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Histopathology of myoepithelial (basocellular) hyperplasias in adenosis and epitheliosis of the breast demonstrated by the reactivity of cytokeratins and S100 protein

An analysis of heterogenic cell proliferations in 90 cases of benign and malignant breast diseases*

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Summary. This study on the different types of epithelial hyperplasia in fibrocystic disease was inspired by the observation of myoepithelial (basocellular) hyperplasia identified by strong expression of S100 protein and a weak reaction with antibodies against cytokeratin (KL1) in cells forming solid and acinar buds. The cells do not contain immunohistochemically detectable actin or desmin. Glandular transformation and proliferation give rise to basocellular circumductal adenosis. Normal breast tissue, 51 cases of fibrocystic disease with mild, florid and atypical hyperplasias, 7 fibroadenomas and 20 cases of carcinoma in situ were studied and a semiquantitative analysis revealed basal buds and adenosis in less than 40% of cases of mild hyperplasia and up to 73% in florid hyperplasia. Epitheliosis is characterized by a heterogeneous cell pattern with cells positive for S100 protein in 30–60%, but in small ducts up to 100% with an immediate connection to the basal cell layer were positive. Carcinoma in situ contained very rare tumour cells positive for S100 protein. The cells expressing S100 protein in terminal ducts, in adenosis and epitheliosis showed only some of the characteristics of myoepithelial cells, since they lack immunoreactivity with antibodies against actin. These basal clear cells are interpreted as transitional or indeterminate cells with features of myoepithelial precursor cells, but with the ability to develop basocellular nodular and glandular hyperplasia in the ductulo-lobular units in cases of adenosis and juvenile fibroadenoma.

Key words: Breast – Myoepithelium – Hyperplasias – Adenosis – Epitheliosis

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Introduction

The most important diagnostic components of fibrocystic disease of the breast are different types of adenosis and epitheliosis, which occur predominantly in the terminal ductulo-lobular units (Wellings et al. 1975).

Adenosis is defined as non-neoplastic glandular hyperplasia, whereas epitheliosis comprises solid or quasi-solid intraductal epithelial hyperplasia (Azzopardi 1979). Both changes are characterized by proliferation of the luminal cells and by normal or hyperplastic myoepithelial cells (MEC). Since the identification of MEC by conventional staining techniques is uncertain, special methods such as silver impregnation (Linzell 1955) and enzyme histochemistry for alkaline phosphatase and ATPase have been developed. These methods stain the MECs selectively but are not specific in terms of the myofibrillary compartment (Bässler and Brethfeld 1968; Puchtler et al. 1974). Electron microscopic investigations showed characteristic bundles of myofilaments in the cytoplasm of these cells (Ozzello 1971, 1979; Ahmed 1974; Ohtani and Sasano 1980), but only the new immunohistochemical techniques with specific antibodies against actin (Bussolati et al. 1980, 1984) and the myoepithelial cytokeratins 5 and 14, (15), 17 (Altmannsberger et al. 1986, Moll 1986, 1991; Jarasch et al. 1988) have allowed reliable identification, allowing better investigation of neoplasms and hyperplasia of this cell system in various diseases (Gusterson et al. 1982; Nathrath et al. 1982; Caselitz et al. 1986; Morinaga et al. 1987; Mori et al. 1987, 1989; Papotti et al. 1988; Tsubura et al. 1988, 1989).

The demonstration of MEC can also be achieved by an antibody against S100 protein, resulting in diffuse staining of the cytoplasm. The exact localization of the staining within the cell is not known. S100 protein is a calcium-binding protein which dissolves in 100% ammonium sulphate. It has two components (S100a, S100b) and was discovered by Moore (1965). Antibodies

against S100 protein have been useful in the diagnosis of benign breast lesions (Egan et al. 1987; Hijazi et al. 1989) and in the differentiation between epitheliosis, in situ carcinomas, invasive breast cancer and its metastases (Nakajima et al. 1982; Schmitt and Bacchi 1989).

The present study on different forms of epithelial hyperplasia was inspired by the observation of focal, segmental and micronodular hyperplasia of basal cells in terminal ducts and in adenosis. These cells were characterized immunohistochemically by a strong expression of S100 protein. This study aims to elucidate the immunohistochemical features and the development of this basocellular hyperplasia in its relationship to adenosis, epitheliosis and juvenile fibroadenomas.

