Original Research Paper

Volume-8 | Issue-4 | April-2018 | PRINT ISSN No 2249-555X

Surgery

# TO STUDY THE ROLE OF SERUM ADENOSINE DEAMINASE LEVELS IN PATIENTS WITH CARCINOMA BREAST.

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**ABSTRACT** Adenosine deaminase was found to be the better probable parameter for the detection of cancer and to assess the development of various stages of cancer whereas 5'-nucleotidase had only diagnostic significance. Serum alkaline phosphatase levels were important for assessing the spread of cancer at secondary sites. After mastectomy a significant decrease was found in the levels of serum ADA and 5'-NT whereas no variations were found in case of serum ALP.

**Aims and objectives**: The potential relationship between adenosine deaminase activity and cancer progression was examined by investigating the activity of total ADA and its isoenzymes in serum and simultaneously in the cancerous tissue of each patient with breast cancer.

**Material and methods**: Twenty five biopsy proved cases of carcinoma breast were selected from department of surgery, medical college and hospital .The control group consisted of 25 age matched healthy females. For all the patients detailed history of the present and past illness, family history and personal history was recorded. Detailed clinical examination and routine investigations were carried out for each patient. The study group included all the patients with following exceptions:

a) Patients who have already received treatment for malignancy in any form.
b) Patients who had acute or chronic infection.

After examination and investigations, all the patients were graded into various stages as per Manchester and TNM classification.

**Conclusions**: Serum ADA activity was significantly higher in patients of carcinoma breast as compared to the controls. The procedure thus has a diagnostic value. The increase in serum ADA activity did not bear any direct correlation with the advancing stage of malignancy.

**KEYWORDS :** Adenosine deaminase ,isoenzymes ,matched .

## Introduction

**Neoplasm** is an abnormal mass of the tissue, the growth of which exceeds and is uncoordinated with that of the adjacent normal tissue The abnormal group persists in the some excessive manner even after cessation of the stimuli which evoked the change initially. Neoplastic cells have altered metabolism as compared to the normal cells and this results in cellular enzymatic imbalance. These enzymatic distrubances have been studied in various malignant conditions by different workers.

Adenosine deaminase partially controls the cell mediated immunity and this response has been seen in various neoplastic processes. Increased levels of serum adenosine deaminase have been shown by various workers in various types of malignancies. (Schwartz and Bodansky, 1959).

Raczynska et al (1966) demonstrated increased plasma ADA activity in 30 patients with liver cancer. Activities were uniformly low in lymphocytes from patients with chronic lymphocytic leukemia and the enzyme levels were elevated in the blasts of patients with acute lymphocytic and myelogenous leukemia. On the other hand, decreased lymphocytic ADA levels were found in the patients with renal adenocarcinoma (Sufrin et al 1977).

There are few reports available about serum adenosine deaminase levels in carcinoma breast patients. Schwartz and Bodansky (1959) found increased level of ADA in these patients.Low absolute lymphocyte counts have been reported in lymphomas, tumours of gastrointestinal tract, carcinoma lung, carcinoma bladder and in others areas (Riesco, 1970). Papatestas and Kark (1974) studied pre-treatment lymphocytic levels in carcinoma breast patients and found that it served as an index of host's competence.

Nirwan et al (1981) found that mean peripheral lymphocyte counts decreased with the advancing stage of malignancies. Gupta (1981) reported a decreasing absolute lymphocyte count with advancing stage of carcinoma breast and the counts increased after surgery in these patients.

### Aims and objectives

The potential relationship between adenosine deaminase activity and cancer progression was examined by investigating the activity of total ADA and its isoenzymes in serum and simultaneously in the cancerous tissue of each patient with breast cancer.

## MATERIAL AND METHODS

Twenty five biopsy proved cases of carcinoma breast were selected from department of surgery, medical college and hospital, u.p The control group consisted of 25 age matched healthy females. For all the patients detailed history of the present and past illness, family history and personal history was recorded. Detailed clinical examination and routine investigations were carried out for each patient. The study group included all the patients with following exceptions

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After examination and investigations, all the patients were graded into various stages as per Manchester and TNM classification.

## OBSERVATION

Serum Adenosine Deaminase levels in patients with carcinoma breast.

Serum adenosine deaminase (ADA) levels were assayed In 25 female patients with carcinoma breast. The patients studied were in the age group of 25-60 years. Mean serum adenosine deaminase level in these patients was 51.05+/-11.97 units/l.

