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General Surgery

A CLINICO-PATHOLOGICAL STUDY OF CARCINOMA BREAST WITH SPECIAL REFERENCE TO SERUM CEA LEVELS & ITS RELATIONSHIP WITH TREATMENT

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ABSTRACT **BACKGROUND:** Carcinoembryonic antigen (CEA) is used as a tumor marker for breast cancer (BC) & follow up of patients pre- or post- chemotherapy. In order to better define clinical usefulness of CEA in breast cancer patients (BCP) we determined its baseline pre-treatment levels and correlated them with main parameters of primary tumor and metastases.**PATIENTS AND METHODS:** The main experimental group consisted of 53 females with histologically confirmed diagnosis of BC. The obtained results have been compared with those of three follow-up groups: pre-operative, immediate post-operative and 2nd follow up Post operative patients with other types and locations of cancer. In both cancer groups the parameters of primary tumor (size, grade) and metastases (time interval to metastases, location, size) have been determined. Circulating levels of CEA were measured by the means of sandwich ELISA assay. Results were processed by means of t-test, two way analysis of variance in p value. **RESULTS:** Baseline levels of CEA in BCP were significantly higher than in healthy women ($p < 0.0001$), and in patients with other types and locations of cancer ($p < 0.007$). There also was significant difference ($p < 0.001$) between serum CEA in other cancer patients and healthy women. Baseline CEA levels were in significant positive correlation with the size of primary tumor both in all BCP ($p < 0.03$) and in hyperCEA BCP ($p < 0.002$), while in other cancer patients such a correlation did not exist. There was no correlation between CEA and degree of differentiation of primary tumor either in BCP or in other cancer patients. The average circulating levels of CEA in metastatic BCP were significantly higher ($p < 0.03$) in comparison to non-metastatic patients, while in other cancer patients such a difference did not show up. There was significant correlation ($p < 0.0001$) between circulating CEA and the size of metastases in all BCP and in subgroup of hyperCEA BCP, while in other cancer patients it was not a case. There was no correlation between serum CEA and other two metastatic parameters either in BCP or in other cancer patients.**CONCLUSIONS:** CEA does not have high tumor specificity for BC since its baseline levels may be elevated in other types of cancer[1]. Circulating levels of CEA in BCP are directly dependable on the size of both primary and metastatic tumor. CEA is a tumor antigen of less differentiated cancer cells. Circulating CEA is a good prognostic marker for patients with metastatic BC.

KEYWORDS : CEA, carcinoembyonic antigen, carcinoma breast

INTRODUCTION

'A cancer is a crab' it claws at the patient, it slides in the sands of the patient's flesh like a crab. It ignores straight walking and progressive sideways – HIPPOCRATES (400 BC). Development of malignant cells is a frequent event and under normal conditions these cells are destroyed by immunological mechanisms. A few of these abnormal cells escape recognition by immune system, the mechanism for which is unknown. These abnormal cells under favorable conditions grow uninhibited to form cancer. Tumor genesis is initiated with the transformation of a single cell with thorough genetic alteration giving rise to a multiplicity of similar altered cells[2]. Such genetic change would induce the synthesis of new protein specimen.

The progression and proliferation of malignancy could be due to impairment of the immunological sufficiency of the host, a failure of response, thus the early fundamental events of malignancy are alteration of initial cell followed by immunological failure of system[3]. The alteration of initial cell subsequently involves escape from regulatory mechanism and changes in relation to it's adjacent cells leading to proliferation and invasion[4]. Cancer breast is the most common malignancy in Europe and America. In India it ranks second just next to carcinoma cervix among females. It is the leading cause of death in women of age more than 30 years. The natural history of cancer breast has been renewed by Bloom in 1968.The mean survival from all reported series of breast cancer is 39.9 months with a range of 30.2 to 46.2 months. In Bloom's series from the Royal Marsden Hospital, the importance of the histological grading of the tumor in determining the ultimate survival of the patient was demonstrated.

The disease commences mostly in the upper and outer quadrant of the breast. The four breast quadrants are affected with unequal frequencies.

A variety of sensitive immunological techniques have demonstrated that many human neoplasm contain antigen which appear to be at least tumor related if not uniquely specific. The tumor associated antigens have been demonstrated in breast cancer. Most tumor associated antigens are associated with cell surface where they are susceptible to immune attack by antibodies or lymphocytes[5]. However, these are more or less specific for the neoplastic states like fetal antigen or carcinoembryonic antigen as reported by Gold and Freedman.