Materials and methods

A total of 90 specimens were selected from patients undergoing biopsies or mastectomy for benign or malignant breast disease submitted to the Department of Pathology and from breast tissue embedded in paraffin received for consultation. Normal tissue was obtained by sampling the specimens far away from the main lesions. The samples were classified as shown in Table 1.

The formalin-fixed tissue was embedded in parablast and stained with haematoxylin and eosin, elastic van-Gieson and periodic acid-Schiff reaction. Additional 4-µm sections were stained immunohistochemically using the avidin-biotin-complex method (ABC Vectastain). The sections were deparaffinized and then treated with hydrogen peroxide to block endogenous peroxidase activity; the section was then incubated with normal serum of the same animal species from which the secondary antibody was produced. The specific primary antibody was followed by a biotinylated secondary antibody. The section was then covered by an avidin-peroxidase complex which was made visible by hydrogen peroxide and aminoethylcarbazole.

The antibodies used are shown in Table 2.

Table 1. Samples of benign and malignant breast tissues ($n=90$)

Category	No. of specimens
Normal tissue	12
Fibrocystic disease	51
– with mild epithelial hyperplasias[a] associated with adenosis (blunt duct)	16
– with florid epithelial hyperplasias[a] associated with adenosis[b] and epitheliosis[b]	26
– with florid epithelial hyperplasias associated with atypical (ductal or lobular) hyperplasias[a]	9
Fibroadenoma	5
Juvenile fibroadenoma (adenofibroma)[c]	2
Carcinoma in situ	
lobular	10
ductal	10

Definitions according to: [a] Hutter et al. (1986), [a] Page and Anderson (1987), [a] Prechtel (1991), [b] Azzopardi (1979), [c] Pike and Oberman (1985)

Results

In the normal breast the luminal epithelial cells of the lobules and ducts are stained by the anti-cytokeratins KL1 and lu 5 with a different intensity of expression. Positive reactions against S100 protein are observed in both MEC and epithelial cells of the lobules and terminal ducts. The staining is distributed diffusely in the cytoplasm and the nuclei of these small cells are also frequently coloured. Anti-actin reacts more distinctly with the MEC and reveals their fibrillary pattern.

Cases of adenosis and mild epithelial hyperplasia generally exhibit a stronger reactivity with antibodies against epithelial cells. The layer of the luminal and the basal cells are differentiated by immunohistochemical staining and can be distinguished more easily.

In cysts the lining cells are compressed to a narrow rim (particularly in larger cysts) and lose their reactivity with antibodies against S100 protein and actin. Apocrine cysts are surrounded by a small layer of MEC expressing actin and often negative for S100 protein.

The second group shows a higher degree of epithelial hyperplasia in ducts (epitheliosis) and lobules (adenosis). These proliferations seem to be more or less homogeneous with conventional staining techniques. Focal basal clear-cell hyperplasias and exophytic proliferations appear in small ducts and adenosis. The expression of cytokeratins (KL1, lu 5) is generally strong within the luminal cell layer, but it is interrupted by cells with weak or no reaction (Fig. 1A, C). The reaction is equally weak in exophytic solid or acinar basal cell groups which bulge against the basement membrane and the adjacent stroma (Figs. 1B, 2A, C). These basal cells, however, exhibit a strong expression of S100 protein; they form basal hyperplasias like a string of pearls and are localized predominantly in adenosis and small ducts, for example in juvenile fibroadenoma (Fig. 2D). The more extensive this hyperplasia, the more often acinar and glandular patterns are formed. This development is accompanied by a reduction of the expression of S100 protein. Net-

Table 2. Antibodies used in this study

Antibody	Origin	Specifity	Source
KL1	Mouse monoclonal	Cytokeratins 10, 8, (6, 11)	Dianova
lu 5	Mouse monoclonal	Cytokeratin	Roche
Anti-S100 protein	Rabbit polyclonal	S100 protein	Dakopatts
HHF 35	Mouse monoclonal	α- and γ-actins	Enzo Biochem.
Anti-desmin	Rabbit polyclonal	Desmin	Dakopatts
VIM 3B4	Mouse monoclonal	Vimentin	Progen

