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Benign Proliferative Disorders of the Breast

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Fibrocystic disease of the breast has been generally regarded as a disorder due to either excess hormonal stimulation or an exaggerated proliferative response by hypersensitive breast epithelium. The unique lobular lesion-adenosis- and its variants have been regarded as non-neoplastic and non-preneoplastic glandular hypertrophy and hyperplasia, and have different organoid patterns and origins. We have examined a total of 242 cases previously diagnosed as 'fibrocystic desease' at the Department of Pathology with the purpose of clarifying the variants of adenosis in detail and refining the infinitely large 'fibrocystic disease' classification as nonproliferative fibrocystic change and proliferative disorders, such as epitheliosis and atypical hyperplasia. In this study, 224 cases (92.5%) were nonproliferative disease, mostly adenosis (40.1%), and 18 cases (7.5%) were proliferative disease, which consisted of moderate to florid hyperplasia and epitheliosis.

Key Words: Fibrocystic disease, adenosis, fibrocystic change

'Fibrocystic disease' of the breast is the most common benign breast disease with fibroadenoma, and it also includes various histologic features, such as stromal fibrosis, cysts, adenosis, apocrine metaplasia, and epithelial proliferation of various degrees. These breast lesions are generally palpated as a diffusely nodular mass, through cyclic hormonally modulated proliferative activity with incomplete resolution, due either to excess hormonal stimulation or an exaggerated proliferative response by hypersensitive breast epithelium (Hutter 1985). A variety of authors reported that women who have undergone a breast biopsy for benign disease have an increased risk of breast cancer of 2-5 times (Davis *et al.* 1964; Potter 1968), and another series of reports for the relative risk of subsequent breast cancer was added which demonstrated the proliferative disease, especially that associated with a marked degree of atypia, elevated the cancer risk (Kodlin 1977; Page *et al.* 1978; Dupont and Page 1985; Page 1986). A family history of breast cancer had little effect on the risk in women with nonproliferative lesions; however, the risk in women with atypia and a family history of breast cancer was 11 times that in women who had nonproliferative lesions without a family history (Dupont and Page 1985).

In this regards, it was necessary to divide the benign breast diseases into low and high risk groups for breast cancer, so Dupont and Page (1985) separated the histologic lesions of excised benign breast tissue into three prognostically meaningful categories: lesions with no appreciable proliferative activity (nonproliferative lesions), and two types of proliferative disease-proliferative disease without atypia and atypical hyperplasia. A consensus meeting of the Cancer Committee of the College of American Pathologists (1986) was developed to define the terms simply and to facilitate their general use, and to categorize the lesions by their relative risk for the subsequent development of invasive breast cancer, and it was suggested that the histologic component should be specified in the pathologic report rather than the nonspecific term, fibrocystic disease.

In accordance with the current tendency, we retrospectively reexamined the benign breast disease diagnosed as "fibrocystic disease' precisely to reclassify the lesions into 'proliferative' and 'nonproliferative' disorders and to observe the characteristics of each histologic subtype, especially 'adenosis', which is the term that occasionally gives confusion to the pathologists, and to provide an aid for pathologic

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diagnosis of benign breast disease.

MATERIALS AND METHODS

Two hundred forty-two cases of breast specimens, diagnosed as fibrocystic disease, were selected from the Pathology files of Severance Hospital, Yonsei University, from January 1984 to March 1989. Cases of 'fibroadenoma' were excluded. All slides were reviewed by hematoxylin-eosin stain and reclassified according to the lesions found, and it was observed whether apocrine metaplasia was associated or not. To make the assignment of histologic categories as specific and reproducible as possible, two pathologists viewed the slides separately. Any differences were subsequently discussed by the pathologists over a double-viewing microscope for resolution.

Our histologic definitions are listed below. We adopted the classification schemes of Wellings *et al.* (1975), Azzopardi *et al.* (1979) and Page and Anderson (1987).

Nonproliferative Diseases

Cystic disease: This is a disease of lobules defined by the presence of walled spaces filled with fluid, which are at least 0.5mm in diameter.

Duct ectasia: Duct ectasia is essentially an inflammatory disorder involving larger and intermediate ducts of the breast. it proceeds by destruction of the elastic network to ectasia and periductal fibrosis.

Sclerosing adenosis: This is a lobular change, involving an enlargement and distortion of lobular units, with a combination of increased numbers of acinar structures and coexistent fibrotic alteration of the specialized lobular stroma while maintaining a normal two-cell populations (Fig. 1).

Microglandular adenosis: This is a rare histologic pattern of increased numbers of acinar-like elements which are not lobulocentric.

