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STUDY OF TUMOUR MARKERS AND HORMONE RECEPTORS IN CANCER BREAST

Thesis

Submitted for Partial Fulfilment of M. Sc.

Degree in General Surgery

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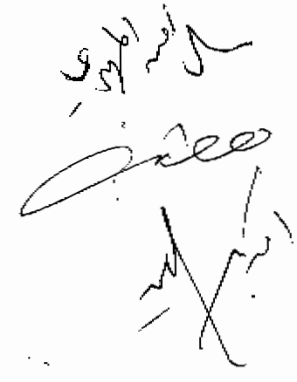
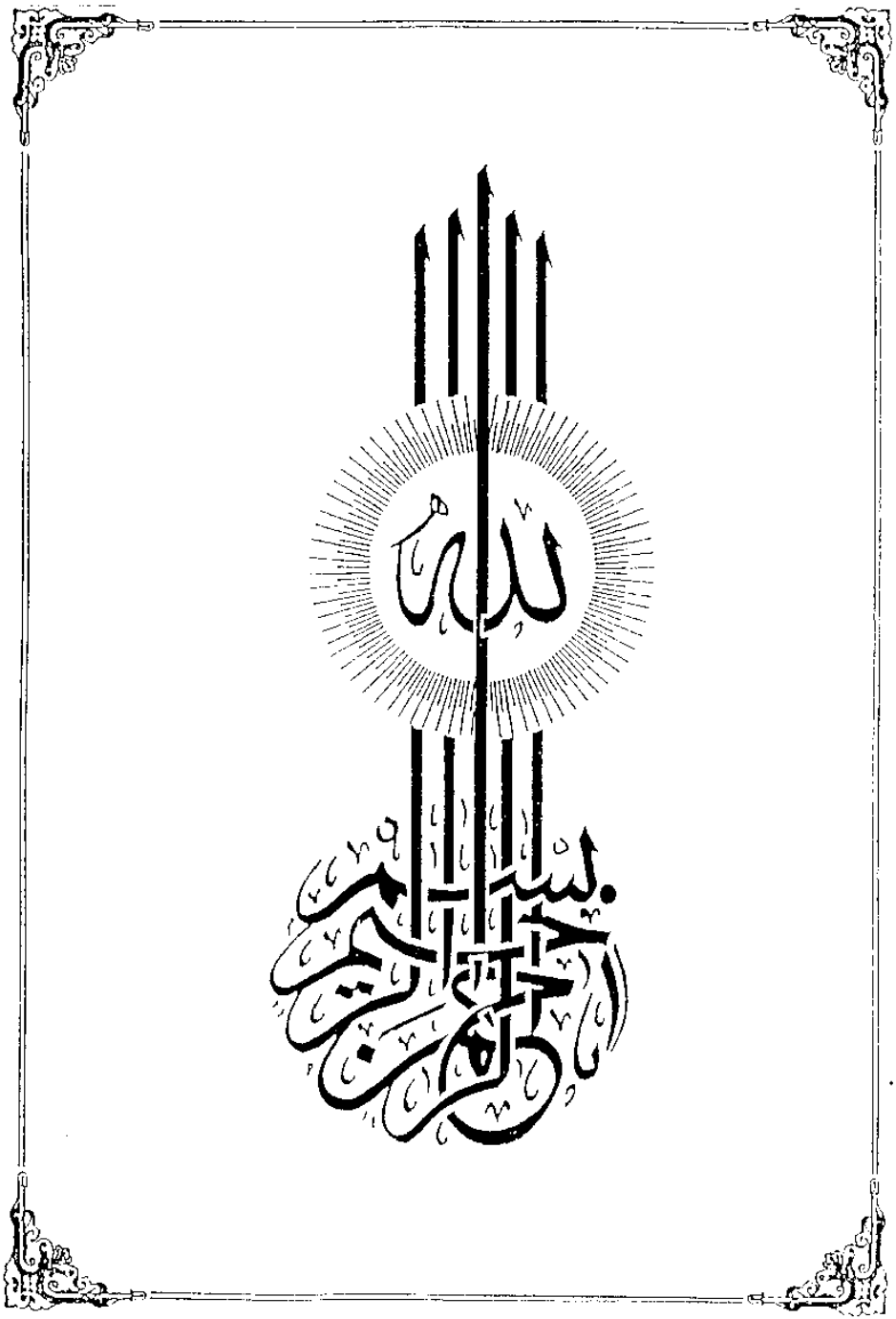
1987



ACKNOWLEDGEMENT

I find great pleasure in expressing may indebtedness and gratitude to ward Prof. Dr. Abu Bakr El Sadik mostafa Professor of Surgery,, Faculty of Medicine, Ain Shams University, for valuable guidance, continous advice and encouragement .