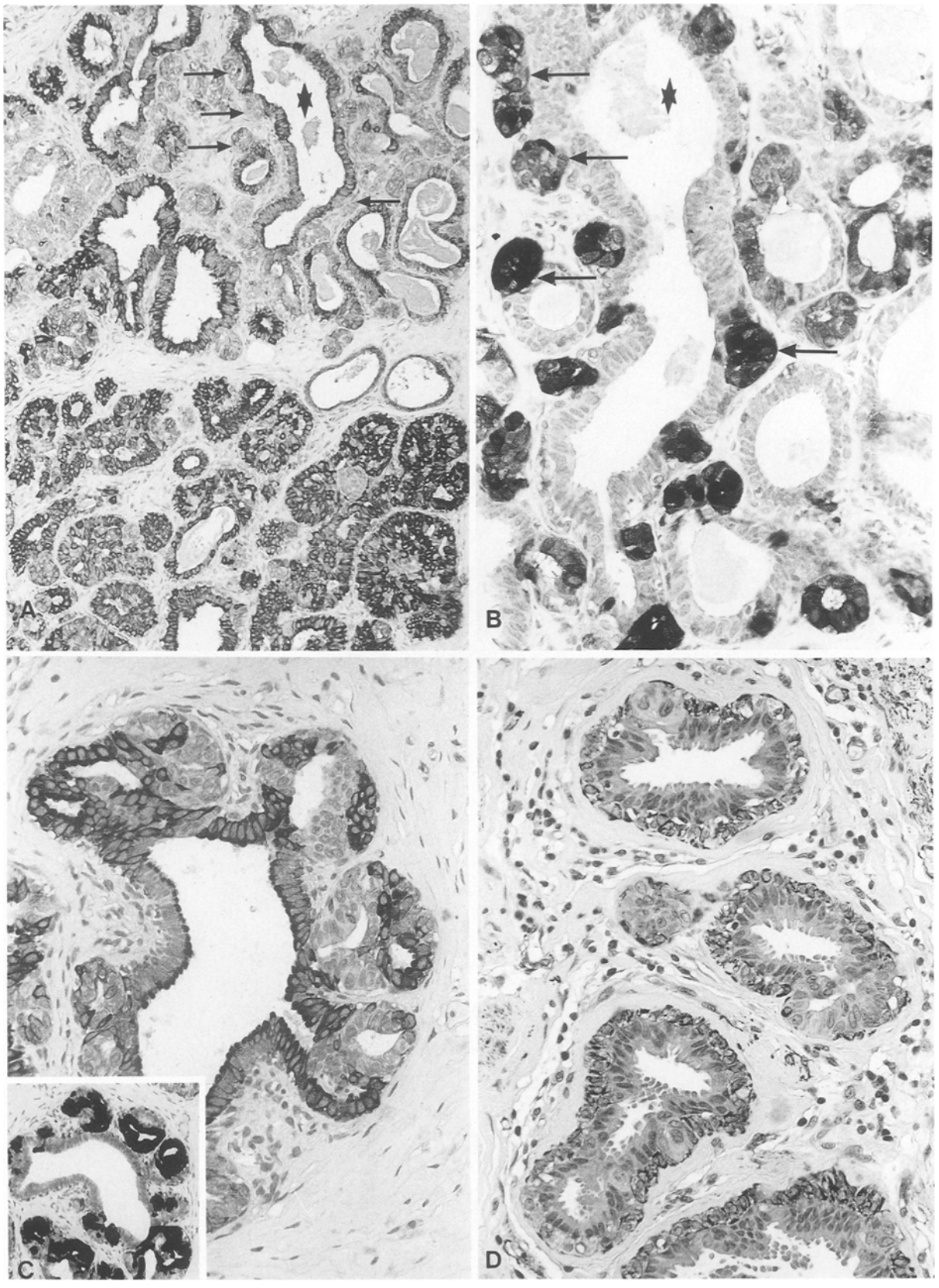

Fig. 1. A Adenosis and epitheliosis with florid epithelial hyperplasia and a strong immunoreactivity for cytokeratin (KL1) is evident in epitheliosis. There is a non-homogeneous or negative staining in the lining and basal proliferating epithelium in the adenosis (*upper part*). ×120. **B** Immunoreactivity for S100 protein in the basal solid and acinar buds of the terminal ducts in the area of adenosis of **A** (*above*). *Asterisk* displays the corresponding duct, the *arrows* the corresponding different expression of cytokeratin and S100 protein. ×300. **C** Terminal duct with acinar and glandular budding. Weak or negative cytokeratin expression corresponds to a strong S100 protein reactivity (*inset* ×120). ×300. **D** Basocellular solid and acinar buds without reactivity for actin. The buds are focally surrounded by a thin or interrupted layer of myoepithelial cells. ×300

