

J. Egypt. Med. Assoc. 70 (1-4) 1987 : 161-174

CONNECTIVE MATRIX CHANGES IN BREAST CARCINOMA

A histochemical and genetic study

By

SOHEIR M. MAHFOUZ, MALAK FOUAD, WAFAA HASSAN,
ABDALLAH M. KHALIL and KAMAL A. EL GHAMRAWY

*From Pathology Department and MEMROCK, Faculty of Medicine
Cairo University, Egypt.*

ABSTRACT

Histochemical and microspectrophotometric studies were carried out on 44 postmastectomy biopsies, to detect the various types of mucopolysaccharides (MPS). A preponderance of acid MPS was observed in 95% of cases, concentrated mainly at the invasive border of the tumour, calling attention to the role of this material in tumour invasion as well as in nutrition, since 73% of tumours with diameters above 5 cms were associated with high MPS levels.

The Histocompatibility (HLA) tests carried out on 88 blood samples from Egyptian cancer breast patients, showed high risk antigens differing in frequency from the 100

control group and varying in nature from other racial groups. Not only were HLA-B5 and B13 associated with susceptibility to carcinoma, but they also appeared to be associated with high tissue levels of MPS as well as with the desmoplastic stromal reaction, incriminating a tumour-dependent, genetically controlled synthetic process.

Other matrix changes observed: elastosis in 52% of specimens, both within and away from the tumour in addition to fragmentation of the reticular fibers in 71 % of cases, especially the high grade neoplasms and patients presenting with a rapid clinical deterioration in the first three years of their disease.

INTRODUCTION

The year 1958 marks the discovery of the first histocompatibility (HLA) antigens by Dausset, who in later studies commented upon the importance of such antigens in providing a possible explanation for allograft rejection (Dausset et al., 1965).

It has been observed that the histocompatibility genes on their own or in linkage-disequilibrium with

a true disease susceptibility gene, may differ amongst different ethnic groups (Sucin-Foca et al., 1980). This work has thus concentrated on trying to find out if there is an HLA association in Egyptian (Middle Eastern Caucasoid) females with carcinoma of the breast and whether the tumour associated stromal reactions are likewise governed by a genetic factor.

MATERIAL and METHODS

The material submitted for the study of the genetic aspects of breast carcinoma by the microdroplet lymphocytotoxicity technique (Terasaki et al., 1978), was in the form of 88 heparinized blood samples taken from Egyptian females suffering from mammary carcinoma and 100 samples from healthy controls.

The peripheral blood of such patients were subjected to HLA typing for 33 HLA specificities 13 in locus A and 20 in locus B. The patients were typed during the period of their clinical follow up after surgery. In all cases the malignancy was confirmed histopathologically and the material gathered was accompanied by full clinical data.

As regards the material subjected to the histochemical and histopathologic evaluation this comprised 44 postmastectomy biopsy specimens and 6 control postmortem healthy breast tissue.

Lymphocytic separation

The method employed was that described by Boyum, (1976), and the separated lymphocytes were then subjected to the microdroplet lymphocytotoxicity technique (Terasaki et al., 1978) to determine the various HLA specificities.

Statistical analysis

The statistical methods adopted in this work included :

1. Chi-square test (Robson and Keele, 1950).

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2. Probability factor, p , which determines whether the results of the Chi-square test are statistically significant or not.

3. Relative risk RR which indicates how many times more frequent the disease is in individuals having the antigen (Woolf, 1955).

Histopathological and histochemical stains used were :

1. Haematoxylin and eosin.
2. Periodic acid Schiff (PAS) : for the study of the fibrillary ground substance elements of the stroma.
3. Toluidine blue : for the demonstration of acid sulphated MPS.
4. Alcian blue for all acid MPS.
5. Hyaluronidase digestion for

hyaluronic acid. Bovine testicular Sigma I.

6. Verhoeff Van Geison to demonstrate collagen and elastic fibers.

7. Gordon and Sweets method for staining of reticular fibers.

Microspectrophotometry

A Zeiss microscope has been used for the purpose of a quantitative measurement of the stromal MPS, by measuring the absorption capacity of light through calcian blue stained acid MPS.

