Proliferative breast disease: epidemiologic aspects, and cytologic diagnosis

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Summary

Purpose: The aim of the present study is to describe the prevalence of proliferative breast lesions in cases of benign and malignant tumors of the breast as well as to assess the contribution of rapid intraoperative imprint cytology in the diagnosis of proliferative breast disease.

Methods: Frozen section and intraoperative imprint cytology were performed on breast tissue biopsies from 486 breast cancer patients who underwent primary surgical treatment. Imprints were stained either by the Papanicolaou (Pap) or the May Grünwald-Giemsa (MGG) or the Hematoxylin eosin (HE) technique. Cytologic diagnoses were compared to the histopathologic ones from paraffin sections.

Results: Sclerosing adenosis was the most common finding in benign breast biopsies while in breast cancer the prevalence of the lesion was reduced by half. On the other hand, atypical hyperplasias in malignant biopsies were almost twice as many as in benign ones. Imprint cytology presented high sensitivity and specificity (99% and 96% respectively) in distinguishing benign proliferative from malignant lesions as a whole, but regarding atypical hyperplasias the specificity was significantly reduced (76% vs 96%).

Conclusion: Clarification of cytologic diagnostic criteria and expertise in cytologic interpretation could show off intraoperative imprint cytology as a useful and inexpensive diagnostic tool providing the surgeon with prompt and accurate information regarding the nature of breast lesions.

Key words: Proliferative breast disease; Epidemiology; Imprint cytology; Sclerosing adenosis.

Introduction

Fibrocystic disease has been used to describe a spectrum of heterogeneous lesions of the breast, reported to occur clinically in 50% and histologically in 90% of women [1]. In 1985, a Consensus Meeting [2] supported by the College of American Pathologists advised deleting the term "fibrocystic disease" and substituting "fibrocystic change" or "fibrocystic condition" to more accurately reflect the changes in the breast [3]. At the same conference, it was elucidated that the most preferred classification of the various histologic diagnoses included in the term "fibrocystic change" should be "nonproliferative lesions", "proliferative lesions without atypia", and "atypical hyperplasias" and the risk factors for malignancy associated with fibrocystic change were clearly delineated [4]. The most important pathologic risk factors recognized were the degree and nature (typical or atypical) of the epithelial proliferation. No elevated risk was related to biopsies showing nonproliferative lesions (cysts, fibroadenosis, apocrine changes, duct ectasia, mild epithelial hyperlasia). Women with proliferative disease (sclerosing adenosis, moderate/florid epithelial hyperplasia) had only a slightly increased risk of cancer development (relative risk 1.9). Atypical hyperplasias (ductal or lobular) were found to imply a relative risk of 4.4, and in combination with a family history of mammary cancer these women were at significantly increased risk (relative risk 8-22) of a subsequent invasive breast carcinoma [1, 5-9]. Bearing in mind that the diagnosis of these lesions is influenced by a marked interobserver variability [10], the need for standardized histologic/cytologic criteria is clearly perceived [11].

For proliferative lesions of the breast with or without atypia, a policy of close observation (self examination, appropriate mammographic screening and regular examination by a physician) is the most commonly recommended management. Recently, new treatment options for high-risk patients include chemoprevention with tamoxifen or with selective estrogen receptor modulators (SERMs) [5, 12, 13]. In cases of a suspicious (clinically or mammographically) lesion of the breast it appears to be of significant benefit to the patient and her physicians to obtain a rapid diagnosis of breast cancer or benign breast lesion, thereby reducing the waiting time and allowing for advanced planning of treatment with participation of the patient [14]. Within this context, aspiration cytology has been widely used for the differential diagnosis of breast lesions and in some institutions it has been accepted as a substitute for frozen sections [15, 16] and the cytologic features of benign and malignant breast lesions have been determined [14].

The aim of the present study is to describe the prevalence of proliferative breast lesions in cases of benign and malignant tumors of the breast as well as to assess the contribution of rapid intraoperative imprint cytology in the diagnosis of proliferative breast disease.

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Materials and Methods

Between 1986 and 2000, 486 patients with clinical or mammographic signs of a breast lump underwent primary surgical therapy at the Gynecologic Clinic, Democritus University of Thrace. The patients underwent a standard preoperative evaluation to assess clinical extent of disease and operative risk. This consisted of history and physical examination, consideration of the mammographic and ultrasound reports, and laboratory studies. Additional laboratory and diagnostic studies, as well as medical consultation were done as indicated by the clinical situation. All inoperable cases were not included in the study population.

