THE VALUE OF NEW TUMOR MARKER CA 15-3 IN DIAGNOSIS AND MONITORING OF PATIENTS WITH BREAST CANCER

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SUMMARY: Serum levels of a tumor-associated antigen, designated CA 15-3, which is defined by two monoclonal antibodies, in 60 untreated breast cancer patients in various stages were determined by immunoradiometric assay. CA 15-3 levels were found to be higher than maximum level of normal control subjects (27 u/ml), in 38,4% of cases in clinical stage-11, 40% of cases in stage-III and 75% of cases in stage-IV. In order to evaluate the correlation between the clinical course and CA 15-3 levels, serial measurements were performed in 32 patients. CA 15-3 levels were lower than initial values in 75% of cases with clinical, radiological, laboratory regression, on the other hand in 87% of cases with progressive disease, CA 15-3 levels were found to be elevated. These observations indicate that CA 15-3 is a sensitive tumor marker for diagnosis and especially for monitoring of breast cancer patients.

Key Words: Breast cancer, tumor marker, CA 15-3.

INTRODUCTION

The association of biologic markers with cancer has been recognized for many decades. The current interest in markers for cancer arose in the mid-1960s with the discoveries of alpha-fetoprotein and carcinoembryonic antigen, called oncofetal proteins because of their presence in high concentrations during embryonic development, their virtual disappearance in the neonatal period and their reappearance with cancer of spesific cell types (5). Today, the main fields of application of tumor markers are detection, diagnosis, monitoring, stating, localization and therapy of various tumors.

Several circulating antigens have been shown to be elevated in association with breast cancer, including casein, alpha-lactalbumin, ceruloplasmin, creatinine kinase, sialytransferases, glycolipids, phospholipids and gross cystic disease protein (3). However, none of these has gained widespread clinical use. CEA is currently the only marker generally accepted as being useful in observing the patients with breast cancer (7).

In recent years, it has become possible to produce large quantities of monoclonal antibodies from the hybrid cell lines of the mice's splenic B-lymphocytes immunized with a specific antigen (2). Studies with monoclonal antibodies in the sera and tumor tissue of patients with breast cancer have led to description of a tumor associated antigen, detected by monoclonal antibody DF3, a high molecular weight glycoprotein which is expressed with differentiation of mammary epitelium. A second type of antigen has also been defined in the sera of breast cancer patients by the use of monoclonal antibody 115D8, originating from human milk fat globule membranes. Subsequent studies have used both monoclonal antibodies DF3 and 115D8 in a bideterminant immunoradiometric assay which has identified a circulating antigen designated CA 15-3 (1,3,4).

A prospective clinical study was undertaken to determine the value of CA 15-3, a new investigate serum assay in diagnosis and monitoring of patients with breast cancer.

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MATERIALS AND METHODS

Sixty untreated breast cancer patients admitted to Ankara Oncology Hospital during the year 1988 were included in the study. The ages of patients were between 28 and 70, with a mean 47.5 years. Table 1 shows the distribution of cases according to stages. Histopathological examination revealed that 54 cases were infiltrative ductal carcinomas, 1 case was lobular carcinoma and 5 cases were anaplastic type. Histopathological examination of axillary lymph nodes was made for 28 cases that the subjected to axillary dissection. It was found that 23 cases had histopathological evidence of lymph node metastases.

Table 1 : Distribution of cases according to clinical stages.

Clinical Stage	Number of cases
II	26
III a	22
III b	8
IV	4
Total	60

Blood samples were taken for CA 15-3 determinations from patients whose diagnosis of breast carcinoma were established.

