EVALUATION OF SOME SERUM ENZYMES LEVELS IN BREAST CANCER PATIENTS

Nidhal Abdul-Mohymen*, *B.Sc., Ph.D.*, **Bushra M. Mahmood**** *B.Sc., Ph.D.*, **Farouk K. Hassan***** *B.Sc., Ph.D.*

Abstract

Background: Breast cancer is the most common gynecological malignancy in many parts of the world. It is the major cause of death for women, and its occurrence has a particular relevance to women's health worldwide. The etiology of breast cancer appears to be multifactorial, since both. Endogenous and exogenous factors are known to increase breast cancer risk

Objective: Detection of some prognostic factors in sera like LDH, ADA.

Patients & Methods: Seventy-three patients with breast tumor were included in this study. Sixty-two with malignant breast cancer and 11 with benign breast tumor. The malignant breast tumor included: 8 patients with Intraductal carcinoma (IDC), 5 with Lobular carcinoma (LC), 49 patients with and infiltrative ductal carcinoma which in turn divided into 11 with well differentiated ductal carcinoma (WDC), 12 patients with moderately differentiated ductal carcinoma (MDC), and 26 patients with poorly differentiated ductal carcinoma (PDC). All cases were admitted to Al-Yarmouk Teaching Hospital and Medical City, during the period from December 1999 to January 2001. Detection of some prognostic factors in sera like Lactic acid dehydrogenase LDH, and adenosine deaminase (ADA), were detected.

Results:

The results indicated that serum levels of LDH were elevated in PDC (267.9±24.01) and in MDC (200.0±37.4).Other types as well as benign tumor were found within the normal range values (80-190) u/L. Serum levels of ADA were elevated in PDC type (32.7±5.21) and slightly elevated in LC. There were no significant differences between malignant types and benign breast tumor ($P<0.05$) whereas significant differences were recorded between healthy control and other types of tumors ($P>0.05$).

Conclusion: The application of enzyme assay (ADA, LDH) is of prognostic value

Key words: Breast cancer, ADA, LDH.

Iraqi J Med Sci, 2004; Vol. 3 (1): 18-21

Introduction

Lactate dehydrogenase is one of the non-plasma specific enzymes. The concentration of such enzyme in tissue is very high, compared with that in plasma[1]. It is widely rich in mammalian tissues, being rich in myocardium, kidney, liver and muscle; it catalyzes the reversible oxidation of lactate to pyruvate with the oxidation of NADH to NAD[2]. LD levels usually are normal in-patients and animals with small, localized carcinomas, whereas levels are increased in those with distant metastases or even local extension. The highest value occurs in patients with metastases to the liver, although increased levels are also found in some patients with only extrahepatic metastases or extension[2].

Adenosine deaminase (ADA), (adenosine amino hydrolase, EG 3.5.4.4), is the enzyme that irreversibly catalyzes the hydrolytic deamination of adenosine and deoxyadenosine to inosine respectively and ammonia[3]. A unit of activity of this enzyme is defined as the amount of enzyme that deaminates one micromole of substrate per minute, under specific steady assay condition. The normal value of ADA in serum range from 2-17 u/L[4]. Studies have suggested a critical role for ADA activity in the normal development of the immune system[5,6]. These studies indicate that a deficiency in this enzyme in human result in an autosomal recessive type of sever combined immunodeficiency diseases (SCID), which is characterized by the loss of both T- and B-cell function[7]. The activity of ADA seems to vary in a number of diseases. Elevated serum ADA has been reported in carcinomas[8]. Patients with acute lymphoblastic leukemia have increased level of ADA activity in their T-cells[9]. However, in some cases of lymphoblastic leukemia, low levels of ADA were found. The levels increased as chemotherapy was introduced[10]. Fluctuated activity of ADA in serum has also been found in breast cancer[11]. The specific activity of ADA

* Dept. Medical Microbiology, College of Medicine, Al-Nahrain University. ** Dept. Microbiology, College of Medicine, Al-Mustansiriya University.

Received 16th February 2003: Accepted 19th January 2004.

Address Correspondence to Dr. Nidhal abdul-Mohymen

measured in serum, of breast cancer patients, shows different value according to the stage of the disease comparing with the control group[12]. In this study we intended to detect some of the prognostic factors in sera like LDH, ADA in breast cancer patients.

Patients & Methods

A total of seventy-three patients presented with breast tumor, were included in this study. The patients were admitted for surgery at Medical City and Al-Yarmok teaching hospital. The history as well as personal information, about each patient was obtained through a form which is developed to fulfill the aims of this study. The patients mentioned were grouped according to their histopathological finding into

Group 1: includes 11 patients with benign breast tumors.