Apocrine change: This category refers to a characteristic change in epithelium to large tall cells with abundant granular eosinophilic cytoplasm (Fig. 2).

Blunt duct adenosis: BDA is a lobular hyperplasia and hypertrophic process of blunt lateral outlines of epithelial structures associated with a specialized type of stroma (Fig. 3).

Nodular adenosis: It is regarded as a microglandular adenosis in which myoepithelial differentiation outstrips epithelial differentiation (Fig. 4).

Fibrosis (Fibrous mastopathy): This is a poorly defined, indurated area consisting of predominantly fibrous tissue. The severity of fibrosis is graded as (+) collagenous fibrosis of interlobular stroma, (++) collagenous fibrosis of intralobular specialized stroma, and (+++) dense fibrous tissue in lobular and interlobular stroma with atrophy of both ducts and lobules.

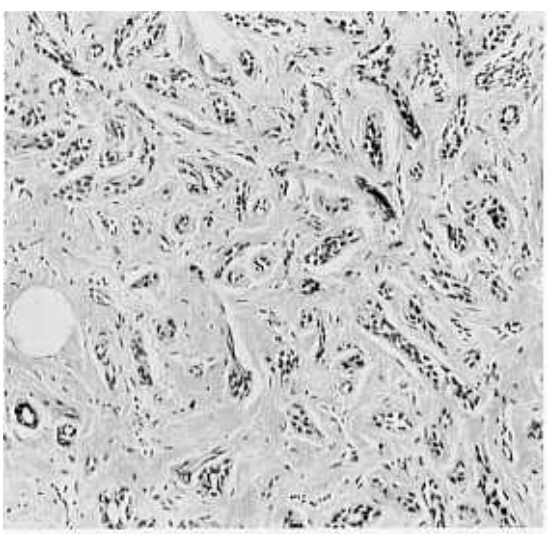

Fig. 1. Sclerosing adenosis. Enlarged lobular units composed of increased numbers of acini surrounded by dense collagenous fibrosis (H & E, ×100).

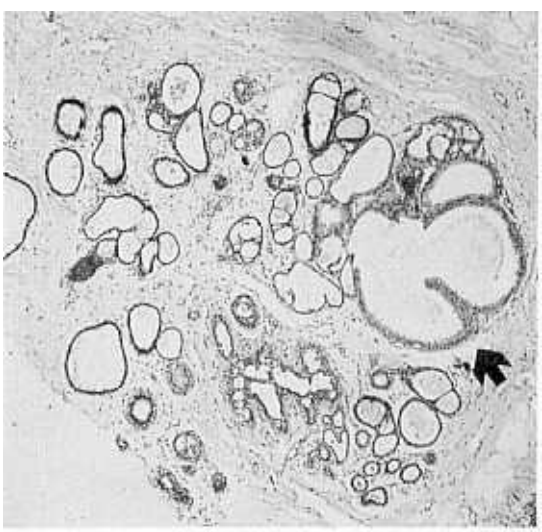

Fig. 2. Fibrocystic change. Some lobular units show variable-sized cystic change with apocrine metaplasia (arrow) (H & E, ×40).

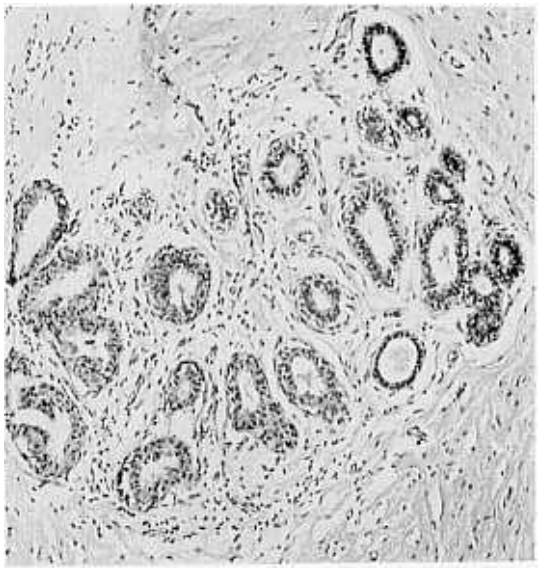

Fig. 3. Blunt duct adenosis. Two layered epithelial structures with blunt endings (H & E, ×100).

