Fibrocystic condition and «at risk» lesions in asymptomatic breasts: a morphologic study of postmenopausal women

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Summary: A series of postmenopausal women who had died without noticing any clinical breast disease in their anamnesis (100 cases, age range 46-90 years, average age 62 years) were submitted to bilateral subcutaneous mastectomy during autopsy in order to evaluate the morphologic profile of asymptomatic mammary glands, at different ages. Submacroscopic changes were found and removed to be processed for histology. Results were as follows: a) 46% of cases did not show any change; b) 54% of cases showed benign changes, namely a fibrocystic condition; c) 14% of cases had in addition epithelial lobular hyperplasia with low grade atypia and d) 3% of cases showed atypical borderline lobules (ABL), i.e., terminal ductal-lobular units characterized by severe epithelial atypia.

Such lesions cannot be easily distinguished from "in situ" carcinoma, and are currently considered at morphologic risk for subsequent cancer when found in breast biopsies. Our data show that: 1) ABL do not represent a common finding in women who never complained of breast pathology during life; 2) ABL are not related to older age; 3) Fibrocystic condition is quite frequent at subclinical levels also in asymptomatic aging women. The latter statement confirms the opinion that fibrocystic condition should be considered as a common "functional" change.

On the contrary, the rarity of ABL gives us a further indirect evidence of their possible precancerous significance. The risk of subsequent development of cancer from the collateral mammary gland could be theoretically higher when ABL are found in breast biopsies of fertile and premenopausal women, who have a longer period of life expectation.

INTRODUCTION

Many observations on cancerous breasts suggest that clinical cancer is a systemic disease arising from a peculiar microenvironment in which atypical borderline lobules (ABL) and multiple microcarcinomas are frequent in the mammary grandular tree collateral to the main tumor ([1-8]). The morphologic analysis of clinically "normal" breasts contributes to understanding that the background here is substantially different ([9]).

The present study has been undertaken to analyse the morphologic profile of two hundred whole mammary glands removed from autopsied women with negative anamnesis for breast disease, in order to search for preneoplastic subclinical lesions in postmenopausal age and in the elderly.

The aim of this work is to further confirm that ABL and microcarcinomas are unusual lesions in non-cancerous

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breasts, even in aging women. This could be a further indirect confirmation that ABL and microcarcinomas should be considered atrisk lesions with a predictive significance of possible development of a clinical cancer in the collateral and contralateral mammary gland, when diagnosed in benign breast biopsies.

MATERIALS AND METHODS

One hundred postmenopausal women who had died without noticing any clinical breast pathology in their anamnesis were submitted to bilateral subcutaneous mastectomy in the course of a series of consecutive autopsies. A part of the present material (42 cases) had been previously considered for other purposes [9]. The entire mammary glandular tree of both breasts of each woman (two hundred breasts) was analysed by subgross scrutiny under a dissecting microscope. The method [10] allowed the three dimensional view of the whole glandular tree in serial thin slices (2 mm thickness). In order to limit the deliterious effect of postmortal changes, each breast was cut as soon as possible in four-five thick slices, then fixed in 10% formalin and finally kept in a refrigerator (−10 °C). Two-three days after, breast specimens were cut in serial slices (2-3 mm) and processed for the subsequent passages. Eight random sections representative of all quadrants were defatted in acetone, hydrated, stained in 50% Harris' haematoxylin, dehydrated, cleared, stored in cedar oil and finally observed under a dissecting microscope equipped for microphotography. The more interesting morphologic changes were removed and then processed for routine histology.

The terminology used here for the elementary lesions was widely detailed by Wellings, Jensen & Marcum [11].

RESULTS

The age range of one hundred women examined at autopsy was 46-90 years, the average age being 62 years. Distribution by age decades was as follows: 5th) 6; 6th) 14; 7th) 32; 8th) 33; 9th) 15. The causes of the patients' death were: a) cardiovascular disease (48); b) malignant neoplasm (27); c) infections (20); d) respiratory disease (5). Gynecological anamnesis was positive for malignant neoplasms in two cases (both were endometrial carcinomas). Moreover, the following lesions were observed at gynecological level during the autopsies: 1) endometrial polyps, 3 cases; 2) cervical polyps, 4 cases; 3) leiomyomas, 2 cases.