All suspicious lesions were submitted to open biopsy and frozen section. The type of major operation ranged from wide local excision of the lump (lumpectomy) to radical mastectomy with axillary lymph node dissection, according to frozen section results and the patient's age and personal preference that had previously been discussed. Imprint cytology was performed on the biopsy specimen prior to frozen section. Samples were palpated and bisected at the hardest areas. Each cut surface was imprinted on two clean, dry slides. The slides were dried in air, fixed in methanol and stained either by the Papanicolaou or the MG or HE techniques. Cytology specimens were examined by the same experienced cytopathologist inside the operating room and they were assigned as "benign", "suspicious", "malignant", or "unsatisfactory". All proliferative lesions of the breast were included in the term "benign" according to the following cytologic criteria [14, 17]:

Simple hyperplasia: the epithelial cells remain uniform, although their nuclei may be slightly enlarged and show a minor degree of overlapping (Figure 1).

Atypical hyperplasia: the epithelial cells show more marked nuclear variation and overlapping, conspicuous nucleoli and a finely granular chromatin pattern. Myoepithelial cells are present (Figures 2, 3, 4).

Sclerosing adenosis: thick clusters of small epithelial cells with with scattered myoepithelial cells (Figure 5).

Absence of myoepithelial cells, variability in cell size, large, hyperchromatic, coarsely granular nuclei with a modified nucleocytoplasmic ratio, multiple nucleoli, mitotic figures, glandlike arrangement of cells, cytoplasmic inclusions and vacuolization were considered cytologic features of "malignancy".

Slides were characterized as "suspicious" when the cellular findings were highly suggestive of malignancy.

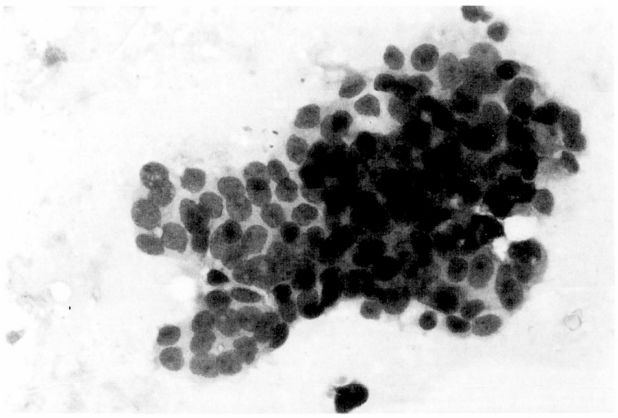

Figure 2. — Ductal hyperplasia with mild atypia. Solid arrangement of epithelial cells with variation in nuclear size, distinct nucleoli and clumped chromatin. Inconspicious myoepithelial cells adjacent to suspicious cells provide an indicator of benignity (MGG x 40).

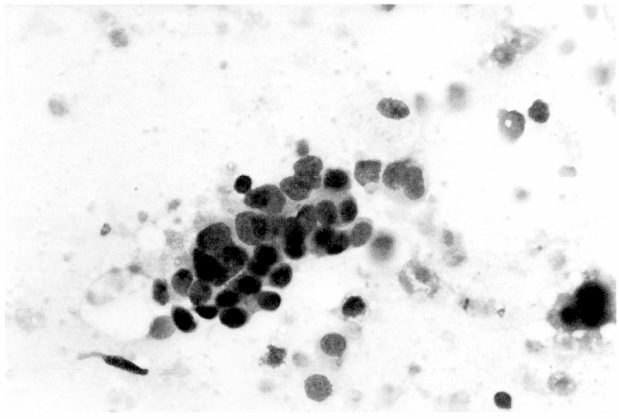

Figure 3. — Ductal hyperplasia with severe atypia. There is a tendency for discohesion, with dispersed cells presenting intact cytoplasm. Marked nuclear variation, overlapping and occasional macronucleoli are misleading. Inconspicious myoepithelial cells help avoiding diagnostic pitfalls (MGG x 40).

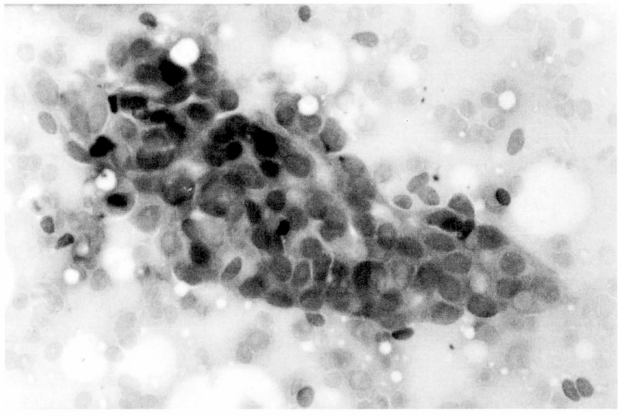

Figure 1. — Ductal hyperplasia without atypia. Large monolayered sheet of epithelial cells, relatively polarized and uniform. Bare oval nuclei (myoepithelial cells) are seen singly and associated with the sheet (Pap x 40).

