invasive lobular carcinoma	4	7.8
Grade of tumor	II	34	66.7
	III	17	33.3
Size of tumor	2 or less than 2 cm	19	37.3%
	More than 2 to 5cm	16	31.4%
	More than 5cm	16	31.4%
Lymph node metastasis	No	45	88.2
	Yes	6	11.8
NPI	2-4	30	58.8%
	5-7	18	35.29%
	>7	3	5.88%
Stage of tumor	Stage 0	4	7.8
	Stage I	16	31.4
	Stage II	20	39.2
	Stage III	8	15.7
	Stage IV	3	5.9

Table 2: Serum CA 15-3

SERUM CA 15-3	N	minimum	maximum	mean	Standard deviation
	51	3	743.2	40.624	103.5
	NO OF CASES			PERCENTAGE	
NORMAL	38			(76%)	
ABNORMAL	12			(24%)	

Table 3: Correlation of serum CA 15-3 with Histological type of carcinoma breast

Histological type	Normal	elevated	total	P value*
Invasive ductal carcinoma	30(58.8)	12(23.5%)	42(82.35%)	0.383
Ductal carcinoma in situ	5(9.8%)	0	5(9.8%)	
Invasive lobular carcinoma	3(5.88%)	1(1.96%)	4(7.84%)	

Discussion

A large number of tumor markers for diagnosis and prognosis are known for carcinoma breast. These markers also help in selecting appropriate treatment strategy. These include tissue markers like ER, PR and Her2/neu and serum markers like CA 15-3, CA 125, CEA. The serum mucinous markers e.g. CA 15-3 and carcinoembryonic antigen (CEA) are commonly used for breast cancer diagnosis and prognosis¹⁸. A number of tumor markers gives an idea whether the treatment used for patient is effective or not¹⁹.

Serum CA 15-3, also called MUC 1 is a glycoprotein residing in the transmembrane region and belongs in the family of mucin, this cancer antigen is over expressed in serum of >90% of breast carcinoma patients and cases with metastasis²⁰. Studies have shown that an elevated level of serum CA 15-3 predicts early metastasis, frequent recurrences after treatment and bad prognosis²¹. The sensitivity of serum CA 15-3 is low in early stages of breast cancer and normal tumor serum levels do not exclude the presence of malignancy however its sensitivity is higher in advanced disease²². Studies are required on serum CA 15-3 to evaluate its role as a prognostic marker in different histological types of carcinoma breast. If developed, a technically simple test with low cost will become available for early diagnosis and prognosis¹⁹.

The utility of measuring CA 15-3 levels in patients with breast cancer remains controversial till time. Expert panels such as NABC and EGTM recommend the routine use of CA 15-3 in monitoring therapy in patients with advanced breast cancer. In contrast the routine use of CA 15-3 in LABC is not recommended by the ASCO panel²². The objective of this study was to find the prognostic role of CA 15-3 after treatment that is chemotherapy by comparing our CA 15-3 results with Histological type, NPI, Stage of tumor, grade of tumor, size of tumor and age of patient. Invasive Ductal carcinoma came out to be the most frequent histological subtype (n=42, 82.4%), followed by ductal carcinoma in situ (n=5, 9.8%) and invasive lobular carcinoma (n=4, 7.8%).

Same result is accepted internationally and even in Pakistan. Our results were supported by Shahida Tasneem et al, 2012 and Mumtaz Begum et al, 2012 from Pakistan and by Ellis et al, 1991(USA), Connolly et al, 2004(Germany), Malhotra et al, 2010(USA) and Lakhani et al, 2012(USA) internationally.

Shahida Tasneem et al, 2012 in her study have seen almost all cases of invasive ductal carcinoma. Mumtaz Begum et al, 2012 found invasive ductal carcinoma

(96%) to be the commonest histological subtype of breast carcinoma she also found that frequency of ductal carcinoma in situ is increasing this is because of earlier and better detection rates by mammography. Moses et al, 2012 in their cross sectional descriptive study in Uganda found 93-96% of invasive ductal carcinoma. Carole et al, 2006 in their prospective study (France) of 89 breast carcinoma patients found 56.17% cases of invasive ductal carcinoma and 6.74% of invasive lobular carcinoma.

When the CA 15-3 levels were compared to the histological types 92.3% of invasive ductal carcinoma cases had CA 15-3 levels above normal limits even after taking neo-adjuvant chemotherapy. While rest of invasive ductal carcinoma had CA 15-3 levels within normal limits. As prognosis of invasive ductal carcinoma is poor as compared to Ductal carcinoma in situ and invasive lobular carcinoma so 92.3% of invasive ductal carcinoma has serum level above normal even after chemotherapy. Hence there are more chances of these cases to metastasize and even recur. Same was reported by Fan et al, 2012 in their study¹⁸.

Only 7.7% of invasive lobular patients had above normal serum level of CA15-3. The remaining 3(7.9%) patients with invasive lobular carcinoma had serum Ca15-3 level within normal range. This shows good prognosis of invasive lobular carcinoma as seen by Fan et al, 2012¹⁸. This also shows that recurrence of invasive lobular carcinoma is lower than invasive ductal carcinoma and responds well to treatment as seen by Fritz et al, 2012.

Out of 5 cases of ductal carcinoma in situ all had their serum Ca 15-3 level within normal range. This shows good prognosis of ductal carcinoma in situ as seen by Ellis et al, 1992 and Khan et al, 2004. Although histological subtypes when statistically compared to raised CA 15-3 levels showed a P value of 0.383 that is not significant. However our results are quite comparable to many international studies where the histological subtypes do not affect the serum CA 15-3 levels. As were seen by Biao geng et al, 2014 in their study²³.

Conclusion

Our study concludes that females of all ages are affected by carcinoma breast but the prevalence is high in patients in younger age group. Serum CA 15-3 levels were found to be higher in patients with advance disease hence it can prove to be a good prognostic marker and help in follow up of carcinoma breast patients. Non-significant association was observed between histological type and serum CA 15-3.

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