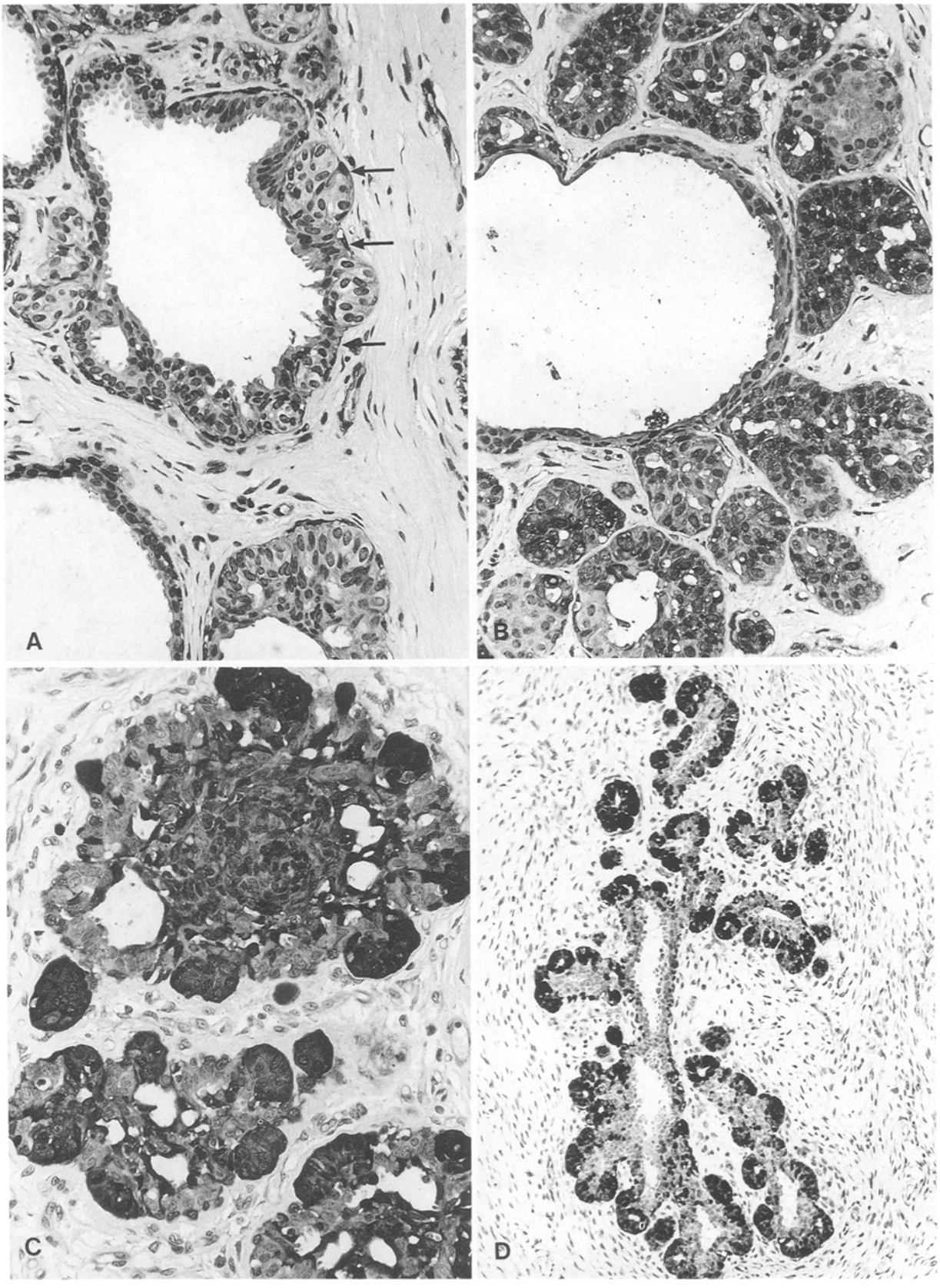

Fig. 2. A Plurifocal basocellular solid and acinar buds in connection with the luminal epithelium and surrounded by a small and interrupted layer (*arrow*) of myoepithelial cells. Anti-actin, ×300. **B** Basocellular solid, acinar and glandular hyperplasia (basocellular adenosis) of an ectatic terminal duct in an area of adenosis with a different S100 protein expression. ×300. **C** Terminal ducts with basal solid buds and epitheliosis containing S100 protein. ×300. **D** Juvenile adenofibroma with plurifocal solid and acinar bud-like basocellular hyperplasia indicated by a strong reactivity for S100 protein. ×120

Table 3. Frequency and types of S100-protein-positive cells in fibrocystic disease (the co-existence of phenomena was common)

Types of fibrocystic disease	No.	Segmental reactivity		Basal buds, solid	Acinar buds	Basal adenosis	Epitheliosis, Mosaic
		mild	strong				
Mild epithelilal hyperplasia	16	15 93.8%	7 43.8%	6 37.5%	4 25%	2 12.5%	9 56.3%
Florid epithelial hyperplasias and epitheliosis	26	26 100%	22 84.6%	19 73.1%	12 46.2%	8 30.8%	23 88.5%
Florid epithelial hyperplasias and epitheliosis together with atypical hyperplasia	9	9 100%	5 55.6%	4 44.4%	3 33.3%	3 33.3%	6 66.7%