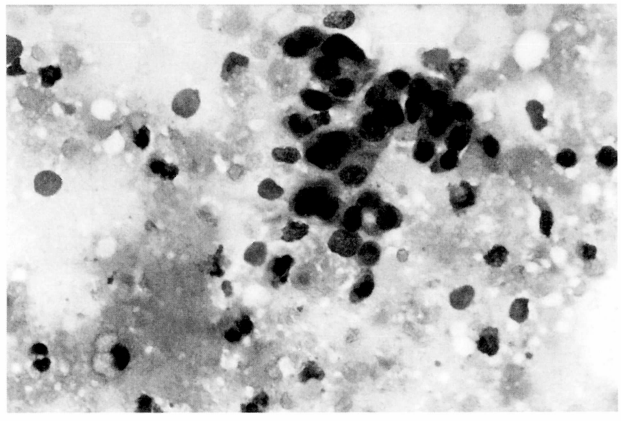

Figure 4. — Ductal hyperplasia with severe atypia misinterpreted as carcinoma. Loss of cohesion, pleomorphic nuclei, hyperchromasia, and some nuclear moulding. Myoepithelial cells are absent (MGG x 40).

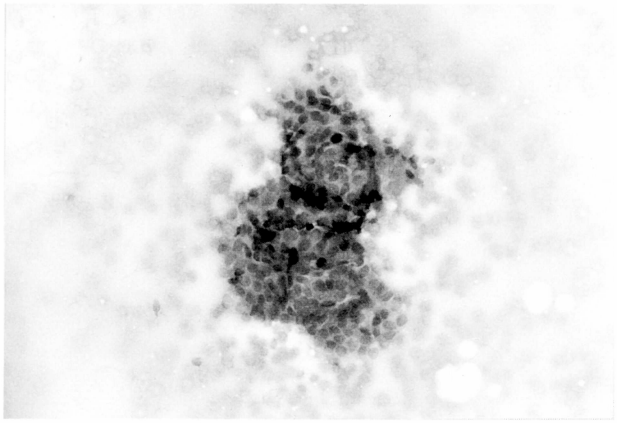

Figure 5. — Sclerosing adenosis. Crowded complex group, consisting of small epithelial cells with scattered myoepithelial cells (Pap x 40).

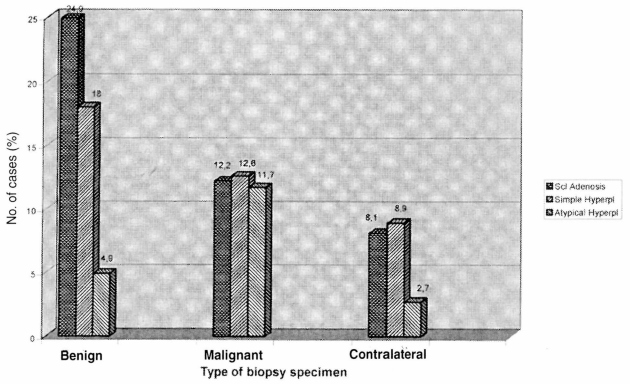

Table 1. — Prevalence of proliferative breast lesions in different biopsy specimens.

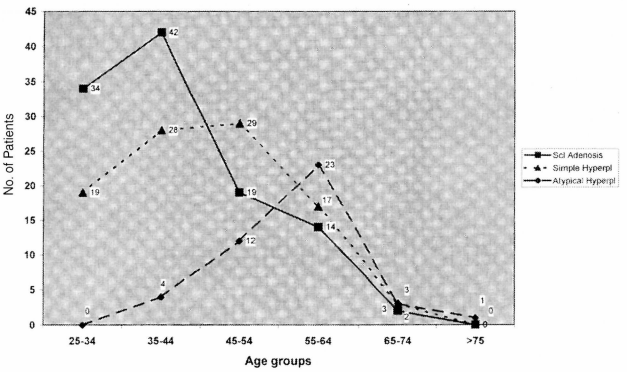

Table 2. — Prevalence of proliferative breast lesions according to age.

Specimens were considered "unsatisfactory" due to scant cellularity, air-drying or distortion artifacts, and obscuring blood or inflammation.

We compared cytologic diagnoses with the histopathologic results obtained from paraffin-sectioned biopsy specimens and not with the "positive-negative" results of frozen section biopsies.

Coexistence of all types of proliferative breast lesions with breast malignancy was commonly found during histopathologic examination of biopsy specimens. For the purposes of our study, the biopsy specimens were classified according to the more severe type of lesion that was detected in the tissue sample. While comparing histopathologic and cytologic diagnoses in our study, we encountered "sclerosing adenosis" as a separate histopathologic entity from proliferative breast lesions because – according to more recent classifications – it is included in a special type of breast lesion named "involution disorders of the breast" [18].