Group 2: includes 62 patients with malignant breast tumors.

Those patients were of two categories: 26 post menopausal patients and 36 pre menopausal patients. The histopathological finding of all patients was tabulated according to Bloom & Richardson grading system (1957) and as presented in Table 1. Twenty apparently healthy women were included as a control. Those ladies had similar age range with those of the patients. Serum of venous blood of patients and control subjects under investigation were collected aseptically, serum of 20 healthy women were included in this study as control

Table 1: Type of specimen tumor under investigation based on Bloom & Rrechardson (1957)

Group	Type of tumor	Number
Malignant breast tumor	WDC	11
	MDC	12
	PDC	26
	IDC	8
	LC	5
Benign breast tumor	Fibroadenoma	4
	Fibroadenosis	6
	Epitheliosis	1

Enzyme Assays:

Adenosine deaminase assay: The method for assay of ADA adopted is based on measuring the rate of ammonia consumption at 620 nm following the reaction. The activity was determined in the serum according to Giust (1981)[14].

Lactate Dehydrogenase (LDH): A colorimetric method was followed in estimation of LDH activity. The principle of this method is based on the reduction of pyruvate to lactate in the presence of NADH by the action of lactate dehydrogenase. Kit of RANDOX UK was used.

Results

The results tabulated in table 2 showed the mean values and standard deviation of LDH activation in different type of malignancies and in benign breast tumor. Serum levels of LDH were elevated in PDC (267.9±24.01) and in MDC (200.0±37.4).Other types as well as benign tumor were found within the normal range values (80-190) u/L. There was highly significant difference between malignant type when compared to normal tissue LDH activity (P=0.0022).

Table 2: Mean±SD of LDH level in different tumor types

Type of tumor	No. of cases	Mean±SD
IDC	8	59.8±9.5
LC	5	82.2±26.5
MDC	12	200±37.4
PDC	26	32.7±8.2
WDC	11	12.9±2
Total malignant	62	64.6±45
Benign tumors	11	12.9±2

P = 0.002

Table 3 shows mean values and standard deviation in different types of malignancies and in benign breast tumors. Serum levels were elevated in PDC type (32.7±5.21) and slightly elevated in LC. There is no significant differences between malignant types and benign breast tumor (P<0.05) whereas significant differences were recorded with healthy control (P>0.05).

Table 3: Mean±SD of ADA enzyme activity in different tumor types

Type of tumor	No. of cases	Mean±SD
IDC	8	1.76±4
LC	5	20.8±0.6
MDC	12	7.4±3.9
PDC	26	32.7±8.2
WDC	11	13±2
Total malignant	62	16.6±30
Benign tumors	11	17.5±2.8
Control	20	16.5±5

P<0.05 between all types, P>0.05 health controls Vs other types

Discussion

One of the best-characterized features of tumor growth is the associated alteration in the enzyme and isoenzyme pattern of tissue in the host organism[15]. LDH is one of the enzyme systems preferentially produced and retained by cancer cells, being necessary to maintain tumor growth[16]. When the LDH isoenzyme are released from neoplastic tissue in the serum, the LDH isoenzyme pattern of serum changes. There have been several reports of anomalies in the synthesis and total LDH activity as well as in the pattern of LDH isoenzymes that correlate with cancer in humans[17].

In these data, the mean concentration of serum LDH was significantly elevated in PDC and MDC groups, this in agreement with previous study which showed significant differences in enzyme activities between benign and malignant neoplasms of the breast when compared with each other and when compared with healthy control, also there were significant enzyme changes between non-metastatic and those with metastasis and when stage I, II cancer were compared with those in stage III and IV. Another study in Iraq[18], recorded an extra band migration anodally to LDH, they observed only an additional LDH band but no other abnormalities in the electrophoretic mobility of LDH isoenzymes. This abnormal band disappeared shortly after surgical removal of tumor and after chemotherapy or radiotherapy was begun.

Our data and others may suggest that this assay may have potentially clinical usefulness, at least for follow-up studies of malignant disease and as indicator for bad prognosis.

ADA deficiency in humans results in an immunodeficiency characterized by severe reduction in T, B and NK cells[19]. The metabolic disturbances associated with ADA deficiency induced apoptosis in developing thymocytes in vivo. Peripheral T and B cells were abnormal in ADA/mice as reflected in the expression of cell surface marker and localization in different zone of lymphoid organ. In addition, mature T cells recovered from spleen of ADA/mice were defective with their regard to their ability to functionally signal through the TCR[20].