Between 50-70 % patients with metastatic breast cancer will have elevations of various antigens like CEA, gross cystic disease protein, CA 15-3,Caesin,Ferritin,pregnancy associated alpha macroglobulin ,betamacroglobulin, sialyltransferase, tissue polypeptide antigen(TPA) or 5-nucleotide phosphodiesterase isoenzyme V(5'NPDV).

The current interest for tumor markers of cancer arose in mid of 1960s with the discovery of oncofetal proteins i.e. carcinoembryonic antigen and Alfa-fetoprotein. They appeared in high concentrations during embryonic development and virtual disappearance in the neonatal period and reappearance with cancer of specific cell types[6]. The CEA level is raised in colonic, pancreatic, bronchogenic, gastric and breast cancer. Tumor markers such as E Rossetes for leukemia, CA-125s for ovarian carcinoma, CA-199 for ovarian adenocarcinoma, CA-15-3 for advance breast carcinoma are also widely used for diagnosis as well as prognosis of the tumor. The determinants of one single tumor marker is not confirmatory of the specific malignancy but it's successive levels give immense help in monitoring the tumor activity[7].

MATERIAL AND METHODS

Study design and sampling

The present study was conducted on the patients admitted in L.L.R. Hospital and in J.K. Cancer Institute, G.S.V.M. Medical College, Kanpur. In this study cancer breast in different stages have been included. This prospective study was conducted on the patients admitted to from January 2019 to October 2020 with breast carcinoma.

INCLUSION CRITERIA

- Carcinoma breast

EXCLUSION CRITERIA

- Patients having diabetes mellitus
- Patient having human immunodeficiency virus infection

- Pregnant women

Patient's selection and classification in the study group

- The patients admitted to the hospital with cancer Breast on the basis of clinical history, physical examination and F.N.A.C. histological – proved to be staged as per the TNM classification.

Serial CEA estimation and follow up of patients after treatment.

- At the time of admission to hospital initially i.e. before treatment was started.
- After one month of initiation of treatment or postoperatively if surgery has been done
- After 3 months of chemotherapy or both. Initiation of radiotherapy or as control CEA levels seen in patients with benign breast disease.

Any level of serum CEA more than 2.5 ng/ml is positive In this study 53 cases with malignant breast lesion taken.

OBSERVATIONS

The present study "Clinicopathological Study of CA Breast with special reference to serum CEA level and its relationship with treatment"' was undertaken in the Department of Surgery. L..L..R.. & Associated Hospitals Kanpur and J.K. Cancer Institute, Kanpur and the Department of GSVM Medical College, Kanpur.

Table 1 shows distribution of cases according to Age in urban and Rural population. The maximum number of cases (total 37.72%) was seen in 6th decade in both urban and rural population. Next highest frequency (total 33.94%) of cases were seen in 5th decade in both urban and rural respectively.

Sl no.	Age group	Urban		Rural		Total	%
1.	0-10	0	0	0	0	0	0
2.	11-20	0	0		0	0	0
3.	21-30	1	1.88	0	0	1	1.88
4.	31-40	4	7.54	7	13.2	11	20.74
5.	41-50	8	15.08	10	18.86	18	33.94
6.	51-60	8	15.08	12	22.64	20	37.72
7.	61-70	2	3.77	1	1.88	3	5.65
8.	71-80	0	0	0	0	0	0

Table 2: Distribution Of Breast Lump According To Duration Of Illness

DURATION	NO.OF CASES
<6 months	6
6 months – 1 years	21
1 year – 1.5 years	14
1.5 years - 2 years	12
Total	53

Table – 2 shows distribution of breast lump according to duration of illness Maximum duration of illness at the time of presentation is 6 months to 1 year (21 cases)

Table 3: Histopathological Examination Showing Types Of Breast Cancer

LESIONS	NUMBER OF CASES
Infiltrating Duct Carcinoma	46
Medullary Carcinoma	3
Lobular Carcinoma	2
Ductal Carcinoma in situ	2
Total	53

Table 3 shows types of Breast cancer according to histopathological examination shows the maximum no. of cases (46) presents as the infiltrating duct carcinoma .

Table 4: Symptomatology Of The Patients

Symptoms	No. of patients
Lump in breast	53
Nipple discharge	27
Skin development	33
Lymph node involvement	43
Bone pain	6
Lung involvement	4
Contra lateral breast involvement	0

In our study, major presenting symptom is lump in the breast (53 cases). In breast cancer another major symptom is involvement of the lymph nodes (43 cases) Common sites of distant metastasis are bone (6 cases), lung (4 cases).