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INTRODUCTION

Many patients presenting with apparently localised breast cancer will already have wide spread occult metastases. If the treatment offered is to be curative rather than palliative,asensitive and reliable marker for cancer breast which will detect early spread is required. Biochemical changes in blood or urine may be associated with avariety of Neoplasia.

Those tumour index substance may be classified according to their properties or origins examples:

1. Tumour associated including avariety of factors produced by organs not involved by tumour.

   These may result from humoral factors released by the tumour, acting directly on alarger organ or via the pituitary or other endocrine organs example.

   Many enzymes and the acute phase proteins .

2. Tumour derived either from the neoplastic cell or from the supporting stroma examples.

   Adreno-cortico-trophic hormone, B-subunit human chorionic gonadotrophin , carcino embryonic antigen, alpha feto protein.

   Human breast carcinoma have been shown to produce a wide variety of substance both in vivo and in vitro.

The study of such products is of interest with regard to aspects of cell growth, differentiation and spread.

Here the value of their study is examined in respect of :

1. Investigating some of the systemic aspects of breast cancer.
2. Assessing the prognosis and monitoring of cancer breast.

In this research we will study some tumour markers of cancer breast, and hormone receptor as tumour markers and hormonal therapy of cancer breast.

TUMOUR MARKERS OF CANCER BREAST IN GENERAL

Some of examples of product released by human breast carcinoma :

1. Hormonal agent.

   Calcitonin- B subunit of human chorionic gonadotorophin-osteolysins .

2. Oncofetal antigens

   Carcino embryonic antigen and related materials - B-oncofetal antigen - Ferritin.

3. Enzymes

   Sialyl transferase - Galactosyl transferase- Lysozyme- placental alkalone phosphatase - alpha 1,4 Glucosidase.

4. Miscellaneous

   Epithelial membrane antigen (EMA) - Nucleasides - Milk proteins- polyamines - placental proteins - CA15-3.

The ideal marker would :

1. Be a substance not normally present in Blood or present in a very small amount .
2. Give auniformly positive test results in all patients.
3. Be present in a concentration proportional to the size or activity of its specific tumour.

However, most current tumour markers are neither highly sensitive nor tumour specific.

The clinical usefulness of some potential tumour makers has been evaluated by Cove et al.,(1979) in 69 patients with stage I and II breast cancer and 57 patients with stage III and IV.

Serum CEA concentrations were raised in 13% of patients with local and 65% of those with advanced breast cancer.

In patient with clinical evidance of progression or regression of tumour, serum CEA levels changed appropriately in 83% of cases.

Taking four of the markers (Carcino embryonic antigen, lactalbumin, alpha subunit and heptoglobin), serum concentrations of one or more were rised in 33% of patients with local disease and 81% of those with advanced breast cancer.

However, marker concentration were often only marginally raised and are unlikely to provide a sensitive guide to tumour burden CEA , lactalbumin and alpha subunit were detectable in 68% , 43% , and 40% respectively of extracts of primary breast cancers (Cove et al.,1979).
Assessment of tumour burden remains a major problem in the management of most patients with cancer.
For breast cancer a satisfactory tumours marker or system of

tumour markers would be of a major clinical importance at all stage of the disease and especially for early recognition of metastatic disease.

Although no single sensitive marker has so far been found for breast cancer, abnormalities of one or more tumour related substances have been reported in over 90% of patients with advanced disease (Coombs et al.,1977).

To develop amultiparametric system for monitoring breast cancer, it is necessary to demonstrate that the components of this system should reflect tumour burden and that abnormal levels are great enough and frequent to be of clinical benefit (Franchimont et al., 1976).

Cove et al.,(1979) study the evaluation of the clinical usefulness of some potential tumour markers, selected because of reported abnormal levels in breast cancer.

To define the relation ship to tumour burden, serum concentration of each potential marker were measured in patient with local disease before and after resection of primary disease, in patients with advanced disease and in a control population.

The proportion of tumour synthesizing the markers was defined by measuring the markers in extracts of primary breast tumour (Tormey et al.,1977) .