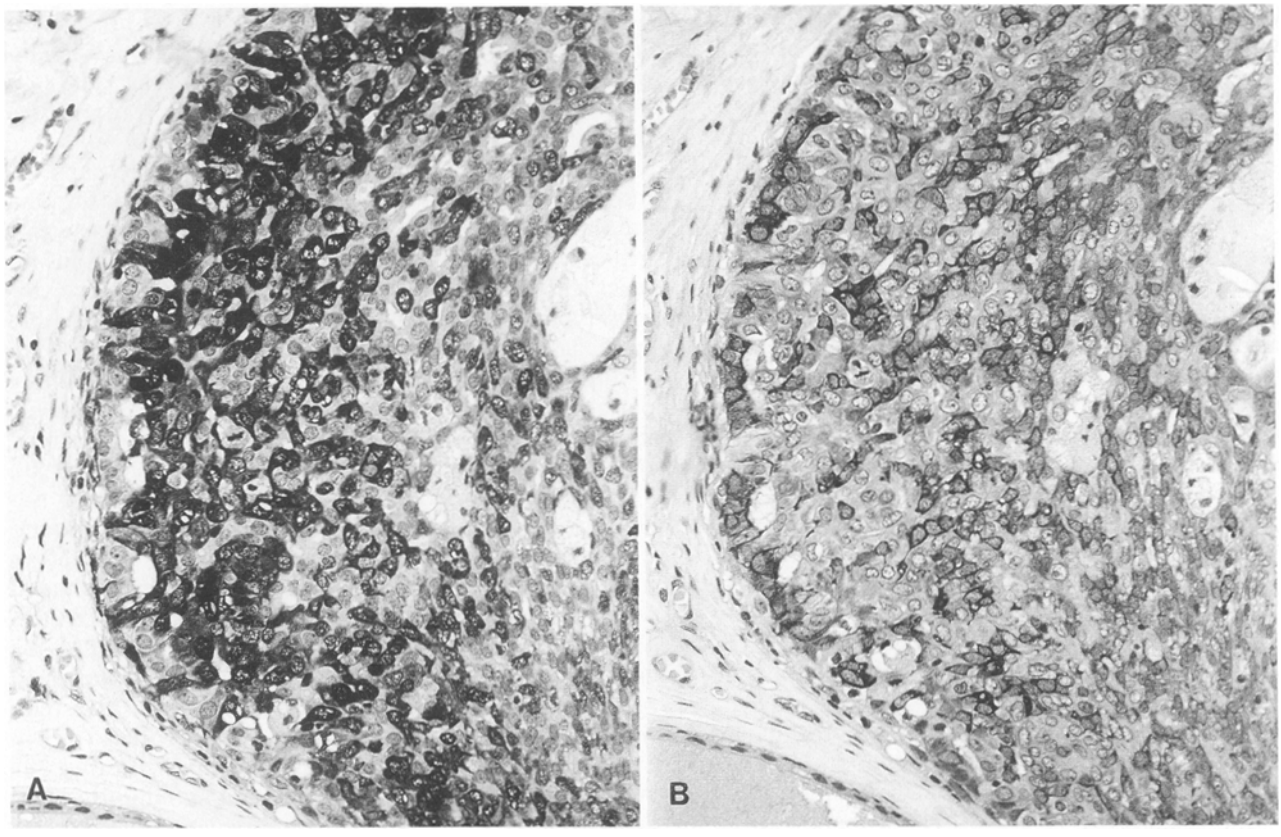

Fig. 3. Epitheliosis in two consecutive slides with a different complementary reaction of hyperplastic epithelial cells for S100 protein (**A**) and for cytokeratin KL1 (**B**). Note the S100 protein expression by the normal myoepithelial cells and by the cells in the outer epithelial layer forming a solid or net-like intraductal hyperplasia (**A**) which reacts negatively or weakly for cytokeratin (**B**), indicating the heterogeneous cell pattern in epitheliosis. × 300

shaped luminal hyperplasias in terminal ducts have S100 protein in 90–100% (Fig. 2C).

Epitheliosis shows cells within the ducts without a tendency towards bud formation against the surrounding connective tissue. The reaction pattern is mosaic-like when stained with antibodies against S100 protein. Of these cells 30–60% exhibit a S100 protein reactivity with a predominance of hyperplasias without atypia (Ta-

ble 3). The expression of cytokeratins (KL1, Iu 5) becomes weaker in cells with a high content of S100 protein (Fig. 3).

Atypical ductal and lobular hyperplasia shows a strong expression of cytokeratin. Only a few cases of atypical lobular hyperplasia (2/9) have cells with a segmental variably positive reaction with antibodies against S100 protein, whereas there is no S100 protein reactivity within atypical ductal hyperplasias. Basal bud-forming hyperplasias are entirely missing.

Lobular carcinoma in situ gives a strong staining with the antibodies used against cytokeratins. Ductal carcinoma in situ contains the cytokeratin group which reacts homogeneously with the antibody KL1. Most tumour cells do not express S100 protein but in 3 cases some positive cells could be observed within the tumour and along the luminal surface of intraductal carcinoma.