The transmission of the substance was measured by the application of the Beer Lambert law $E = 1/\delta$ where δ is the measured transmission. (Zeiss microscope operating manual Mpmoik microscope photometer).

RESULTS

Genetic Results

Genetic susceptibility to cancer

In the group of 88 cancer breast patients that were tissue typed and compared to 100 healthy controls, there was an increased frequency of antigen HLA-B5, $P < 0.05$ RR 2 and a decreased frequency of HLA-B15, $P < 0.02$, RR 0.21 and B35, $P < 0.05$, RR 0.49 (table 2).

Genetic association of certain HLA antigens and the stromal reaction in 44 breast carcinoma cases :

*HLA antigens and increased ground substance :

An increase in the amount of ground substance material above levels found in the control group was estimated roughly by micro-

spectrophotometry. The normal amounts of ground substance allowed a 75-90% light transmission, where as in cases of increase in the amount of ground substance, less than 75% light transmission values were obtained.

A significant genetic association was observed between increased amounts of ground substance in 19 cases and increased frequency of certain HLA antigens, B5, $P < 0.001$, RR 2.9 and B13, $P < 0.05$, RR 1.17. No association was found between decreased amounts of ground substance material (9 cases) and HLA frequencies.

*HLA antigens and the fibrous tissue reaction in tumour and tumour bed:

The 16 cases showing stromal desmoplasia (productive stromal fibrosis), were strongly associated with higher frequencies of HLA-B5, $P < 0.05$, RR 3 and B13, $P < 0.02$.

*HLA antigens and stromal elastosis:

No significant association could be observed as regards a genetic association of certain HLA antigens with the stage grade and course in breast cancer patients.

In 23 patients presenting with stage I and II there was an associat-

ed increased frequency of HLA-B17, $P < 0.05$, RR 4, and an absence of B12, $P < 0.05$, RR 0. In stages III and IV no associations could be discerned.

A stationary course for more than 5 years was found in association with 13 out of 81 patients having increased frequencies of HLA-A10 antigen, $P < 0.05$, RR 3.59.

Since in situ and grade I tumours formed a statistically insignificant group, only grades II and III antigen frequencies were determined. In this group an elevation in HLA-B5 was noted $P < 0.05$, RR 2.76.

Histopathologic and histochemical Results

1. Ground Substance

Normal breast showed little amounts of acid non sulphated MPS (ANSMPS) with a light transmission of 80-90% and a major component was hyaluronic acid.

In breast carcinoma 95% of the cases (42/44) showed increased AMPS levels both sulphated and non sulphated. 41 cases showed increased ground substance levels in the tumour and 42 in the tumour bed. ASMPS were present in 19 cases whilst ANSMPS were in 32 cases (table 1).

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Table (1) : Distribution of AMPS in normal and Malignant breast tissues

| Normal breast n = 6 | | ASMPS | ANSMPS |
|----------------------------|-----------------------------------|-------|--------|
| Breast carcinoma n = 44 | MPS normal/ decreased n = 2 | | 2 |
| | MPS increased n = 42 | 19 | 32 |

MPS : Mucopolysaccharides ; ASMPS : Acid sulphated mucopolysaccharides.

ANSMPS : Acid non-sulphated mucopolysaccharides.

Inside the tumour the ASMPS were present in 43% of cases whereas the ANSMPS were in 58% ; in the latter the connective tissue ANSMPS were increased in all cases, whilst epithelial AMPS were increased in 70% (Fig. 1, 2).

In the tumour bed on the other hand 29% of cases only showed high levels of ASMPS, whilst the ANSMPS were increased in 76% of cases showing the same values for connective tissue and epithelial components.

In the nearby normal breast the ground substance was increased in 42 % of cases, 43 % in mammary

dysplasias and 66% in inflammatory states.



Figure 1 : Increased AMPS in the stroma of an invasive duct carcinoma particularly in the region of the tumour bed (Alcian blue X 100).

2. Stromal Fibers

Elastosis

Elastosis was evident in 57 % of breast cancer cases and in 30 % of the nearby healthy tissue. No observable association with the clinical outcome, stage or grade of tumour could be found (Fig. 3).