Assessment of all patients include full medical history and examination, chest X-ray, routine haematology and measurement of serum urea, electrolyte, alkaline phosphatase, 5 Nucleotidase , aspartate transaminase and gamma glutamyl transpeptidase level, Bony metastases were identified by radiology and followed by repeated X-rays . Brain scaning was performed when indicated on clinical grounds . The identification of markers within primary tumours is of clinical important for several reasons.

1. The screening of patients for metastatic disease either by serum measurements of markers or by radio-isotopic technique might be best limited to patients with marker positive primary tumours.

2. The presence of marker may be related to biological characteristic of clinical significance such as lactalbumin and hormonal responsiveness (Woods et al., 1977) , and prognostic significance of inappropriate production of pregnancy proteins by breast cancers (Horne et al.,1976).

3. The synthesis of tumour products by tumours grown in cell or tissue culture or transplanted into Nude (immunosuppressed) mice is important inresearch into tumour differentiation and proliferation, and may be of clinical value if such methods are used to test tumour sensitivity to therapeutic regimes.

Woods et al.(1979) examined milk proteins casein and Lact albumin as appropriate product in breast cancer . Perhaps because of the heterogeneity of casein, wide variation in abnormal level is found (Monaco et al.,1977) .

The markers of value in clinical management are usually present in serum in concentrations many times more than normal (Rosen et al.,1975).

Abnormalities of the Bio-chemical marker in patients with breast cancer. Cove et al., (1979).

Biochemical parameter	Range in normals and in those with benign disease.
1. CEA	< 0.1- 20 ug/I.
2. Ferritin	< 10 - 150 ug/l
3. Total alkaline phosphatase	0.25-9 I.U/I
4. Sialyl transferase	1300-3400 u/mg
5. Acid glycoprotein	0.35-0.88 g/I
6. P.A.G.	0- 140 g/L
7. Alpha antitrypsin	0.8-3.2 g/L .
8. C-reactive protein	< 10 mg/L .
9. Haemopexin	0.8-1.6 g/L
10. Haptoglobin	1.5-4.1 g/L
11. Caeruloplasmin	0.27-0.45 g/L
12. Lysozyme	5.8-9 g/L
13. Calcitonin	< 0.1 ug/L
14. BHCG	< 2 ugL
15. Placental alkaline phosphatase	0-0.85 I.n.I.
16. Alpha lact albumin	0-20 ug/L.

CARCINO EMBRYONIC ANTIGEN

[1] CARCINO EMBRYONIC ANTIGEN CEA

This is a complex glycoprotein molecule or more accurately a family of gluco proteins.

Synthesized by some tumour cells and also by normal colonic epithelium.

CEA is a large molecule approximately 2000000 daltons with numerous antigenic sites.

Its sedimentation rate is 7 S - 8 S.

- The carbohydrate : protein ratio is 6:1 to 1:1.
- The sialic acid content is markedly variable.
- N-acetyl glucosamine content is high, N-acetyl galactosamine trace .
- Normal plasma level 2.5 ng/ml.
- CEA is present chiefly on the wall of tumour cell and found in breast cancer and also other tumours particularily colon cancer.

It may also be shed in circulation and has been detected in the sera of patients with avariety of neoplastic as well as non neoplastic disease.

Thus in human, a high CEA levels above 2.5 ng/ml have been found in breast cancer and also in other tumours (Doyle et al., 1981).

It is present in non neoplastic disease such as emphysema, ulcerative colitis, pancreatitis and alcoholism and in serum of heavy smokers.

Significance of CEA estimation :

The national istitute of health (NIH) of America 1981 recommended that plasma CEA level should be measured in two situation pre-operatively in patients with breast carcinoma and the informations obtained be added to the data for clinical and pathological staging ; and post operatively to show whether atumour has been effectively removed where the value should return to normal within 6 weeks.

The serial CEA assay in patients whose tumours produce CEA elevations in blood can be avaluable monitor of the response and effectiveness of therapy.

A. The role of CEA as a tumour marker in breast cancer

The study of serial measurement of CEA in breast cancer has shown one clear role. The patients with advanced disease will have elevated levels at the time that therapy is started.

Present methods of assessing the response to therapy are entirely clinical and cannot therefore be evaluated until the patient has been treated for several months. Clearly an accurate biochemical monitor of the disease course can only improve patient management.