IMMUNOLOGICAL CHANGES IN BREAST CANCER PATIENTS

THESIS

Submitted for the Degree

of

Ph. D. PATHOLOGY

By

NAFISSA MOHAMED AMIN EL-BADAWY

M. B. ; B. Ch. M. Sc.

Supervisors

Prof. Dr. MOURAD A. SHERIF

Prof. Dr. SAMIR ABOU-ZEID

Assist. Prof. Dr. RASHA Y. KHALIL

Faculty of Medicine

Ain Shams University

1985

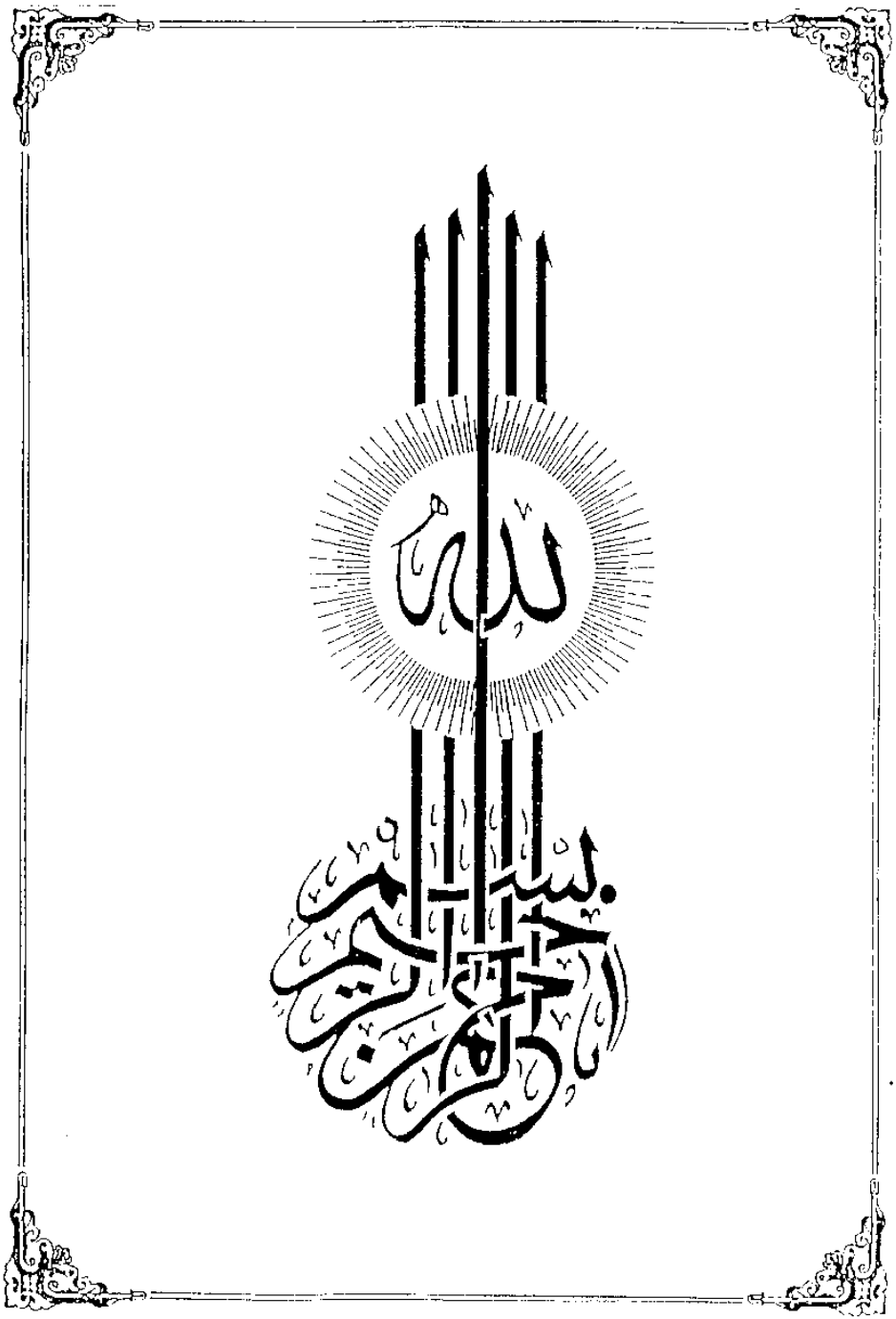
ACKNOWLEDGEMENT

I wish to express my deepest gratitude and indebtedness to **Prof. Dr. M.A. Sherif**, Head of the Pathology Department, Faculty of Medicine, Ain-Shams University, for his valuable supervision throughout the whole work. Without his vital concern and continuous encouragement this work would have never been completed.

My most sincere gratitude is also extended to **Prof. Dr. S. Abou-Zeid**, Prof. of Surgery, Faculty of Medicine, Ain Shams-University , for his great interest and valuable cooperation throughout the work.

I am also very grateful to **Dr. Rasha Y. Kalil** , Asst. Prof. of Bacteriology, Faculty of Medicine, Ain Shams University,for her keen supervision and unfailing advice. To her cooperation and valuable suggestions this work owes a lot.

Last but not least, I express my deepest gratitude to **Dr. Mohamed El-Shawarby**, Asst. Prof. of Pathology , Faculty of Medicine, Ain Shams University for his kind help and support throughout this work.



CONTENTS

INTRODUCTION

INTRODUCTION

The possibility that immunological defects are of aetilogic importance in breast cancer has been investigated by various workers and discussed widely. The presence of neoplasia has been shown to be accompanied by distinctive alterations in the T-cell immunity of the host, namely, occurence of cell - mediated immune reactions against tumour-assciated antigens on one hand and depression of cell-mediated immune function on the other. The latter finding has been confirmed by most investigators. However, although cell - mediated immunity is certainly impaired in many patients with advanced disease, it is uncertain whether this state is common in early breast cancer. The role of humoral immunty in the aetiology of the disease is even less clear.