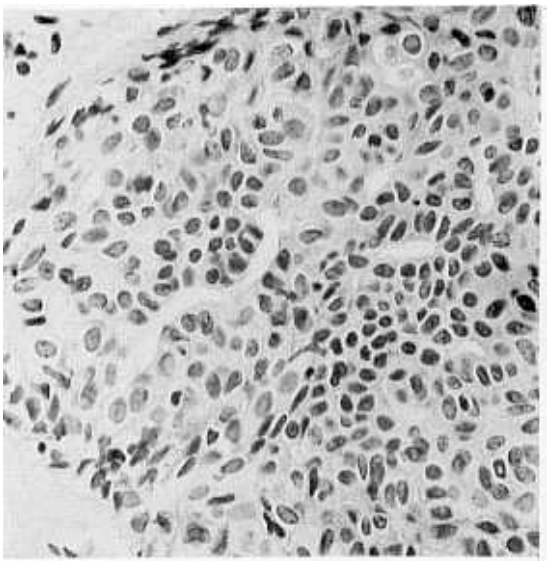

Fig. 5. Florid hyperplasia with small peripheral spaces remaining (H & E, ×400).

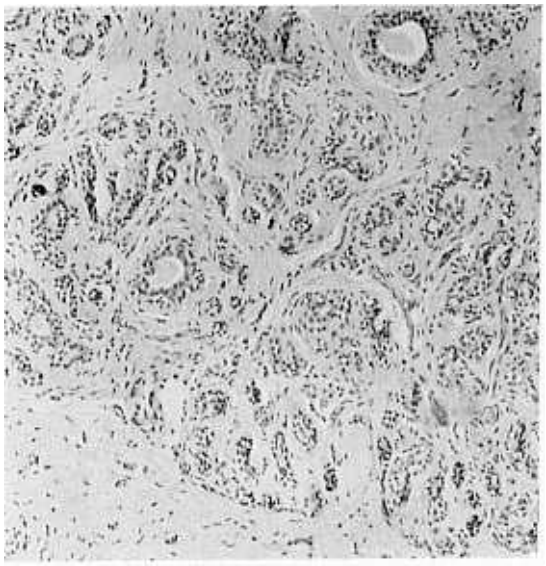

Fig. 4. Nodular adenosis. Florid adenosis without obvious organoid pattern in the non-specialized fibrous stroma (H & E, ×100).

Fibrocystic change: This condition is regarded as a cystic disease accompanied with various degrees of fibrosis (Fig. 2).

Fibroadenomatous hyperplasia: This condition has an ill-defined margin and the features of fibroadenoma and fibrocystic change.

Proliferative Disease

Epithelial hyperplasia: Mild hyperplasia–The epithelium is greater than two but not more than four cells deep. Moderate hyperplasia–The epithelium is five or more cells above the basement membrane with distension of involved spaces and crossing of the space by hyperplastic cells. Florid hyperplasia–It is recognized when distension and filling of spaces is of a marked degree (Fig. 5).

Atypical hyperplasia (ductal or lobular): It refers to lesions that have some features of carcinoma in situ but not enough to make an unequivocal diagnosis of carcinoma in situ–the so-called borderline lesion.

RESULTS

Table I indicates the reclassification based on histologic examination of benign breast diseases diagnosed as 'fibrocystic disease'; 224 biopsy specimens (92.5%) contained nonproliferative disease and 18 (7.5%) contained proliferative disease. Within cases showing proliferative disease, a total of 5.4% showed moderate or florid hyperplasia of the usual type and 2.1% papillomatosis. Among cases of non-

Table 1. Reclassification of benign breast disease diagnosed as 'fibrocystic disease'

	No.	Percent	Mean age (yrs)
Nonproliferative disease (224)			
Involution	12	5.0	40.4
Nodular adenosis	16	6.6	33.8
Sclerosing adenosis	8	3.3	40.4
Blunt duct adenosis (microcystic)	68(7)	28.1	35.4
Adenosis NOS	5	2.1	32.8
Fibroadenomatous hyperplasia	8	3.3	32.8
Fibrosis	56	23.1	37.8
Fibrocystic change	37	15.3	39.8
Duct ectasia	9	3.7	35.5
Lactation change	3	1.2	31.5
Juvenile hypertrophy	2	0.8	17.0
Proliferative disease (18)			
Moderate hyperplasia	11*	2.9	37.0
Florid hyperplasia	6	2.5	38.2
Papillomatosis	5	2.1	39.0
Total	242	100.0	36.8

* Four cases of moderate hyperplasia are also contained in papillomatosis.

