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Utility of CA 15-3 as Diagnostic and Prognostic Marker in Breast Cancer

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Abstract: *CA 15-3 which detects soluble forms of MUC-1 protein is the most widely used serum marker in patients with breast cancer. Its main use is for monitoring therapy in patients with metastatic disease. For monitoring therapy, CA 15-3 should be used in conjunction with diagnostic imaging, clinical history and physical examination. CA 15-3 is particularly valuable for treatment monitoring in patients that have disease that cannot be evaluated using existing radiological procedures. Sera of 91 women, normal control, benign breast lesion and malignant breast lesion in pre, postoperative and follow up period were assayed for CA 15-3 by ELISA. In the malignant group (n=76), 43 cases had shown elevated value of CA 15-3 suggesting the sensitivity of this marker about 56% and the specificity of the marker about 100%.Elevated preoperative serum levels of CA 15-3 were significantly correlated with the presence of metastatic disease. In metastatic group the elevated value was seen in 100% of cases but in non-metastatic group it was variable. Elevated concentrations of CA 15-3 over the cut off may be a useful diagnostic and reliable indicator for the prognosis and also was useful in monitoring the therapy.*

Keywords: *CA 15-3, prognostic marker, follow-up, metastasis, breast cancer.*

I. Introduction

The CA 15-3 is tumor associated antigen which detects soluble forms of MUC-1 protein. In normal breast tissue MUC-1 is expressed in the duct and acini, but with neoplastic transformation normal cell polarization and tissue architecture is disrupted leading to shedding of MUC-1 in the blood, where it can be measured by immunoassay. It is the most widely used serum marker in patients with breast cancer. Its main use is for monitoring therapy in patients with metastatic disease. In monitoring therapy in this setting, CA 15-3 should not be used alone but measured in conjunction with diagnostic imaging, clinical history and physical examination (1).

Healthy women are expected to have CA 15-3 assay values below 30U/ml (2). The upper limit of the range varies depending on the laboratory and kit used for the test. The elevation of CA 15-3 (values over 120kU/L) is found in over 30% of breast cancer patients with advanced disease (3).

Serum CA 15-3 has been extensively studied mainly to monitor the response of breast cancer to the treatment or to detect early relapse in breast cancer follow-up (4).

CA 15-3 may also be used in the postoperative surveillance of asymptomatic women who have undergone surgery for invasive breast cancer. In this setting, serial determination can provide median lead-times of 5-6 months in the early detection of recurrent/metastatic breast cancer. It is unclear however, whether administering systemic therapy based on this lead-time improves patient outcome.

II. Objectives

The objective of this study is to evaluate the role of CA 15-3 in pre-operative, postoperative and follow up period to monitor the disease for metastasis or recurrence.

2.1. Material and Method

The present study was conducted from June 2012 to December 2014 in the department of pathology, G. S.V.M. Medical College, Kanpur. The cases were collected from L.L.R hospital and J. K. Cancer Institute hospital. For the study biopsy proven breast carcinoma cases were taken. A total of 91 cases are studied including normal healthy adult control (n= 05), benign cases (n= 10) and malignant lesions (n= 76).

A correlation of serum CA 15-3 levels were also done with histological findings of lumpectomy and mastectomy specimen (with axillary clearance), received in the Department of Pathology.
CA 15-3 estimation was done by Enzyme Linked Immunosorbant Assay, CA 15-3 Elisa kit.

2.2. Sample collection and handling

5 ml of blood was collected in plain sterile vial and the serum was separated.

The CA 15-3 Enzyme linked immunosorbent assay (ELISA) provides material for the quantitative determination of the cancer associated antigen CA 15-3 in serum and plasma.

The CA 15-3 ELISA KIT is a solid phase enzyme-linked immunosorbent assay based on the sandwich principle. The microtitre wells are coated with a monoclonal antibody directed towards a unique antigenic site on a CA 15-3 molecule.

The CA 15-3 ELISA test is based on the principle of a solid phase enzyme-linked immunosorbent assay. An aliquot of a patient sample containing endogenous CA 15-3 is incubated in the coated well with enzyme conjugate ,which is an anti-CA 15-3 monoclonal antibody conjugate with Horseradish peroxidase. After incubation the unbound conjugate is washed off.

The amount of bound peroxidase is proportional to the concentration of CA 15-3 in the sample.