Table 1. – *Frequency of pathologic changes in 200 clinically asymptomatic breasts of 100 postmenopausal autopsied women.*

Pathologic changes	Cases (%)
Hyperplastic changes	
Persistent lobules	19
Large lobules	4
Duct hyperplasia	1
Adenosis	6
Sclerosing adenosis	16
Cystic changes	
Cystic ducts	12
Cystic lobules	11
Spheric cysts	9
Metaplastic changes	
Apocrine lobules	33
Apocrine cysts	13
Regressive changes	
Sclerotic lobules	27
Benign tumors	
Fibroadenomas	12
Intraduct papillomas	6
Atypical changes	
Mild/moderate lobular epithelial atypia	14
High grade lobular epithelial atypia (ABL)	3

First of all it is interesting to notice that there were no substantial differences regarding the morphologic profile between right and left breasts of the same woman. Therefore, both beasts can be considered as a single case. The majority of breasts (94%) showed an atrophic background (Fig. 1, i.e., without lobules or with atrophic lobules, as was to be expected according to age (average age, 72 years). Diffuse lobulo-alveolar differentiation (Fig. 2), similar to the physiologic adenosis of younger women with menstrual cycles,

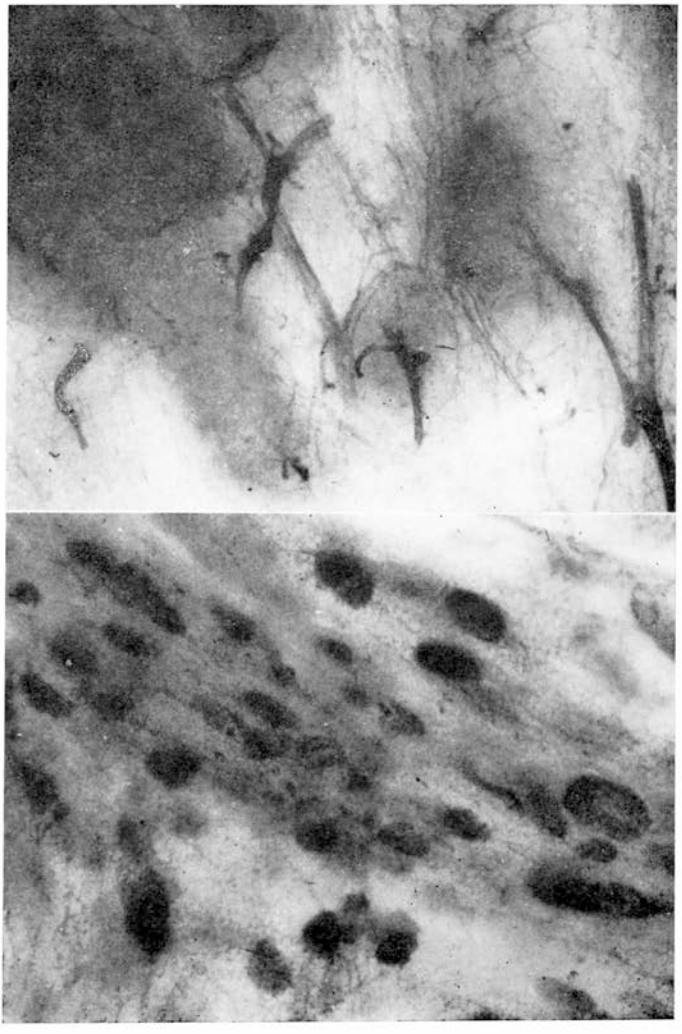

Fig. 1. — Submacroscopic view of an atrophic mammary glandular tree. Harris' haematoxylin, × 10.

Fig. 2. — Submacroscopic view of an adenosic mammary glandular tree. Harris' haematoxylin, × 15.

was present in 6 women (average age, 51 years). Only 46% of the breasts showed no change and they were atrophic. The remaining atrophic breasts (48%) and all the adenotic breasts (6%) showed different types of changes (Table 1) variously associated and with the following relative frequencies: lobular apocrine metaplasia (33%), sclerotic lobules (27%), persistent lobules (morphologically normal) in atrophic breasts (19%), sclerosing adenosis (16%), atypical lobules (14%), apocrine cysts (13%), fibroadenomas (12%), cystic ducts (12%), cystic lobules (11%), duct epitheliosis (11%), spheric cysts (9%), adenosis (6%), intra-