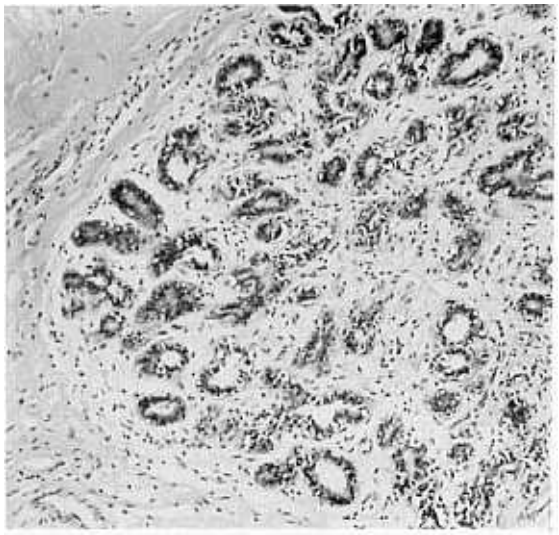

Fig. 6. *Adenosis, NOS. Enlarged lobular units with increased numbers of acini (H & E, ×100).*

Table 2. The lesions associated with apocrine metaplasia

Types	Cases
Lobular lesions (32)	
Blunt duct adenosis	13
Fibrocystic change	11
with duct ectasia	1
Fibrosis	3
Sclerosing adenosis	3
Fibroadenomatous hyperplasia	1
Lobular and ductal lesions (8)	
Florid hyperplasia	4
with fibrocystic change	1
with nodular adenosis	1
Papillomatosis	2
Total	40

proliferative change, the most common was blunt duct adenosis (28.1%) followed by fibrosis (23.1%) and fibrocystic change (15.3%). The lesion of lobular hyperplasia without characteristics of specific subtypes was designated as 'adenosis NOS (Not otherwise specified)' (Fig. 6). The mean age of patients with proliferative disease was 36.7 years and that of patients with nonproliferative disease was 37.9 years and there were no significant differences.

Apocrine metaplasia of varying degrees was demonstrated in 41 cases, of which the dominant patterns were blunt duct adenosis and fibrocystic change, the so-called lesions of lobular units (Table 2).

Table 3. The lesions associated with moderate epithelial hyperplasia

Types	Cases
Nonproliferative lesion (7)	
Blunt duct adenosis	4
Fibrocystic change	2
Involution after lactation	1
Proliferative lesion (4)	
Papillomatosis	4

Eleven cases of moderate epithelial hyperplasia were accompanied with other categories, which were papillomatosis (4 cases), blunt duct adenosis (4 cases), fibrocystic change (2 cases) and involution after lactation (1 case) (Table 3).

DISCUSSION

For many years there has been controversy about the relationship of benign breast disease to the risk of subsequent carcinoma. Recent cohort studies that have included careful pathological classification of benign breast disease are now resolving these problems (Page *et al.* 1978; Tavassoli and Norris 1983; Dupont and Page 1985; Rosenblum *et al.* 1986). Dupont and Page separated the histologic lesions of excised benign breast tissue into only three prognostically meaningful categories: nonproliferative lesions, proliferative disease without atypia and atypical hyperplasia (Dupont and Page 1985). The important thing was that the risk of breast cancer is not uniform in women with benign breast disease but is concentrated in those with proliferative lesions, and this is substantially increased in atypical lobular or ductal hyperplasia. The risk of breast cancer in women with atypical hyperplasia was 5.3 times that in women with nonproliferative lesions (Dupont and Page 1985), and atypical hyperplasia was more frequently observed in the remaining tissue of breast cancer than benign breast lesions (Han *et al.* 1975). This risk is further increased in patients with a familial history of breast cancer, which is 11 times that in women who had nonproliferative lesions without a family history (Dupont and Page 1985). In a recent consensus meeting of the Cancer Committee of the College of American Pathologists (1986), the effort to categorize the lesions by their relative risk for subsequent breast cancer was performed. Although the consensus indicated that cystic change was not a risk factor, there has been continued debate over the significance of cystic change without epithelial hyperplasia, and many authorities still consider that cysts, particularly of the apocrine type, are a marker for subsequent malignancy (Dixon *et al.* 1985; Page and Dupont 1986). In this context, we attempted to reclassify all benign lesions diagnosed as the old cateory of histologic 'fibrocystic disease' according to criteria that can be reliably reproduced and are consistent with terms and concepts currently in use by most practicing pathologists, and to observe the histologic characteristics of each lesion.