Effect of surgery on Serum ADA levels in patients with carcinoma Breast:

The effect of surgery was studied on serum adenosine deaminase levels in 23 patients with carcinoma breast. Two patients out of 25 patients had stage IV disease and hence no surgery was undertaken.

Serum adenosine deaminase levels were estimated prior to surgery and on the seventh postoperative day. A decrease in serum adenosine deaminase was found after surgery. Before surgery, mean value was 51.05+/-11.97 units/l which was significantly higher than the control group. The value decreased to 40.19+/-12.3 units/l after surgery. The value was higher than the control group but the decrease after surgery was not significant.

**Combined effect of surgery and chemotherapy on serum ADA levels in patients with carcinoma breast:**
Twenty one patients out of study group of twenty-live were given chemotherapy after surgery in the form of CMF or CAF with Tamoxifen, The serum adenosine deaminase levels were estimated pre-treatment, after surgery on the seventh post-operative day, after half the dosage of chemotherapy and on the completion of chemotherapy. Follow up was done for a period of 2-6 months. Two patients out of 25 were in stage IV of the disease and hence chemotherapy was given as the sole treatment.

In the control group, mean serum adenosine deaminase value was 14.2+-2 .65 units/l which was significantly less than the mean value of the patients before any treatment (Mean 51.05+/-11.97 units/l, p<0.001) . After surgery and chemotherapy the serum adenosine deaminase levels started falling and the mean value after half the dosage of chemotherapy (29.75+/-6.86 units/l was significantly lower than the pre-treatment level [p<0.001).

One patient on follow-up for chemotherapy developed local recurrence with pleural effusion. Serum adenosine deaminase was done and it demonstrated elevated value very close to the pre-treatment value.

**Combined Effect of Surgery and Radiotherapy on Serum ADA levels in patients with Carcinoma Breast:**
The combined effect of surgery and radiotherapy was studied on serum adenosine deaminase level in two patients. In these patients, serum adenosine deaminase levels were estimated prior to surgery, on the seventh post-operative day and after completion of radiotherapy.

Before treatment the mean value was 65 units/l. After surgery and completion of radiotherapy the mean value decreased to 38.6 units/l. The decrease was not significant and this could be explained due to small study group.

**Serum adenosine deaminase levels in relation to staging of carcinoma Breast:**
The patients were classified into clinical staging( Manchester). There were 6 patients in stage II, 17 in stage III and 2 in stage IV. All the patients showed equally higher serum adenosine deaminase activity than the controls. But this increase was not directly proportional to the advancing stage of the growth.

In patients with stage II, mean serum adenosine deaminase value was 49.06+/-4.24 units/l. While, in patients with stage III the mean value was 51.8 +/-14.33units/l and in patients with stage IV had value of 50.5+/-24.73 units/l. There was no significant correlation between the serum adenosine deaminase levels and the stage of malignancy.

**Absolute lymphocyte count in control subjects and in patients with carcinoma breast:**
The mean absolute count in subjects was 3067+-480/cumm while in patients with ca breast was 2264+-512/cumm which was significantly less when compared with the control group.

**Effect of surgery on Absolute lymphocyte count(ALC) in patients with carcinoma breast:**
The effect of surgery was studied on ALC in 23 patients with carcinoma breast. ALC was done prior to surgery and on 7th post-operative day.

Before surgery, the mean value was 2264+-512/cumm which was significantly less than the control group (mean 3067+-480/cumm) (p<0.001). After the surgery, the mean value of ALC increased significantly to 2368+-480/cumm when compared to pre-operative levels. The mean value post operatively was significantly lower than the control group(p<0.001).

**Combined effect of surgery and radiotherapy on Absolute lymphocyte count in patients with carcinoma breast:**
The combined effect of surgery and radiotherapy was studied on ALC in 2 patients with carcinoma breast. In these patients ALC was done prior to surgery, on 7th post-operative day and after completion of radiotherapy. Mean absolute count before treatment was 2240+-1107/cumm was lower than the control group 3067+-590/cumm. But this difference was not significant due to very few patients in this study group. After surgery the mean value increased to2525+-883/cumm. The increase was also not significant. After the completion of radiotherapy there was a decline in the mean absolute lymphocyte count(mean 1585+- 162 cumm). This decrease again was not significant due to only 2 patients in this study group.

**Effect of surgery and chemotherapy on ALC in patients with carcinoma Breast:**
Effect of surgery and chemotherapy was studied on 21 patients with carcinoma breast. ALC was done prior to surgery, on 7th post-operative day and after the half dosage of chemotherapy. Mean absolute count before surgery was 2247+-457/cumm which was signifiacantly lower than the control group in which the mean was3067+-480/cumm(p<0.001). After chemotherapy, the levels started falling and mean value found was 1917+-328/cumm which was significantly lower than the pretreatment value (p<0.001). the value was significantly lower than the control group.