Reticular fibers

In normal breast tissue reticular fibers formed a fine sub-epidermal network of brown black fibers with Gordon and Sweet silver stain, periductal distribution was another common feature.

In breast carcinoma, the areas exhibiting hyalinized tissue was devoid of reticular fibers, whereas 83% of the carcinoma stroma showed fragmentation of these fibers (Fig. 4). Aggressive grade II and III tumours also showed this phenomenon in 72% of cases compared to 41% in grade I and in situ neoplasms and rapidly deteriorating cases. (table 3) Fibrous tissue.

The majority of breast tissue was made up of the loose mature (LM) type, the loose reticular variety was present only within the lobules. Apart from the red colour obtained with the Verhoeff van Geison stain, collagen due to its glycoprotein composition also gave PAS positive reactions of moderate

intensity. Depolymerization was observed in 4 of the cancer breast cases in the form of faint PAS staining.



Figure 2 : Metachromatic sulphated AMPS in the stroma of an invasive duct carcinoma (Toluidine blue X 200).



Figure 3 : Periductal and stromal elastosis (Verhoeff Van Geison X 200).

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In breast carcinoma all 4 types of fibrous tissue reactions (loose reticular (LR), loose mature (LM), dense mature (DM) and dens sclerotic (DS) were observed in both tumour and tumour bed, displaying no association with survival, by Chi square test.



Figure 4 : Fragmented reticular fibers in the stroma of an invasive duct carcinoma (Gordon and Sweets X 400).

3. Abnormal stromal deposits

4 out of 95 cases of breast carcinoma contained identifiable calcification in their stroma by routine haematoxylin and eosin.

Table (2) : Frequency of HLA antigens associated with breast carcinoma

| HLA Locus | Frequency of the antigens (%) n = 88 | Control n = 100 | P | RR |
|-------------|---|--------------------|------|------|
| HLA-B Locus | | | | |
| B 5 | 32.9 | 20 | 0.05 | 2.00 |
| B15 | 3.4 | 14 | 0.02 | 0.21 |
| B35 | 11.3 | 23 | 0.05 | 0.49 |

Table (3) Genetic and histochemical factors affecting prognosis

| Factors | Good outcome | bad outcome |
|------------------|--------------------------|--|
| HLA | A 10, B 17 absent B12 | B5, B13 |
| Ground subt. | — | Increased levels of MPS above normal tissue content of area associated with large size tumours |
| elastosis | — | Fragmented |
| reticular fibers | — | — |
| Desmoplasia | — | — |

DISCUSSION

88 Egyptian cancer breast patients were tested for antigen frequencies and compared to 100 controls. A high frequency of HLA-B5, $P < 0.02$, RR 0.02 and B35, $P < 0.05$, RR 0.49 were observed (table 2).

In a similar study carried out on Americans an HLA-A1 frequency was found to be high (Takasaki et al., 1973), compared to our lower levels than normal of this antigen. Patel et al., (1972) found that HLA-A7 was higher than in the control group. In other studies working also on Caucasians with breast cancer no significant associations with the HLA system were observed (Cordon and James, 1973 ; Oh and Maclean 1975 and Dejong Bakker et al., 1974).

In general 15 % of all breast carcinomas were found to be familial, having a genetic element (Lynch, 1981). That is why family studies are constantly being stressed by researchers (Albano et al., 1981).

In the 23 patients with clinical stage I and II tumours, high levels of HLA-B17 $P < 0.05$ RR 4 were observed, where as those patients with stage III and IV showed no genetic association with the HLA system.

Histological grades were also studied as regards to antigen patterns, these gave information as regard the high grade tumours in the form of high antigen frequencies of HLA-B5 $P < 0.05$ RR 2.76. The B5 antigen in Caucasians was found to correlate with a poor survival in Hodgkins disease yet with better survival in epithelial neoplasia, as in lung carcinoma (Osoha and Falk, 1978 and Weiss et al., 1980). Whether such findings may be of relevance to us is doubtful as racial differences exist in the set of patients studied, also the survival rate that was considered, was only 1 year in duration.