Following local, systemic or combined modalities of treatment, serial measurements of CA 15-3 were made with 1 to 3 month-intervals in 32 cases. The types of treatment used in those cases that were followed-up are shown in Table 2. Physical examination, erytrocyte sedimentation rate, liver function tests, chest X-Ray scinfillation scanning of liver and spleen, whole body bone scan, abdominal ultrasonography and computerized axial tomography were used for evaluation of patients at the time when blood samples were taken for CA 15-3 deteminations. With the aid of the above data, patients were separated into three groups:

Group 1: Those cases in whom all signs and symptoms disappeared for at least four weeks (complete remission) or those cases in whom more than 50% reduction in the sum of tumor area was detected (partial remission).

Group II: Those cases in whom more than 50% increase in the tumor size was found or new lesions appeared (progressive disease).

Group III: Those cases that could not be included in Group I and II (stable disease).

Table 2: Types of treatment.

Treatment modality	Number of cases
Surgical Procedure	
- Incisional biopsy	3
- Tumorectomy	7
- Simple mastectomy	7
- Modified radical mastectomy	11
- Radical mastectomy	4
Total	32
Pre-operative Neodjuvant chemotherapy	4
Post-operative adjuvant chemotherapy	18
Post-operative estrogen receptor antagonist	4
Post-operative radiotherapy	27

Figure 1: Clinical stages and CA 15-3 levels.

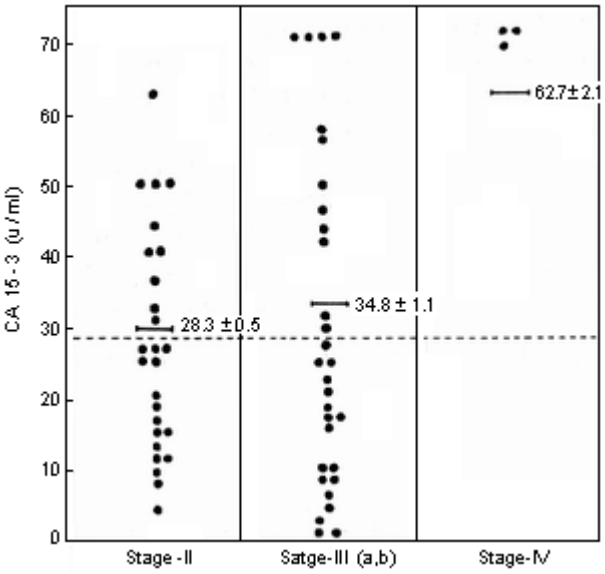

Table 3: Distribution of CA 15-3 levels according to stages.

Clinical Stage	Total Number of cases	Cases with CA 15-3 level > 27 μ/ml	Mean CA 15-3 level (μ/ml) ± SEM *
II	26	10 (38.4%)	28.3 ± 0.5
III (a, b)	30	12 (40%)	34.8 ± 1.1
IV	4	3 (75%)	62.7 ± 2.1

* SEM : Standard error of mean.

Immunoradiometric assay has been used to determine CA 15-3 levels in all cases. Student's t-test was used for the decision of statistical significance between the groups.

RESULTS

The distribution of CA 15-3 levels according to clinical stages is seen in Figure 1. Table 3 shows the levels of CA

15-3 higher than 27 u/ml, which is the maximum level of control subjects, and their distribution in various stages. The correlation between the CA 15-3 levels and lymph node metastases is seen in Table 4, and the difference between the two groups is statistically significant ($p<0.05$).

CA 15-3 levels with clinical course. Seventy-five percent (12/16) of patients with documented regressive disease had 40,5% decrease in CA 15-3 levels, on the other hand eighty-seven percent (7/8) of patients with progressive disease had more than 100% increase in the levels of the