In our data, elevated ADA activity was recorded in PDC and LC and there was significant elevation, in comparison with healthy control. Cancer cells have increased ADA activity and this might be a physiologic attempt of the cancer cells to provide more substrate needed by cancer cells to accelerate the salvage pathway activity. Furthermore, high ADA activity might also a play role in the detoxification process of high amount of toxic adenosine and deoxyadenosoduced from celerated purine metabolism in the cancerous tissue.

References

1. Cahn, R.D., Kaplan, N.O., and Zwilling, E.: Nature and development of lactic dehydrogenase. Science, 1982; 136: 962-9.
2. Anderson, G.R., and kovasik, J.: LDH an unusual oxygen sensitive lactate dehydrogenase expressed in human cancer Nath Acad Sci USA, 1981; 78: 3209-12.
3. Dinjens, W.N.M., Kate, J., Vanderlinden, E.P.M., Wijnen, J.T., Khan, P.M., and Bosman, F.T.: Distribution of adenosine deaminase complexing protein (ADCP) in human tissue. J Histochem Cytochem, 1989; 37: 1869-75.
4. Giusti, G.: Adenosine deaminase. In: Methods of enzymatic analysis. Vol. 2, 2nd ed., 1981; Verlag chemic international. Deerfield Beach, Florida.
5. Thompson, L.F., and Seegmiller, J.E.: Adenosine deaminase deficiency and sever combined immunodeficiensy disease. Adv Enzymol, 1980; 51: 167-210.
6. Webster, A.D.B.: Metabolic defects in immunodeficiency disease. Clin Exp Immunol, 1982; 49: 1-10.
7. Bollinger, M.E., ArredondoVegra, F.X., Santisteban, I., Santisteban, I., Schwarz, K., Hershfield, M.S., and Lederman, H.M.: Brief report: hepatic dysfunction as a complication of adenosine deaminase deficiency. N Eng J Med, 1996; 334: 1367-71.
8. Winsten, S.: Enzyme in carcinoma. In: Bio-chemistry of women: Methods for clinical investigation. Curry, A.S., and Hewitt, J.V., eds. CRC Press.1974; pp 219-234.
9. Hatzistillanou, M., Athanassiadou, F., Catriu, D., Makedou, A., Hitoglou, S., and Papaeconomou, A.: Prognostic significance of adenosine deaminase in children with malignancies Pediatr Hematol Oncol, 1996; 13: 339.
10. Meier, J., Coleman, M.S., and Hutton, J.J.: Adenosine deaminase activity in peripheral blood cells of patients with hematological malignancies. Br J Cancer, 1976; 33: 312-9.
11. Sergy, G., Michael, R., Rodney, E., Patrack, T., and Michail, V.: Adenosine deaminase eficiency increases thymic apoptosis and cause defective T cell receptor signal. J Clin Invest, 2001; 108:131-41.
12. Al-Amiry, E.W.H.: Enzymatic, cytogenetic and drug resistance studies on blood from patients with breast cancer, M.Sc. thesis in Biology, College of Education for Women, University of Baghdad, 1999.
13. Bloom, H.J.C., and Richardson, W.W.: Histological grading and prognosis in breast cancer. Study 1409 cases of which 359 have been followed for 15 years. Br J Cancer, 1957; 11: 359-77.

14. Giusti, G.: Adenosine deaminase. In: Methods of enzymatic analysis. Verlag Chemic international. Deerfield Beach, Florida Vol. 2, 2nd ed., 1981.
15. Podlasek, S.J., Mc Pherson, R.A., and Threatle, G.A.: Characterization of apparent lactate dehydrogenase isoenzyme B. A lactate-independent dehydrogenase Clin Chem, 1984, 30: 266-70.
16. Rijke, D., and Trienekens, P.H.: Variant expression of lactate dehydrogenase complexes interfering with isoenzyme analysis. Clin Chim Acta, 1985; 146: 135-45.
17. Anderson, G.R., and Kovasik, J.: LDH an unusual oxygen sensitive lactate dehydrogenase expressed in human cancer. Nath Acad Sci USA, 1981; 78: 3209-12.
18. Al-Samarai, I.H.: Studies on some proteinic factors in malignant and benign breast tissues and their correlation with esrotgen receptor. Ph.D. thesis, College of Science, University of Baghdad, 2000.
19. Buckley, R.H.: Human severe combind immuno deficiency. Genetic phenotype and functional diversity in one hundred eight infants. J Pediat, 130: 378-87.
20. Aspsov, S.G., Chen, I.F., Smith, P.T.: A receptor-depended and A receptor independent effects of extracellular adenosine on murine thymocytes in condition of adenosine deaminase deficiency. Blood, 2000; 95: 3859-67.