In the work carried out by Ryder and Svejgaard (1976), no association between the HLA system and survival were observed, yet in a study carried out on 185 breast cancer cases of Caucasoid origin, surviving disease free for more than 16 months, a high frequency of HLA-B8 twice the frequency of those who died (Falk and Osoha, 1977).

In this series HLA antigen frequencies in patients surviving disease-free for five years or more, showed high levels of HLA-A10 $P < 0.05$, RR 3.5. Those deteriorating rapidly or dying in the first 5 years

showed no association with the HLA system.

The increase in MPS material as judged by the microspectrophotometric method of quantitative evaluation was carried out on 44 breast carcinoma specimens, 95% of cases showed more MPS in the ground substance than the control group. In these cases with high MPS the HLA antigen patterns were determined. These patterns were sought after because of a suggestion made by Cameron (1969), whereby he claimed that there was probably some underlying genetic factor responsible for MPS synthesis in malignancy. Our results were quite encouraging with respect to this statement and high frequency of HLA-B5 and B13 were found.

The role of the MPS material in growth and spread of tumours has been shown in the present work in the association of large sized tumours with increased MPS levels, this property has been demonstrated by (Liotta et al., 1982 and Fridman et al., 1985). It appears that the synthetic properties responsible for this increase is due to both stromal and tumoral cells (Toole et al., 1979 and Iozzo, 1984).

The fact that the few tumours possessing B5 or B13 yet showing no increase in their stromal MPS

levels, may be explained by the fact that in such cases some form of protective or suppressive gene probably exists linked to the HLA system, which is able to check MPS synthesis by tumour or stromal cells. Another factor, may be the occurrence of incomplete penetrance on such cases, whereby the trait of increased synthesis is not expressed in a certain generation even when the gene is considered dominant (skipping of generations) (Mat Sunaga, 1978).

From the results of Ishimoto, et al., (1966), a postulate has been put forward stating that hyaluronic acid synthesis is important for tumour invasion, as well as releasing the cell from contact inhibition and controlling tumour cell interactions with the surrounding environment.

Increased MPS levels in carcinoma have been shown to exist irrespective of the histological type of the tumour and the patient's age (Ozzello and Speer, 1958), a finding in agreement with the present findings. Other constituents have also been incriminated such as increase in sulphated MPS and fibronectin (Friedman et al., 1984).

HLA-B5 and B13 ($P < 0.05$ and 0.02) were increased in breast tumours showing stroma desmoplasia, this was observed in 66% of cases studied.

Koury, et al., (1981) believe that although breast cancer susceptibility has not yet been proven to be genetically controlled, yet the host response most probably is, particularly susceptibility to desmoplasia (Duran-Reynals, 1942).

Genetic association with abnormal elastic tissue stromal accumulations, have not been looked for by investigators, this feature has been studied in this work, yet no genetic element can be incriminated at present.

The ground substance present in normal breast connective tissue is of the AMPS type, especially hyaluronic acid. In general the amount of this material is low even in loose types of stroma, where water appears to be the major element (Ihnen and Perz-Tamayo, 1953). The interlobular stroma on the other hand contains very little amounts of neutral MPS (Ozzello and Speer (1958).

In malignancy the ground substance is greatly increased especially in the tumour bed region in tumours with productive fibrosis and metastasizing ones (Bottigliani and Priodi, 1957, Cameron, 1966 and Iozzo et al., 1982). In the present series this feature was observed in 95% of cases examined, as well as in 42% of the nearby uninvolved tissues displaying inflammation or mammary dysplasia.

All grades of breast cancer displayed increased levels of stromal MPS and no statistical relationship was found to exist between survival rates and the increase in this material a finding in common with (Machinami, 1976). This indicates that the rise in ground substance MPS could act as possible indicators of a malignant process, this is not a decisive factor since some benign conditions have displayed this phenomenon (Spicer et al., 1962), but it is the demonstration of ASMPS which appears to be important, since this material was hardly detectable by the methods employed in other conditions.

Elastosis has been described mainly in association with mammary malignancy (Erlandson and Carstens, 1972). It has been reported as being non grade but age related, increasing postmenopausal in malignancy (Machinami, 1976 and Masters et al., 1978). The distribution of this material appears to be around ducts vessels and scattered in the stroma (Fig. 3), Ghosh et al., (1980) also demonstrated elastic fibers intracytoplasmically by the electron microscope.