**Effect of chemotherapy alone on ALC in patients with carcinoma breast:**
There were only 2 patients in stage IV disease for which chemotherapy was given as the sole treatment. Mean ALC in these patients was 2268+-1086 prior to chemotherapy as compared to control group(mean 3067+-480). After chemotherapy the mean ALC was 1830+-523. The decrease was not significant(p>0.1).

**ALC in relation to staging in patients with carcinoma breast:**
The patients were divided into 4 groups according to clinical staging (Manchester's). There were 6 patients in stage II, 17 patients in stage III, 2 patients in stage IV and no patient in stage I of the disease. Mean ALC of patients in stage II was 2359+-743/cumm, 17 patients in stage III had mean ALC of 2231+-375/cumm and 2 patients in stage IV had mean ALC of 2268+-1086/cumm. Control goup had mean ALC of 3067+-480/cumm. The patients in stage III disease had a significant decrease of ALC as compared to the controls. Mean ALC of patients in Stage IV and Stage II had lower values as compared to the control group but the decrease was not significant. It was found that the decrease was not directly proportional to the advancing stage of the disease.

**DISCUSSION:**
Adenosine deaminase is a purine metabolising enzyme and is widely distributed in human tissues. It partially controls the cell mediated immunity and the response has been observed in many neoplastic processes. Increased levels of adenosine deaminase (ADA) have been reported by several workers, in various types of malignancies. Adenosine deaminase levels have been shown to correlate with cellular immune competence. Sufrin et al (1977) studied lymphocyte and erythrocyte ADA levels in patients with renal adenocarcinoma. Compared with controls, patients with renal adenocarcinoma showed decreased lymphocyte ADA levels. Patients with low stage lesions had a significant reduction of lymphocyte ADA levels in contrast to the relatively normal value of patients with high stage lesions. Erythrocyte ADA levels bore no direct relation to tumor stage, grade or histologic cell type. Nephrectomy resulted a rise in both lymphocyte and erythrocyte ADA activity. Koehler and Benz (1962) reported increased activity of serum ADA in cancer patients and suggested that a non-specific response may, indeed, exist.

In the present study, the mean value for serum ADA levels, in the age group of 25 patients of carcinoma breast was found to be significantly higher when compared to controls and the rise was evident in all the patients studied. The increased level of serum ADA in these patients suggest increased utilisation of adenosine. Since there is an unchecked proliferation, the levels of adenosine are increased due to increased metabolic activity of the malignant cell which may be a result of the de novo synthesis or due to the stimulation of the salvage pathway. Ishi and Green (1973) reported that adenosine is toxic to the cultured mammalian cells and that it interferes with the pyrimidine biosynthesis. Increased levels of this enzyme thus represent a detoxiction mechanisms thereby preventing the accumulation of adenosine so that proliferative process can proceed, uninterrupted.

**Effect of surgery on serum ADA levels.**
In the present study, surgery was done in 23 patients of carcinoma breast. In these patients serum ADA levels were estimated prior to surgery and on the 7th post-operative day. Post-operatively, a decrease in serum ADA levels was noticed when compared with their pre-operative levels. The decrease in serum ADA levels may be due to decrease in tumour mass.

**Combined effect of surgery and radiotherapy on patients with carcinoma breast:**
The combined effect of surgery and radiotherapy was studied on serum adenosine levels in two patients.

Levels of serum ADA were done pre-operatively, on the 7th post-operative day and after completion or radiotherapy. After surgery and after completion of radiotherapy, there was a decline in serum ADA levels which was not statistically significant due to small number of patients in this group.

Lal et al(1987) reported reduction in serum ADA levels after radiotherapy in patients with head and neck cancer.

**Relationship of serum ADA with the stage of malignancy:**
Serum ADA levels were estimated in relation to the various stages of breast cancer. It was found that there was no positive correlation between serum ADA levels and the advancing stage of carcinoma breast and that the enzyme levels in all the stages of malignancy were significantly higher than the control group.

**Absolute Iymphocyte count in Carcinoma breast:**
Decreased number of absolute lymphocyte count has been observed in many malignant conditions like lymphomas, tumors of gastrointestinal tract, carcinoma lung and carcinoma bladder etc. (Riesco 1970). In the present study absolute lymphocyte count (ALC, were done along with serum ADA levels in the group of 25 normal, healthy females and 25 with carcinoma breast. There was a significant decrease in ALC in breast cancer patients compared to the control subjects.