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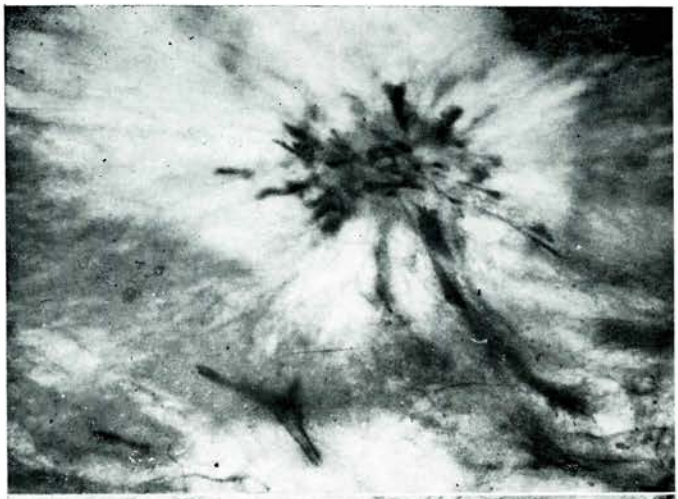

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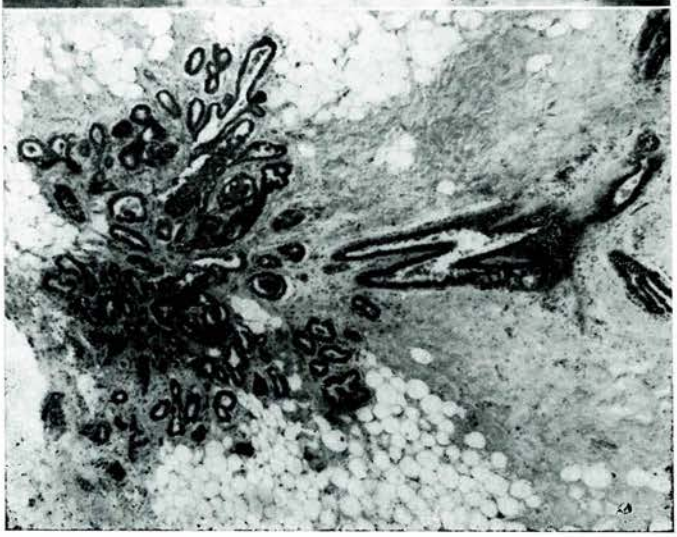

Fig. 3. — Submacroscopic view of a subclinical focus of sclerosing adenosis. Harris' haematoxylin, × 20.

Fig. 4. — Histologic view of the sclerosing adenosis in fig. 3. Haematoxylin-eosin, × 40.

duct papillomas (6%), large lobules (4%). Atypical lobules, when present, showed mainly a mild or moderate degree of atypia (11 cases). A severe grade of epithelial lobular atypia was only found in three cases, which were considered as borderline lesions with an uncertain significance. True occult foci of "in situ" cancer and microcarcinomas were never detected.

In summary, 46% of autoptic cases did not show any change, 54% of cases showed benign changes (Figs. 3-6) and 14% of cases showed atypical lobules (Figs. 7-10), rarely with a borderline appearance (3% of total cases).

Fig. 5. — Submacroscopic view of an intraductal papilloma. Harris' haematoxylin, × 20.
Fig. 6. — Histologic view of the papilloma in fig. 5. Haematoxylin-eosin, × 40.

DISCUSSION

The submacroscopic-histologic analysis of random sections of the entire mammary glandular tree of two hundred autoptic breasts shows that morphologic changes of different types are common findings in postmenopausal women without positive anamnesis for breast disease. Indeed only 46% of cases actually showed no change, while 54% displayed subclinical elementary lesions, variously associated to compose the different morphologic pictures of the so-called "fibrocystic disease". In recent years, the term "fibrocystic disease" has been considered no longer acceptable because of lack of speci-