Table 5: Comparison Of Cea Levels In Premenopausal & Postmenopausal Breast Cancer Patients

Mean Value of Serum CEA in premenopausal breast cancer patients ± SD(ng/ml) (n=18)	Mean Value of Serum CEA in postmenopausal breast cancer patients ± SD(ng/ml) (n=35)	P Value	Inference
18.05 ± 12.34	14.11 ± 13.0	0.2871	P>0.05 Not Significant

Table 6: Comparison Of Pre-operative & Post-operative Values Of Serum Cea In Breast Cancer Patients

Mean Preoperative Value of Serum CEA (ng/ml) (n=42) [A]	Mean Postoperative Value of Serum CEA 1st follow up (ng/ml) (n=42) [B]	Mean Postoperative Value of Serum CEA 2nd follow up (ng/ml) (n=42) [C]
9.98±8.65	1.66±1.76	1.22±1.21

P = Probability level for Significance

Significant Correlation Between The Groups (pre-operative & Post-operative

Groups	T	P	Inference
A v/s B	6.72	<0.001	Highly Significant
A v/s C	6.79	<0.001	Highly Significant
B v/s C	2.78	<0.050	Significant

t = Student t test for testing the significance between groups
P = Probability level for Significance

Table 7: Comparison Of Pre-chemotherapy & Post Chemotherapy Values Of Serum Cea In Breast Cancer Patients

Mean Pre chemotherapy Value of Serum CEA in (ng/ml) (n=11) [A]	Mean Value of Serum CEA after Chemotherapy after 1st follow up (ng/ml) (n=11) [B]	Mean Value of Serum CEA after Chemotherapy after 2nd follow up (ng/ml) (n=11) [C]
34±1.34	5.97±10.54	4.27±8.14

SIGNIFICANT CORRELATION BETWEEN THE GROUPS

Groups	T	P	Inference
A v/s B	9.08	<0.001	Highly Significant
A v/s C	10.97	<0.001	Highly Significant
B v/s C	2.56	<0.050	Significant

t = Student t test for testing the significance between groups
P = Probability level for Significance

DISCUSSION

Cancer breast is a burning issue now a day as its incidence is rising in developing countries as well. As patients and how to manage their treatment and known the prognosis, several tumor markers have been studied. Serum CA 15-3- Casein, CEA, Gross cystic disease protein, Ferritin, pregnancy associated beta 2-macroglobulin, Sialyltransferase. Tissue polypeptide antigen. The current interest in tumor markers arose in mid of 1960's with the discovery of oncofetal proteins, CEA and Alfa fetoprotein. They appear in high concentrations during embryonic development and virtual disappearance in neonatal period and reappearance with cancer of specific cell types.

The distribution of cases according to Age in urban and Rural population. The maximum number of cases (total 37.72%) were seen in 6th decade in both urban and rural population. Next highest frequency (total 33.94%) of cases were seen in 5th decade in both urban and rural respectively.

The religion wise distribution, 92.46% patients were the Hindus and 7.54%patients were the Muslims.

In study group of 53 malignant cases incidence was maximum in 6th decade (37.72%) and 5th decade (33.94%), Next in frequency in 4th decade 20.74%. Low frequencies were seen in 3rd (1.88%) and 7th decade (5.65%).

The distribution of breast lump according to duration of illness Maximum duration of **illness at the time of presentation is** 6 months to 1 year (21 cases). In our study the major presenting symptom is lump in the breast (53 cases). Another major symptom was involvement of the lymph node (43 cases). It include peau d'-orange, skin fixity, tethering of skin and ulceration. Nipple discharge is present in both malignant and benign cases. Common sites of distant metastasis are bone (6 cases), lung (4 cases) and liver (1) in decreasing order. The most common involved quadrant of the breast is upper outer (58.49%). Next in frequency is subareolar region (15.09%), upper inner quadrant (9.43%), lower outer quadrant (7.54%) and lower inner quadrant (3.77%). Common sites of distant metastasis are bone (6 cases), lung (4 cases). There are total 2 cases with lobular carcinoma but no one shows involvement of opposite breast. No significant changes in serum CEA level were seen in premenopausal &post menopausal patients of breast cancer. In our study most of the patients seen belonged to the anatomical group. Stage III (37.7%), stage II (33.39%), (20.75%) patients belonged to Stage IV& (9.43%) in Stage I. In this study we have studied clinicopathology of carcinoma breast patients with special reference to serum CEA and its relationship with treatment. We selected 53 patients suffering from carcinoma of breast. In malignant cases 48 patients of infiltrating duct carcinoma, 2 cases of lobular carcinoma, 2 cases of medullary carcinoma and 2 cases of ductal carcinoma in-situ.