We concentrated on the nonproliferative lesion, especially 'adenosis'. Two diagnostically unified terms of adenosis are sclerosing adenosis and microglandular adenosis. Blunt duct adenosis (BDA) is a process of an organoid hypertrophy rather than actual hyperplasia (Azzopardi 1979). This has little diagnostic usefulness because of the loose application of the term to various histological patterns and lack of clinical correlation. In this study, BDA showed changes of epitheliosis (moderate hyperplasia) at the same site in four cases. But by thinking that BDA is a pathological hypertrophic and hyperplastic process of the lobule associated with a specialized type of stroma identical with intralobular stroma of the normal breast and fibroadenoma, a series of disease processes can be considered. That is, in our opinion, the BDA in which the specialized stromal connective tissue overgrows and with which ductal epithelial hyperplasia is associated will become fibroadenomatous hyperplasia, and if this process rapidly progresses with formation of the capsule, fibroadenoma will be developed. According to this hypothesis, BDA, fibroadenomatous hypoplasia, and fibroadenoma are a series of pathologic lobular and ductal hypertrophy and hyperplasia produced by certain stimulating factors, such as hormones. The changes of enlarged lobular units without specific pattern were designated as 'adenosis NOS (Not Otherwise Specified)' in the present study. But these lesions could be a physiologic process after lactation or pregnancy rather than a pathologic lesion.

'Cystic disease' is a disease of lobules and not of ducts, but is histologically confused with 'duct ectasia'. This shows ovoid or round cystic contours rather than the irregular tube-like contour seen in 'duct ectasia' (Azzopardi 1979; Page and Anderson 1987). Cystic walls in 'cystic disease' demonstrate no elastic tissue because lobules do not contain elastic tissue, and apocrine metaplasia is a very common finding in cystic disease. This study also showed apocrine metaplasia in 35.2% (13/37 cases) of cystic disease. So these

features may be helpful in distinguishing the two lesions.

Interlobular or intralobular fibrosis could be found in most cases (210 cases), of which 157 cases were categorized to other lesions. Fifty-three cases of these belonged to 'fibrosis' (fibrous mastopathy), but 15 cases showed only a mild increase of interlobular fibrous tissue with preservation of lobular units; the (+) degree of fibrosis. It is thought that these changes belong to the spectrum of physiological changes of the breast because the degree of fibrosis is minimal and other pathologic findings are not present.

REFERENCES

Azzopardi JG: *Problems in Breast Pathology.* Philadeliphia W.B. Saunders, *1979, 25-91*

Consensus Meeting, Cancer Committe of the College of American Pathologists: Is 'fibrocystic disease' of the breast precancerous? *Arch Pathol Lab Med 110:171-173, 1986*

Davis HH, Simons M, Davis JB: Cystic disease of the breast: Relationship to carcinoma. *Cancer 17:957-978, 1964*

Dixon JM, Lumsden AB, Miller WR: The relationship of cyst type to risk factors for breast cancer and the subsequent development of breast cancer in patients with breast cystic disease. *Eur J Cancer Clin Oncol 21(9)1047-1050, 1985*

Dupont WD, Page DL: Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med 312: 146-151, 1985*

Han WS, Kim TS, Choi IJ, Lee YB, Kim DS: The histopathologic study of atypical lesion in the benign and cancer breasts. *K J P 9:31-35, 1975*

Hutter RVP: Goodbye to "fibrocystic disease". *N Engl J Med 312:179-181, 1985*

Kodlin D, Winger EE, Morgenstern NL, and Chen U: Chronic mastopathy and breast cancer. A follow-up study. *Cancer 39:2603-2607, 1977*

Page DL: Cancer risk assessment in benign breast biopsies. *Hum Pathol 17:871-874, 1986*

Page DL, Anderson TJ: *Diagnostic Histopathology of the Breast.* Edinburgh, Churchill Livingstone, *1987, 43-156*

Page DL, Dupont WD: Are breast cysts a premalignant marker? *Eur J Cancer Clin Oncol 22(6):635-636, 1986*

Page DL, Zwaag RV, Rogers LW, Williams LT, Walker WE, Hartmann WH: Relation between component parts of fibrocystic disease complex and breast cancer. *J Natl Cancer Inst 61:1055-1063, 1978*

Potter JF, Slimbaugh WP, Woodward SC: Can breast carcinoma be anticipated? A follow-up benign breast biopsies. *Ann Surg 167:829-838, 1968*

Rosenblum MK, Purrazzella R, Rosen PP: Is microglandular adenosis a precancerous disease? *Am J Surg Pathol 10(4):237-245, 1986*

Tavassoli FA, Norris HJ: Microglandular adenosis of the breast. A clinicopathological study of 11 cases with ultrstructural observations. *Am J Surg Pathol 7:731-737, 1983*

Wellings SR, Jensen HM, Marcum RG: An atals of subgross pathology of the human breast with special reference to possible precancerous lesions. *J Natl Cancer Inst 55:231-254, 1975*