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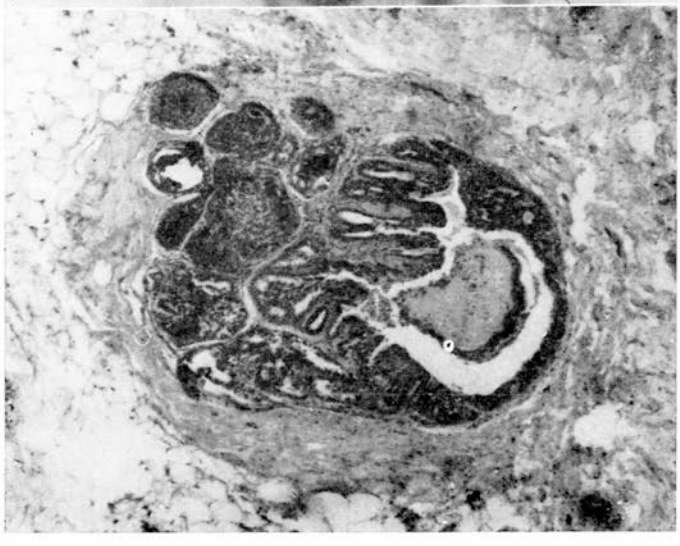

Fig. 7. — Submacroscopic view of an atypical lobule. Harris' haematoxylin, × 40.
Fig. 8. — Histologic view of the atypical lobule in fig. 7, characterized by a severe epithelial atypia (ABL). Haematoxylin-eosin, × 80.

ficity, in particular with regard to the relative risk of breast cancer development ([12]). The terms "fibrocystic changes" or "fibrocystic condition" have been introduced so as to emphasize that it is not necessarily a pathologic status. Our results confirm this point of view, as the morphologic findings related to the fibrocystic complex are often present also in clinically asymptomatic breasts. Recent follow-up studies of patients submitted to curative biopsy for benign breast disease suggest that some of the lesions associated with the fibrocystic condition are not completely innocent. Consequently, the component parts of the fibrocystic complex

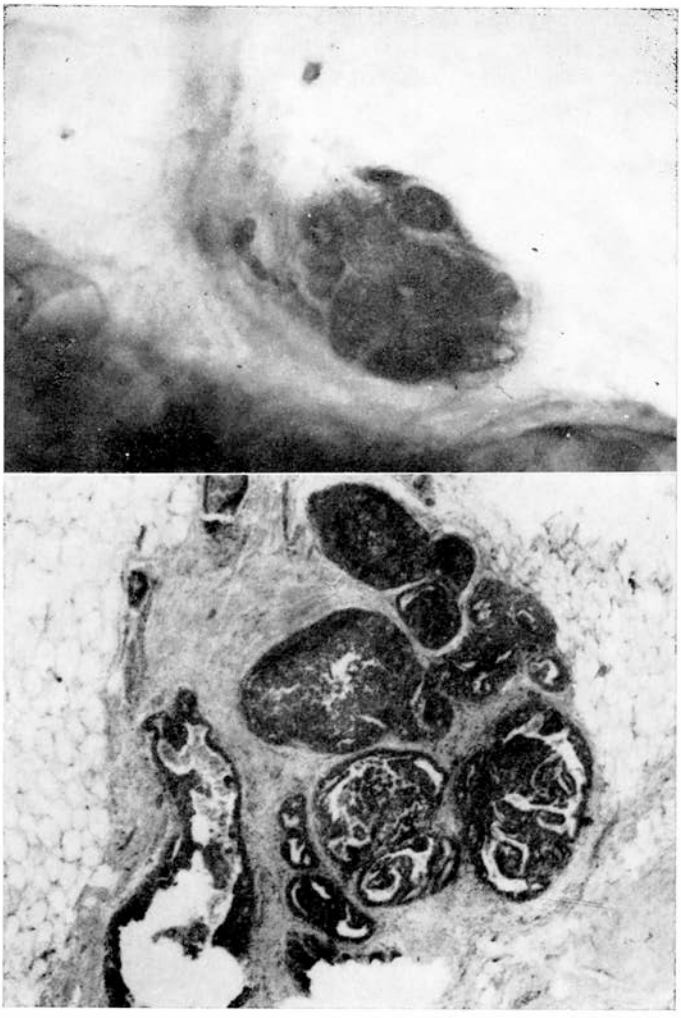

Fig. 9. — Submacroscopic view of an atypical lobule. Harris' haematoxylin, × 20.
Fig. 10. — Histologic view of the atypical lobule (ABL) in fig. 9. Haematoxylin-eosin, × 40.

have to be clearly specified in bioptic material, in order to inform in each case about the risk of breast cancer development ([12]). Retrospective studies of preinvasive carcinomas treated only by biopsy revealed subsequent carcinoma in 30-40% of patients, the frequency of subsequent cancer being nine times higher than expected ([13]).