Types of Breast lump according to histopathological examination shows the maximum no. of cases (46) presents as the infiltrating duct carcinoma.

The most common site is upper outer quadrant of the breast (58.49%). Next in frequency is sub areolar (15.09%). Involvement of upper inner quadrant is 9.43%, lower outer 7.54% and lower inner quadrant 3.77%. In our study, Stages of the disease mainly presents as the early stage of disease (43.39%).

In the study group patient with breast cancer 3.77% i.e. 2/53 were nulliparous, they did not breast fed. 7.54% that means 4/53 are primipara One life born baby), 34 patients out of 53 are multipara (64.15%), 24.52% patients 13/53 are grand multipara > 5 life births).

Lymph node positive patients shows higher level of serum CEA level than lymph node negative patients. Histologically there are 5 cases in Stage I, 18 cases in Stage II and 19 cases belong to Stage III. and 11 cases in Stage IV. (I had Infiltrating ductal carcinoma-3 cases, Ductal carcinoma in situ-2 cases In stage I with mean serum CEA level(2.7 ng/ml) , Infiltrating ductal carcinoma-15,lobular -1 and medullary-2cases in stage II with mean CEA level(8.12ng/ml), Infiltrating ductal carcinoma-18 cases andlobular-1 case in stage III with mean CEA level(24.2), Infiltrating ductal carcinoma-10 casesmedullary-1 case in stage IV with mean CEA level (35.2 ng/ml).

Post operative and post chemotherapy value of serum CEA level decreases significantly with treatment shows that effect of treatment can be predicted with decreasing level of serum CEA level In patients under treatment for metastatic breast carcinoma (n=11) CEA level was elevated in all with visceral and osseous metastases. **Wang DY et al** studied serum CEA in the diagnosis and prognosis of women with breast cancer. He found CEA measurements were of no diagnostic value. There were more patient with breast cancer with values in access of 10 ng/ml measured preoperatively (7%) or after mastectomy (5%) then in controls (3%). But the difference is of marginal significance. In our study CEA level was elevated with similar percentage both in pre-operative and post operative patient. The histological pattern does not affect the incidence of serum CEA increase consisted with **Wahren et al 1978.**

In our study the cut Off mark has been 2.5 ng/ml which is same as that used by **AM Steward et al in 1974.** The method of **Egan et al, 1972** agrees with this technique if cut off mark is fixed at 12.5ng/ml. This study is also consistent with the results obtained by **B. Wahren et al in 1978.**

In our study a good clinical patients response to therapy was mirrored by a fall of CEA level in the serum from the pre treatment level.

Though the fall in S.CEA level did not have similar trend in cases where surgery was done in 38 of 42 patients the S. CEA levels reduced postoperatively while in 4 cases the level was still raised although there was clinical improvement.

Guadagni F et al (2001) reported that elevated CEA and CA 15.3 levels were found in 16.7% and 33.0% of patients, respectively. CEA sensitivity rose to 41.3% and CA 15.3 sensitivity rose to 80.8% in metastatic patients. The adjunct of CEA increased the CA 15.3 sensitivity by 6% in the overall population and by only 2.1% for patients with metastases. During postsurgical follow-up, CEA was elevated in 38.0% and CA 15.3 in 70.2% of patients with recurrence. The combination of CEA and CA 15.3 increased the overall sensitivity by only 1.4%. Longitudinal monitoring of 53 metastatic patients undergoing chemotherapy demonstrated that, when positive, both CEA and CA 15.3 paralleled response to treatment, although CA 15.3 was a significantly more powerful marker for determining response to treatment. The cost effectiveness ratio of CEA was clearly less favorable than that of CA 15.3.

CEA level increased after one month although recurrence was not apparent. In two out of four cases, here radiotherapy and chemotherapy given, the serial value of Serum CEA increased, though no change in clinical conditions was observed.

In few cases the second level (S. CEA) decreased but the 3rd sample was found to have a serum CEA level higher than that of the initial treatment. In our study 43 patients out of 53 (81.11%) patients of cancer breast have serum CEA values more than 2.5 ng/ml.