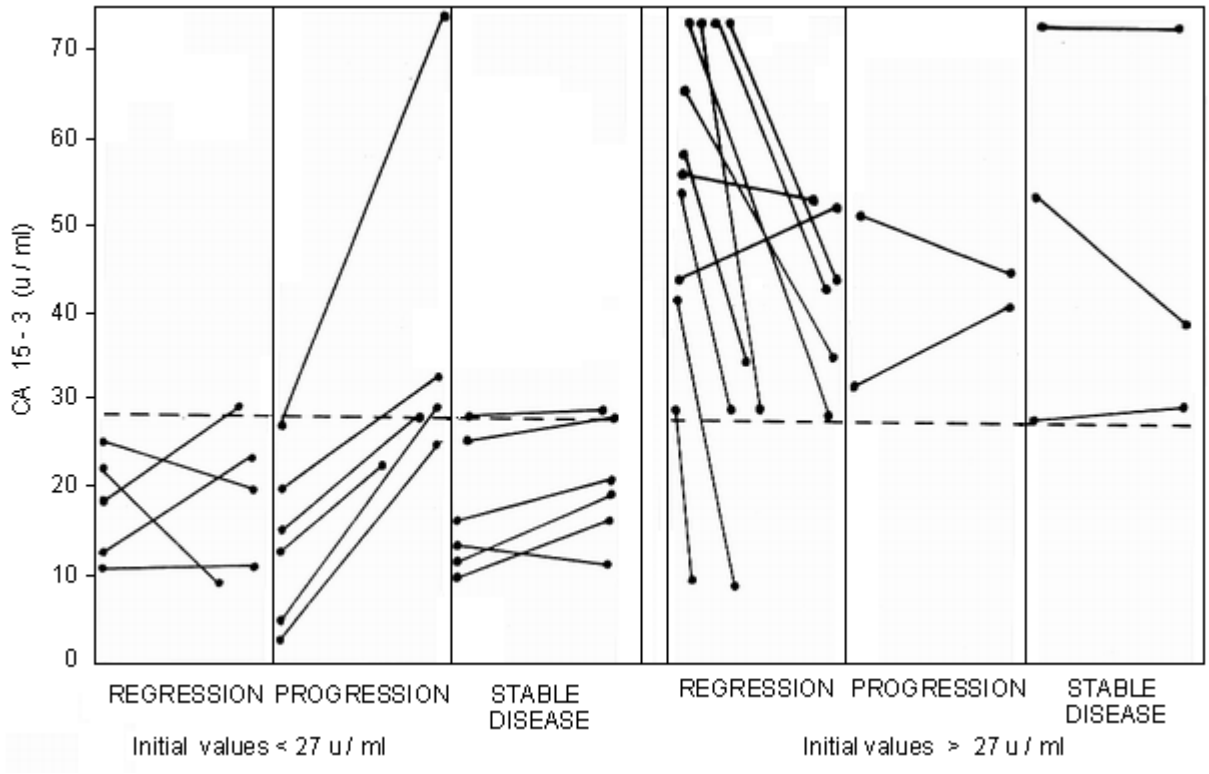

Figure 2: Correlation between CA 15-3 levels and clinical course.

The relationship between the clinical course and antigen levels is shown in Figure 2. The most prominent changes were in those cases whose initial values were low but increased with progressive disease. Those, whose initial levels were high also had significant decrease of the antigen level with regression. Figure 3 shows the changes in

Table 4: Axillary lymph node metastases and CA 15-3 levels.

Axillary lymph node status	Total Number of cases	Cases with CA 15-3 level > 27 μ/ml	Mean CA 15-3 level (μ/ml) ± SEM *
Lymph node metastases (+)	23	15 (68%)	39.1 ± 1.2
Lymph node metastases (-)	5	1 (20%)	18 ± 1.1

* SEM : Standard error of mean.