The aim of the present work was to study the immunological status of breast cancer patients, including both its cellular and humoral aspects in an attempt to assess the significance of immunologic factors in the pathogenesis, diagnosis and prognosis of breast cancer. Both humoral and cellular aspects of the immune response were studied in breast cancer patients . Patients with benign breast lesions and normal adult

nongravid females were used as controls. The techniques employed in the study included quantitation of serum immunoglobulins and complement component (C_3), immunofluorescence study of tissue sections and sera by direct and indirect techniques, and the leucocyte migration - inhibition assay.

REVIEW OF LITERATURE

Anatomy of the Breast

In the male and immature female breast the mammary glands are similar. The nipple and areola are fully formed and the breast consists of a system of ducts embedded in connective tissue. The ducts do not extend beyond the margin of the areola (Snell, 1973).

At puberty the female breast enlarges and thereafter retains the female form throughout life. The female form is variable indeed, but the size of the base of the breast is fairly constant (Last , 1972). Its base extends vertically from the second to the sixth ribs, and at the level of the fourth costal cartilage it extends transversely from the side of the sternum to near the mid axillary line. The nipple usually lies at the level of the fourth intercostal space (Sinclair, 1961). The superolateral part of the breast is prolonged upwards and laterally towards the axilla , forming the axillary tail, which extends along the lower border of the pectoralis major and may pass through the deep fascia to lie in close relationship to the pectoral group of axillary nodes (Warwick , and Williams , 1973). The breast lies over the

pectoralis major and extends beyond the border of that muscle to lie on the serratus anterior and external oblique. The breast is, however, separated from these muscles by the deep fascia, and between the breast and deep fascia there is a zone of loose areolar tissue, the retromammary or submammary "space", which allows the breast some degree of movement on the deep fascia covering the pectoralis major. Advance of mammary carcinoma may, by invasion, fix the breast to the pectoralis major (Warwick and Williams 1973).