Results

The prevalence of proliferative breast lesions and sclerosing adenosis in benign and malignant biopsy specimens as well as in blind biopsies performed on the contralatteral breast in cases of malignancy is presented in Table 1. We notice that sclerosing adenosis is the most common finding in benign breast biopsies while in breast cancer the lesion is reduced by half. On the other hand, atypical hyperplasias in malignant biopsies are almost twice as many as in benign ones. A considerable percentage of atypical hyperplasias (almost 3%) is detected in blind contralatteral biopsies.

Table 2 presents the distribution of proliferative breast lesions by age. The prevalence of sclerosing adenosis peaks at the fourth decade of life. Simple hyperplasias reach a plateau at the fourth and fifth decade and then decline. Atypical hyperplasias present an increasing inclination from the third to sixth decade and then they descend rapidly.

Table 1 shows a detailed comparison of histologic and cytologic diagnoses established for each biopsy specimen. All hyperplastic breast lesions that were detected as concomitant findings in malignant histologic biopsy specimens are not stated in the table, as they are included in the last group of breast cancer lesions. It is easily noticed that the most suspicious cytologic diagnoses (3/19) were related to the group of atypical hyperplasias.

The diagnostic value of rapid intraoperative imprint cytology in distinguishing benign proliferative breast lesions from breast cancer is described in Table 2. It is easily perceived that the method presents a high sensitivity and specificity concerning benign and malignant lesions as a whole, but regarding atypical hyperplasias the specificity is significantly reduced (76% vs 97%).

Discussion

It has been stated that breast cancer is probably the result of a series of genetic events, each with its own histopathologic correlate in the hyperplasia to carcinoma sequence and there have been studies based on breast cancer markers and proliferation-apoptosis balance which investigate the progression from hyperplasia to atypical hyperplasia to carcinoma [21, 22]. From this point of view, it is very important to identify women at risk and counsel them appropriately with regard to possible treatment options. Our study results are in agreement

with previous epidemiologic reports [5, 19, 20] indicating that a considerable number of young and fertile women are predisposed to the future development of a non-invasive or invasive breast cancer due to proliferative changes developing in the breast tissue. The management of benign proliferative breast lesions follows a standard procedure which still prevails: frozen section followed by surgical treatment. Aspiration biopsy offered an alternative to the common diagnostic approach of breast lesions and in some institutions it has been accepted as a substitute for frozen sections with satisfactory diagnostic accuracy [14, 15, 19]. Intraoperative imprint cytology is a rapid diagnostic technique which has been utilized for the detection of lymph node metastases of breast cancer [23], but, to our knowledge, there are no reports in the literature appreciating the method for distinguishing benign from malignant breast lesions. In the present study we made an effort to test the validity of intraoperative imprint cytology in the diagnosis of the benign proliferative breast lesions. The results clearly suggest that a cytologic diagnosis of carcinoma carries with it a minimal error rate, as well as the diagnosis of simple hyperplasias and sclerosing adenosis. The reliability of benign diagnoses depends on the quality of imprints and the competence of the interpreter. However, it must be recognized that a benign diagnosis on imprint cytology as well as on frozen section does not necessarily rule out carcinoma and regarding benign lesions our study results are similar to the ones reported for frozen section [20]. The false negative results may be due to inadequate sampling or timid interpretation of scanty evidence by an inexperienced observer. For this reason, the concordance of clinical and mammographic findings with the cytologic diagnosis offers an additional precaution. The cytologic diagnoses of "benign" abnormalities have no significance in the presence of abnormal mammographic findings.

It emanates from our results that while imprint cytology is highly predictive of separating benign from malignant lesions, it is less reliable in adequately subclassifying prognostically significant lesions such as atypical hyperplasias. We used the criteria of Peterse and coworkers in an attempt to differentiate benign proliferative atypical breast lesions from malignancy [17]. Cell dissociation, arrangement in small epithelial clusters, nuclei greater than, irregular nuclear membranes, anisonucleosis and necrosis are considered features of malignancy. Benign features are large monolayers, nuclei less than 16 μ without significant variation in nuclear size, and the presence of bipolar nuclei in the monolayers. However, even with those criteria, we had false positive and suspicious results in this type of lesion, which were all due to lack of myoepithelial cells in the cytologic specimen. Bearing in mind the considerable number of young women who would benefit from an early and accurate diagnosis of atypical breast hyperplasia as a benign and curable entity, we suggest that more strict cytologic criteria should be established for distinguishing these lesions from breast cancer.

Large series of patients and more expertise in interpretation of cytologic specimens are necessary before imprint cytology can be established as a reliable intraoperative diagnostic technique. However, we believe that within the hands of an experienced cytopathologist, the method could act as an alternative or complementary diagnostic tool to frozen section, providing the surgeon with prompt and accurate information regarding the nature of breast lesions.

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