Having added the substrate solution, the intensity of color developed is proportional to the concentration of CA 15-3 in the patient sample. Absorbance is measured on the microplate ELISA reader at 450 nm. Cut off value of CA 15-3 is less than 230U/ml.

Calculate the average absorbance value (A 450) for each set of reference standards, control and samples using the mean absorbance value for each sample, determining the corresponding concentration of CA 15-3 in U/ml.

The range of detectable concentration of CA 15-3 by this kit is 5-240U/ml.

2.3. Results.

The levels of CA 15-3 with in normal range in the sera of benign breast disease patient and apparently healthy women used as normal control (Table 1). The mean serum CA 15-3 levels (±2SD) in these women was 16.05 ± 2.03 U/ml while in the sera of 76 malignant breast lesion patient was 45.89 ± 7.37U/ml (Table 2).The difference being statistically significant ($P < 0.05$). All normal controls had CA15-3 concentration less than 30 µ/ml, suggesting a test specificity of 100% for the ability of this marker to exclude normal individuals. In the malignant group (n=76), 43 cases had shown elevated value of CA 15-3 suggesting the sensitivity of this marker about 56% (Table 3). Further, the percentage sensitivity was seen highest in stage 4(100%) followed by stage 3 (48%), stage 2 (34%) and lowest in stage 1(22%). In metastatic group the elevated value was seen in 100% of cases but in non-metastatic group it was variable (Table 4).

In the follow up period 6% cases had no clinical evidence of disease, 29% cases with a single metastasis and 65% with two or more metastasis. The elevated value of CA 15-3 was seen in these cases suggested the elevated value of this marker had a reliable prognostic value in the breast cancer. In the post therapeutic group only 5% cases having elevated value of CA 15-3 (Table 5). These cases developed recurrence in follow up period. Rest of the case who have normal value of CA 15-3 had shown good response to therapy suggesting that it is a valuable indicator of monitoring therapy of breast cancer.

III. Discussion

In the present study value of CA 15-3 were observed within the sera of 05 apparently healthy woman used as a Control. Samples of 10 patients with histologically confirmed benign breast lesions none had level of CA15-3 above 30 U/ml. The percentage sensitivity of patients with abnormal value of CA 15-3 is 54%, which is quite different from that of patients with benign breast disease and healthy normal control. Similar observations were reported by previous studies (5). In malignant breast lesions patients about 56% cases which have shown the elevated values of CA 15-3 above 30U/ml.

In the post therapeutic patients who had a good prognosis (i.e. good response to therapy) gave the lowest percentage 5% of CA15-3 positive scoring, in comparison to preoperative patients with 58% sensitivity or the postoperative patients with 45% sensitivity and the Metastatic group with 100% sensitivity. According to previous studies, the result was in good agreement showing near about similar values (6).

Further studies of CA 15-3 in different stages revealed that in metastatic group the elevated values was seen showing the highest percentage of 100% by (7, 8). In the stage 3 it was 48%, in the stage 2 (34%), in the stage 1 (2%). Similar mean values were also seen by other studies which also found the elevated value of CA 15-3 in stage 3 more than normal value (9, 10).

The correlation between the histological classification of human malignant mammary carcinomas and percentage sensitivity of CA 15-3 antigen was also examined. The higher values (58%) of CA 15-3 are associated with the invasive pure forms of breast malignancy. These results confirmed analogues findings by other studies (11).

The percentage sensitivity of this marker increases according to the stage, a higher percentage of positive results were observed in patients with more advanced cancer Stage I-22 %, Stage II-34 %, Stage III- 48 %, and Stage IV-100.0%. This was also in accordance with the other studies (12). O. P. Kallioreni (1998) revealed that in the postoperative follow-up 9% of patients with no clinical evidence of disease, 33% with a single metastasis and 67% with two or more metastases had elevated values (13). In conclusion, serum CA 15-3

levels had prognostic value in breast cancer, reflected the extent of clinically detectable disease and the presence of occult metastatic disease which is also in concordance with the present study showing the 6% patients with no clinical evidence disease, 29% with a single metastasis and 65% with two or more metastases.

According to the Wojtacki. J et al, the higher values of CA15-3 were observed in patients with distant and multiple metastases and the lower when the metastatic involvement of only supraclavicular lymph nodes were noticed (14).

The CA15-3 sensitivity rates were higher in patients with multiple or distant metastasis (60%) as compared to the lower values when metastases in supraclavicular lymph nodes (40%). While the specificity is much higher about 100% as none of the patient having benign breast lesions showed the elevated values. In fact, according to the current literature, CA 15-3 is not specific or sensitive enough to detect early breast cancer However, CA15-3 seems to be a reliable prognostic predictor for monitoring disease progression in follow up period.