The proportion of positivity increases with increased tumor spread. This is consistent with the results obtained by A.M. Steward et al. 1974, Douglas Tormeyetal 1977. Steward et a1 showed that out of 17 patients with benign breast disease only one had a value greater than 2.5 ng/ml (that level was 2.9 ng/ml). Among the cancer breast patients they found 42 of 64 cases (66%) to have a serum CEA value of more than 2.5 ng/ml**. Douglas et al got similar results in 1977.**

Among the disease was localised to the breast, the mean serum CEA level is 2.7 ng/ml in stage I we have a value greater than 2.5 ng/ml. In stage II (i.e. disease involving the axillary lymph node) mean serum CEA level is 8.12 ng / ml.

In patient under treatment for advanced stage breast carcinoma, CEA level was elevated in 45.45% of patients with visceral metastases and 54.54% of patients with osseous metastases. Results are similar with the study of **Hangensen DE et al** where study show 15% of patients with soft tissue metastases, 38% with visceral metastases and 50% with osseous metastases. **Palazzo S et al** studied the role of CEA in post mastectomy follow up of primary breast cancer and in the prognostic evaluation of disseminated breast cancer. CEA become positive in 2 of 3 who subsequently relapsed (66.6%). In CEA was positive in 23 of 38 patients (60.5%) with active disease. Response to medical therapy occurred in 6.6% of CEA negative patients compared to 55% of CEA positive patient.

CONCLUSION

We are able to conclude the following findings from the present study. In our study, Stages of the disease mainly presents as the Early stage of disease (43.39%).

The mean value for Stage I is 2.7 ng/ml, for Stage II is 8.12 ng/ml ng/ml) for Stage III 24.2ng/ml for Stage IV 35.2 ng/ml .In patients under treatment for metastatic breast carcinoma CEA level was elevated in all patients with visceral metastases and osseous metastases. Initial high serum CEA level is related to advanced tumor stage, rapid progression and prognosis of disease. Metastasis rate was high for bone more than lung and liver

In our study of serum CEA in the follow up of disease free breast cancer patients after modified radical mastectomy, relapse rate was 11.90%. In relapsed patients 2 out of 5 shows increased serum CEA level.

Considering the follow up of post-operative patients, serum CEA has good prognostic value. It was found positive more in active disease than in the patients who subsequently relapsed. Our study shows serum CEA is of little diagnostic value. Its main role is in the management, detection of the early recurrence, in follow up and prognosis of the Though the fall in S.CEA level did not have similar trend in cases where surgery was done in 38 of 42 patients the S.CEA levels reduced postoperatively while in 4 cases the level was still raised although there was clinical improvement.

REFERENCES

1. Ahmed M. Kabel : Tumor markers of breast cancer: New prospective. / Journal of Oncological Sciences 3 (2017) 5e11.

2. Bruna Karina Banin Hirata, Julie Massayo Maeda Oda, Roberta LosiGuembarovski, Carolina Batista Ariza, Carlos Eduardo Coral de Oliveira, and Maria Angelica Ehara Watanabe : Molecular Markers for Breast Cancer: Prediction on Tumor Behavior. Disease Markers. Volume 2014, Article ID 513158, 12 pages.
3. Faridi SH, Khan MA, Siddiqui B, Maheshwari V, Aggarwal T. Role of serum carcinoembryonic antigen (CEA) as a tumor marker in breast cancer. Int J Adv Med Health Res 2014;1:57-60.
4. Guadagni F, Ferroni P, Carlini S, Mariotti S, Spila A, Aloe S, D'Alessandro R, Carone MD, Cicchetti A, Ricciotti A, Venturo I, Perri P, Di Filippo F, Cognetti F, Botti C, Roselli M : A re-evaluation of carcinoembryonic antigen (CEA) as a serum marker for breast cancer: a prospective longitudinal study. Clin Cancer Res. 2001 Aug;7(8):2357-62.
5. Nicolini A, Carpi A, Ferrari P, Morganti R, Mazzotti V, Barak V, Duffy MJ : An individual reference limit of the serum CEA-TPA-CA 15-3 tumor marker panel in the surveillance of asymptomatic women following surgery for primary breast cancer Manag Res. 2018 Dec 13; 10:6879-6886.
6. Serdarević, N. and Mehanović, S. : "The possible role of tumor antigen CA 15-3, CEA and ferritin in malignant and benign disease", Journal of Health Sciences, 2012; 2(2), pp. 138-143.
7. Shao Y, Sun X, He Y, Liu C, Liu H : Elevated Levels of Serum Tumor Markers CEA and CA15-3 Are Prognostic Parameters for Different Molecular Subtypes of Breast Cancer. PLoS One. 2015 Jul 24;10(7):e0133830