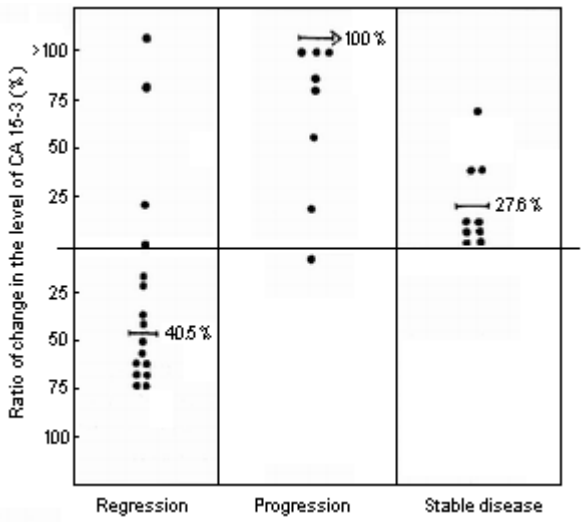

Figure 3: Changes in CA 15-3 levels with clinical course.

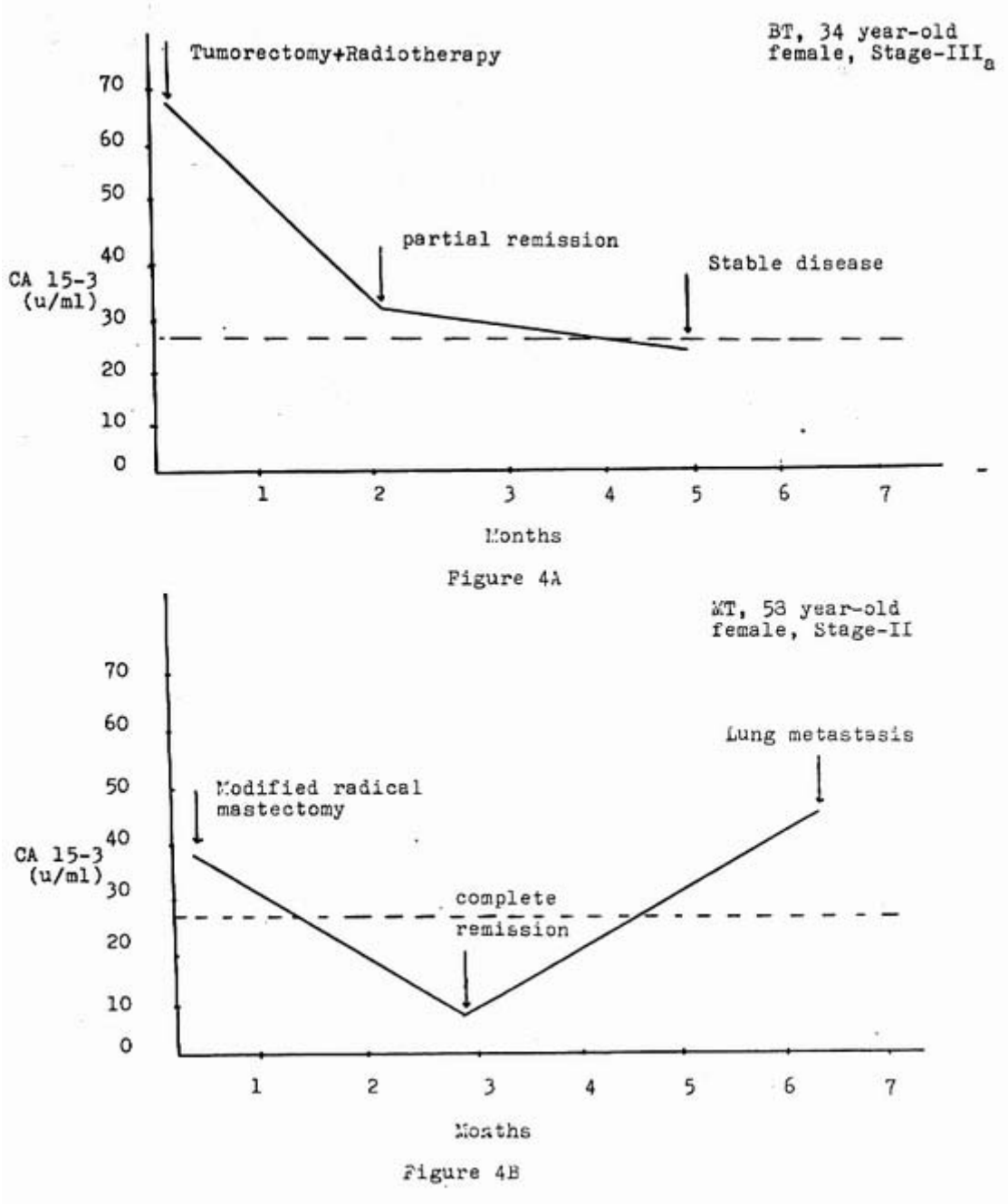

Figure 4: Correlation between CA 15-3 levels clinical course. Serial measurements were determined for two patients.

antigen. The correlation between the clinical course and the circulating CA 15-3 levels measured sequentially for two patients are shown in Figures 4A and 4B.

DISCUSSION

The present study demonstrates that CA 15-3 immunoradiometric assay is not a highly sensitive marker for Stage II and III cases of breast cancer, since only 40% of these patients have elevated levels of the antigen. Therefore we believe that CA 15-3 should not be used as a screening test for neoplastic lesions of the breast. On the other hand, CA 15-3 measurements may have a diagnostic value for metastatic breast cancer since the level of antigen is remarkably high in these cases.

Axillary lymph node metastasis is one of the most important prognostic factors in breast carcinoma. Sixty-eight percent of cases with proven axillary lymph node metastasis had elevated CA 15-3 levels. Only twenty-percent of patients without lymph node metastasis had elevated levels of the antigen, and the difference was statistically significant. Based on this finding, it can be considered that patients in clinical Stage II and III with elevated levels of CA 15-3 whose axillary lymph node status could not be assessed, carry an unfavorable prognosis, and this may be an indication to institute systemic chemotherapy.

Although the level of the antigen is related to the stage of the disease , it is not possible, however, to ascertain the kinetics of the relationship with respect to the absolute number of tumor cells in the host. Such a correlation must await in vivo and in vitro investigations of the synthesis, secretion, catabolism, and excretion of CA 15-3.