Blood Supply of The Breast :

This is derived from the lateral thoracic artery by branches that curl around the border of pectoralis major and by other branches that pierce the muscle. The internal mammary artery sends branches through the intercostal spaces beside the sternum, those of the second and third spaces are particularly large. Similar perforating branches arise from the intercostal arteries. Pectoral branches of the acromio-thoracic artery supply the upper part of the breast. Venous return simply follows the above mentioned arteries (Last , 1972).

Lymph Drainage :

The lymphatic drainage of the mammary gland is of considerable clinical importance because of the frequent development of cancer in the gland and the subsequent dissemination of the malignant cells along the lymph vessels to the lymph nodes.

The lymphatic capillaries of the breast form an anastomosing network, which is continuous across the midline with that of the abdominal wall. The efferent lymphatic vessels from this network accompany the arteries supplying the gland. The lateral part of the gland is drained into the anterior axillary or pectoral nodes. The medial part of the gland is drained into nodes lying along the internal thoracic artery. A few lymph vessels follow the posterior intercostal arteries and drain posteriorly into the posterior intercostal nodes. The axillary lymph nodes commonly receive more than 75 per cent of the lymph from the breast (Warwick and Williams, 1973).

The superficial lymphatic plexus beneath the areola (subareolar plexus), and the deep plexus in the fascia covering the pectoralis major(submammary plexus) are no longer regarded as especially important in the drainage of lymph from the mammary gland (Snell, 1973).

Embryology of the Breast

The first stage in the development of the mammary glands takes the form of a pair of ectodermal thickenings, the mammary ridges or lines, which extend on each side of the ventral body wall from the base of the forelimb bud to the region medial to the hind-limb bud (Hamilton and Mossman, 1972). The upper or anterior part of the mammary ridge shows a definite rounded mass of cells but the remainder is only recognizable as a slight thickening of the epidermal layer (Frazer, 1967). The caudal two-thirds of this ridge normally disappears before the end of the embryonic period. The thoracic part remains and very slowly increases in thickness, to form the mammary primordium, up to the third month, when it begins to extend into the underlying mesenchyme forming a solid epithelial mass. Later, in the fifth month this solid mass branches to give fifteen to twenty five downgrowths or sprouts (Snell, 1973). During the fourth month fat begins to form in the shape of minute granules deposited in the bodies of groups of cells in the subcutaneous region (Frazer, 1967). In the eighth or ninth month of intrauterine life the initial downgrowth and the sprouts become canalized. The secondary outgrowths become the lactiferous ducts and the tertiary sprouts from them form

the alveoli and small ducts of the gland. The original epithelial downgrowth now appears as an epidermal pit into which the lactiferous ducts open. At about full term or later a proliferation of the mesoderm underlying the pit causes its elevation above the surface of the adjacent skin to form the nipple (Hamilton and Mossman, 1972).

Histology of the Breast

The mammary gland is a specialized cutaneous gland located within the subcutaneous tissue. It is a modified sweat gland and has an apocrine type of sercetion (Leeson and Leeson,1968). Each mammary gland comprises fifteen to twenty five irregular lobes of the compound tubuloalveolar type whose function is to secrete milk during lactation (Junqueira and Carniero, 1980) . Each lobe is provided with an excretory duct 2 to 4.5 mm. in diameter and lined by stratified squamous epithelium. This is the lactiferous duct , which runs toward and opens on the nipple and has an irregular, angular form in cross section. Each duct under the areola has a local dilatation, the sinus lactiferous, it then becomes constricted again and, curving toward the surface of the skin, emerges at the summit of the nipple as an independent opening (Ham, 1974).

Each lobe is subdivided by layers of connective tissue into lobules in various orders. The interlobular connective tissue is of the dense type. The intralobular connective tissue is much more cellular than the interlobular tissue and contains fewer collagenous fibers and particularly no fat. The layer of loose connective tissue about the ducts undoubtedly has a functional significance in providing an easily distensible medium for the