A decrease in cellular response in patients with carcinoma breast, has been reported by several workers by simple lymphocyte counts (Riesco 1970, Papatestas and Kark 1974, and Nirwan et al 1941). Mohammad Amin and Robert (1974) reported lymphocytopenia in cases of carcinoma bladder in the end stages of the disease. The exact cause of lymphocytopenia in malignancies is not well known but various hypotheses have been given.

Effect of surgery on absolute lymphocyte count was observed in 23 patients with carcinoma breast. Following surgery there was a statistically significant increase in the peripheral absolute lymphocyte counts. McCredie et al (1973) showed that operation of radical mastectomy in patients with carcinoma breast produced an increase in the number of lymphocyte counts in peripheral blood.

The increase in absolute lymphocyte counts after curative surgical resection could be either due to enhanced immunological response or due to toning up of hemopoietic system which becomes more sensitive after excision of the tumor.

The patients, who were subjected to radiotherapy and or chemotherapy or combination therapy, showed lymphocytopenia , which might be due to bone marrow depression. They reported that levels on follow up were still significantiy lower than the control group. McCredie et al (1973) observed a prolonged lymphocytopenia (for 6 months control or longer) in cases of carcinoma breast who were given prophylactic radiotherapy after radical mastectomy.

The reason for persistence of lymphocytopenia after radiotherapy is not known. Possible explanations are that, radiotherapy selectively destroys the Iong lived lymphocytes or damages the thymus or produces a humoral factor which depresses the formation of lymphocytes.

The decrease in lymphocyte counts after deep x-ray therapy could result from increased destruction of lymphocytes in blood, lymph nodes, bone marrow and thymus because lymphocytes are most radio-sensitive blood cells (McCredie et al 1972). Sykes et al (1960) found that marrow in the sternum was replaced by fibrofatty tissue when prophylactic post-operative deep x-ray therapy was given in cases of carcinoma breast, and this could be the cause of lymphocytopenia after deep x-ray therapy.

The explanation for lymphocytopenia in malignancy is speculative. A growing body of circumstantial evidence attests to the importance of cellular immune mechanism in cancer homeostasis and several observations are note.An alternative explanation is a lymphocytopenia inducing effect exerted by malignant tumours. However, it is tempting to speculate that quantitative deficiency in circulating lymphocytes may reflect failure of homoeostatic mechanisms concerned with the destruction of malignant cells. The prognosis was better in breast cancer patients who were having higher lymphocytic count. McCredie et al(1973) found that the prognosis in patients with carcinoma breast was not related to any time to lymphocyte count. In present study, follow up is too short to make any comment.

**Absolute lymphocyte counts and staging of malignancy:**
on evaluation of the relationship between different stages of malignancy and lymphocyte counts, it was found that there was no significant decrease in ALC with advancing stage of the disease An inverse correlation between the absolute lymphocyte count and tumor stage as well as in association between lymphocyte counts and prognosis has been reported in patients with breast cancer (Reisco, 1970; Papatestas and Kark., 1974 and Nirwan et al, 1981).

## CONCLUSION:
Serum adenosine deaminase and absolute lymphocyte counts(ALC) were estimated in 25 patients of carcinoma before and after surgery, surgery and radiotherapy, chemotherapy and surgery, and chemotherapy. The control group consisted of 25 age matched healthy females. Serum ADA activity was assayed as per technique reported by Giusti (1974).

Serum ADA activity was significantly higher in patients of carcinoma breast as compared to the controls. The procedure thus has a diagnostic value. The increase in serum ADA activity did not bear any direct correlation with the advancing stage of malignancy.

Serum ADA activity decreased Patients having diseases associated with lymphocytosis, such as infectious mononucleosis or chronic lymphocytic leukemiain patients after surgery and in patients with advanced malignancy after treatment who received chemotherapy alone. The decrease in serum ADA activity was also noted in patients who received surgery and radiotherapy, though, this decrease was not very significant.

Follow-up was possible in all the patients for a period of 2-6 months only. During the follow-up period, there was a general trend towards decrease in the levels of serum adenosine deaminase. In one of the patients in the present study, residual disease or recurrence was noted during the period of follow-up and this correlated well with increase in serum ADA activity in that patient. The number of the patients is too small to draw any conclusion and a prolonged follow-UP is needed to evaluate a prognostic significance of estimation of serum ADA levels.

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