Serial measurements of the antigen to demonstrate the relation with clinical course revealed prominent changes in two distinct groups. First, in those cases whose initial values were low but increased with documented progressive disease. Second, patients with high initial values who had significant decrease with regression. Twenty-seven percent increase in the level of CA 15-3 in patients with stable disease is in accordance with the published data (3), this finding, in our opinion, may reflect a subclinical progression.

Eighty-seven percent of cases with progressive disease had more than 100% increase in CA 15-3 levels. Striking changes in the level of marker in this group were seen in three cases with lung and bone metastases. Hayes *et al.* detected elevated levels of the antigen in 91% of the cases with breast cancer (3), Yoshimoto reported this ratio as 64% (8).

Seventy-five percent of cases with regressive disease had 40,5% decrease in CA 15-3 levels compared to initial values, Hayes (3), reported 50% decrease in the same group of patients. Schmidt, in his study reported that elevated CA 15-3 plasma concentration was noted a few months before clinical diagnosis of new metastases (6). This finding emphasises the value of sequential measurements of the tumor marker during the asymptomatic period for early detection of local recurrences and distant metastasis.

It has been reported in the published data that the elevated levels of CA 15-3 can be detected in 1% of normal population, 3-20% of benign breast lesions, 36-40% in hepatites, 14-70% in gastrointestinal, over and lung cancers (1,3). Since the introduction of this investigative serum assay is quite new, studies to demonstrate the sensitivity and specifity of the test are required. Limited number of studies have shown that CA 15-3 is a more sensitive and specific tumor marker than CEA for cases of breast carcinoma (3,8).

ýIn conclusion, CA 15-3 is a considerably spesific tumor marker in diagnosis and especially monitoring of patients with breast cancer.

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