Elastosis can therefore be considered as a good index for the presence of malignancy, whereby early invasion could thus be suspected (Azzopardi and Laurini, 1974). Yet the prognostic significance is not

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yet clear (Ghosh et al., 1980 and Glaubitz et al., 1984).

83% of cases showed fragmented stromal reticular fibers, 82% of these patients showed rapid clinical deterioration in the first 3 years of the disease, similarly grades II and III aggressive tumours showed fragmentation in 72% of cases meaning that the more aggressive the tumour the greater the likelihood of demonstrating fragmented reticular fibers in the stroma of both tumour and tumour bed. The observation of fragmentation of these elements was observed by Cameron (1966) in cases of aggressive invasive neoplasms (table 3).

As the tissue content of the denser varieties of collagen increases the outcome of the disease has been observed to be more favourable, since this retards invasion and prevents the cells from reaching the vascular channels (Schurch et al., 1981). The statistical analysis of the present results have been inconclusive as regards the type of tissue

and the clinical course. Nearly half the cases with DM stromal collagen (type I) were found to deteriorate. Hamlin (1968) also observed that a correlation existed between dense collagen in mammary carcinoma and high mortality rates.

The present work has definitely shown distinctive disease associated antigenic differences which are racially dependent, thus pointing out the importance of studying other disorders in our Egyptian patients and not totally relying on international studies on disease related genetic associations.

What one can also assume from this work is that such genetic associations with the histological and histochemical changes accompanying malignancy are of importance in directing the physician's attention to the biologic and behavioral outcome of breast carcinoma, thus giving an idea about the prognosis as well as guiding the therapist in his choice of the most suitable treatment policy for each individual case.

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دراسة هيستوباثولوجية ووراثية لتغيرات السداة فى سرطان الثدي

سهير محمود محفوظ ، ملك فؤاد ، وفاء حسن ، عبد الله خليل ، كمال الغمراوى
(من كلية الطب - جامعة القاهرة)

يقوم البحث على دراسة العوامل الهيستوباثولوجية والهيستوكيميائية الموجودة بأورام الصدر للتعرف على العلاقة بينها وبين نسبة وجود أنواع من المولد المضاد للملائمة النسيج . كما تهدف الدراسة الى التعرف على بعض الحقائق التى تؤثر على طبيعة نمو وانتشار الخلايا السرطانية ، وما قد ينعكس على ذلك من نتائج .
أجريت الدراسة على ٨٨ عينة من الدم و ٤٤ من النسيج السرطانى بالإضافة الى ١٠٠ عينة دم كمجموعة مقارنة .

وقد أوضحت هذه الدراسة ارتفاع نسبة بعض المولدات المضادة للملائمة للنسيج فى حالات سرطان الثدي أكثر من نسبتهم فى المجموعة المقارنة ومن ثم يمكن الإشارة الى وجود علاقة وراثية بين مولد المضاد للملائمة النسيج والتغير السرطانى ولكن هذا لا يكفى بمفرده أن يفسر الميل الى حدوث الكرسينوما ويمكن اعتبار ذلك بمثابة نذير لاحتمال حدوث سرطان الثدي .

أما بالنسبة لمرضى الكرسينوما فإن تحديد أنواع هذه المولدات المضادة للملائمة النسيج سيسهم فى التعرف على الطريقة التى ستجوها هذه الخلايا فى انتشارها وتأثير ذلك على فرص الشفاء . من ثم يسهم كل ذلك فى المعاونة على اختيار أنسب طرق المعالجة والتكهن باحتمالات نتائج العلاج فى هذه الأورام .

وقد أظهرت هذه الدراسة دور المركبات السكرية فى نمو انتشار وتليف النسيج المسجرات فى حالات سرطان الثدي ، وعلاقتها ببعض المواد المضادة للملائمة للنسيج .

كما أظهرت الدراسة تغيرات أخرى فى السداة مثل : كثرة النسيج المرن ، وتفتت النسيج الشبكي وتأثيرهما على نسبة الشفاء فى هذه الحالات . (٨٧/٢٣)