Borderline lesions, namely atypical epithelial hyperplasia with some features of "in situ" carcinoma but insufficient to perform an unequivocal diagnosis ([12]), reveal a moderately increased risk (5 times) for breast cancer. Mild-moderate atypical hyperplasia is probably associated with a lower risk, but the entity of such risk has not yet been well established. Fi-

nally, moderate or florid typical hyperplasia (more than four in depth epithelial cells) and intraduct papillomas slightly increase (1.5-2 times) the risk for developing cancer. All other benign elementary changes are not predictive of cancer ([12, 14]). In our material, we never discovered "in situ" carcinomas or invasive microcarcinomas. Furthermore, only 3 women showed atypical lobules characterized by severe atypia (ABL) similar to those which are considered at moderately increased risk for cancer when found in breast biopsies. These data suggest that ABL are not usual changes related to the elderly and can also explain the origin of breast cancer from completely asymptomatic and atrophic mammary glands. Moreover, the rarity of ABL indirectly confirms their predictive value especially when they are present in women with many years of life expectancy. However, there is no agreement in the literature as to the frequency of preneoplastic lesions and microcarcinomas in autoptic material. This may derive from different 1) methods of study, 2) criteria of women selection and 3) terminology. Rush and Kramer ([15]) discovered 3 foci of "in situ" carcinomas and 1 small focus of infiltrating carcinoma in both breasts of 2 women older than 70 from their autoptic series (10% of cases). Nielsen *et al.*, 1984 ([16]) found 7 cases of infiltrating breast cancer and 14 cases of "in situ" carcinomas among 83 autopsied women (age range 22-89 years; average age 67 years). Six cases of invasive breast cancer were established by biopsy during the lifetime of the patients in question. The Authors observed that the frequency of "in situ" carcinomas in their study was higher than the values found in common surgical materials and concluded that this discrepancy was caused by the greater accuracy of their histologic investigation. Nielsen *et al.*, 1987 ([17]) found malignancy in 22 women (20% of cases) in the course of 110 medicolegal autopsies (age range 20-54 years). Only 1 woman was known to have had clinical invasive breast cancer. At autopsy, 2 women had invasive carcinomas and 20 had "in situ" carcinomas. The Authors noticed that malignancy was significantly more frequent among women older than 40, with late age at first full term pregnancy, with alcohol abuse and with steatosis and cirrhosis of the liver. They concluded that clinically occult "in situ" breast cancer is frequent in young and middle-aged women, and they did not suspect any selection of high risk women in their study, except for a hypothetic alcohol-induced increases in the frequency of cases of breast malignancy. Alpers and Wellings ([18]) found primary foci of cancer in 5.9% of 185 breasts from random autopsies, examined by a submacroscopic-histologic method. They found additional primary foci of cancer in 52.5% of 63 cancer-containing breasts and in 47.7% of 44 breasts controlateral to cancer containing breasts.

Such data were obtained by the same method of observation used in the present study and were similar to our results. Bartow *et al.* ([19]) only found 2 cases with "in situ" breast carcinomas in a forensic autopsy series of 519 women older than 14 years.

Finally, we found no correlation between the presence of "at risk" lesions and gynecological pathology. As a matter of fact, women with benign pathologic changes at gynecological level did not shof any proliferative atypical breast lesions. Two women with endometrial carcinoma (53 and 76 years, respectively) had no atypical lesions in their mammary glandular tree, which was completely atrophic. The bilaterality of preneoplastic lesions and early cancers, demonstrated in clinical breast cancer, suggest a systemic endocrine operating factor. However, we found no suspicious endocrine changes in the pituitaries,

adrenal or ovaries. Other Authors have reported similar observations ([14]).

In summary, our results indirectly agree with follow-up studies: 1) fibrocystic complex is frequently present at subclinical levels in asymptomatic women and therefore it could be considered a physiopathological status rather than a true disease; 2) ABL are rarely found in postmenopausal and aging women. It is likely that ABL are not innocent changes related to the elderly but have a precancerous significance, especially in the young and premenopausal female population.

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