IV. Tables

Table 1 Distribution of cases under study

CATEGORY	Total no. patient	No. Patient having elevated CA 15-3 value
Diagnosis		
Benign	10	0
Malignant	76	43
Staging		
Stage 1	07	02
Stage 2	30	10
Stage 3	24	11
Stage 4	15	15

Table- 2 Incidence of elevated Serum CA 15-3 in Benign and malignant breast cancer patients

Cases	No. of cases	No. of cases with elevated CA 15-3 level	% of cases with elevated CA 15-3 value
Benign lesions	10	None	0 %
All breast cancer patient			
Pre-operative	25	15	58 %
Post-operative	26	12	45 %
Post therapeutic	10	01	5%
Metastatic group	15	15	100 %

Samples of 10 cases with histologically confirmed benign breast lesions, none have CA 15-3 value above than cut off value 30U/ml. Samples of 76 cases with histologically confirmed malignant breast lesions, 58% cases from the preoperative group, 45% cases from post-operative group, 5% cases from the post therapeutic have shown elevated values. In the metastatic group 100% cases have shown elevated values. Out of the total 76 cases 43 cases have shown elevated value suggesting the sensitivity about 56% and none of the benign cases have shown elevated value suggesting the specificity about 100%.

Table – 3 Sensitivity of Tumor marker CA 15-3 in breast cancer cases in different groups using cut off value <30U/ml (%)

Cases in different groups	% sensitivity of CA 15-3
Pre-operative group	58 %
Post-operative group	45 %
Post therapeutic group	5 %
Metastatic group	100 %

Samples were taken from all the cases from malignant group (n=76). In the pre-operative group15 out of 25 cases have shown elevated value revealed the sensitivity about 58%. In the post-operative group12 out of 26 have shown elevated value revealed the sensitivity about 45%. In the post therapeutic group 1 out of 10 have shown elevated value revealed the sensitivity about 5% and from the metastatic group 15 out of 15 have shown elevated value revealed the sensitivity about 100%.

Table 4 Correlation of CA 15-3 value in normal control, benign and malignant breast cancer cases

	No. of cases	Value of CA 15-3	Mean ± SD	P value
Normal or control	05	<30U/ml	14.74 ± 1.11	>0.05
Benign lesions	10	<30U/ml	16.05 ± 2.03	>0.05
Malignant lesions	76	>30U/ml	45.89 ± 7.37	<0.05

Mean serum value of CA 15-3 in normal control was 14.74 ± 1.11 U/ml. Mean serum value of CA 15-3 in benign breast lesions was 16.05 ± 2.03 U/ml. Mean serum value of CA 15-3 in malignant breast lesions was 45.89 ± 7.37 U/ml.

After comparison among normal control, benign breast lesions and malignant breast lesions CA 15-3 value was statistically non-significant (> 0.05) between normal or control and benign lesions cases. But the values between benign and malignant breast lesions were statistically highly significant (P value < 0.05).

Table 5 Incidence of cases developed advanced disease in the follow up as per value of CA 15-3 using the cut off value 30U/ml

During follow up	No. of cases	Percentage
No clinical evidence of disease	03	06%
Single metastasis	13	29%
Multiple Metastasis	27	65%
	Total n=43	

In the preoperative and post-operative cases in the follow up period total (43) cases who have shown elevated value > 30µ/ml, out of them only 03 cases (06%) have not developed any sign or symptoms of residual disease or recurrence of disease. From 43 cases 13 (29%) have developed single metastasis to the axillary lymph node While the 27 cases (65%) have developed multiple metastasis including the multiple lymph node or distant metastasis to organs.

V. Conclusion

Serum markers in breast cancer are helpful for clinicians in providing more effective management of the disease. To this end, different markers have been proposed in the last years. In particular, Carcinoembryonic antigen (CEA) and MUC1 (CA 15-3) are the most widely used and investigated in the breast cancer follow-up period. Initial studies indicate that CA 15-3 is abnormal in the majority of patients with metastatic breast cancer and the antigen levels are correlated with changes in the clinical status of breast cancer patients.

However, CA 15-3 is not recommended as screening tool in early detection for breast cancer, even though it remains an important asset to monitor the efficacy of medical therapies after surgery.

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