In evaluating the reactivity with the antibody against S100 protein semi-quantitatively, three groups with different proliferative activity were selected; classification was determined by the predominant component. Atypical hyperplasia was evaluated separately (see above). Segmental reaction of cells containing S100 protein is the rule (Table 3). Mild epithelial hyperplasia exhibits basal buds and basal adenosis in less than 40% of cases. Basal bud-like proliferations and basal adenosis are found most often in cases with florid hyperplasia without atypia (up to 73%).

Discussion

Benign epithelial hyperplasia of the breast produces proliferation of luminal epithelium and myoepithelium in variable compositions. Solid or quasi-solid epithelioses (Azzopardi 1979) or florid intraductal epithelial hyperplasias of usual type (Page and Anderson 1987) show different cellular patterns in their epithelial compartment, which differ from the ductal cylindrical epithelium and from the myoepithelium.

Myoepithelial hyperplasia is an important component of diffuse and nodular forms of sclerosing adenosis as well as of the rare variants of adenomyothelial hyperplasias (Kiaer et al. 1984; Eusebi et al. 1987). A number of reports have described the MEC and the various myoepithelial hyperplasias by conventional staining, by ultrastructural investigation (Fisher 1976; Ohtani and Sasano 1980; Bussolati et al. 1981; Murad and Van Haam 1986) and by immunohistochemical techniques (Franke et al. 1980; Caselitz et al. 1986; Joshi et al. 1986; Gerald et al. 1987).

Only one investigator, Hamperl (1970), made an attempt at a classification of the myoepithelial lesions of the breast, the skin and the salivary glands. He noted epimyoepithelial islands and focal myoepithelial hyperplasia in ducts and supposed many years before the development of immunohistochemistry in diagnosis that "intracanalicular hyperplasias" may be caused by a proliferation of MEC. In 1991, Tavassoli suggested a new classification of myoepithelial lesions into three categories using histopathological and clinical features: myoepitheliosis, adenomyothelioma and malignant myoepithelioma (myoepithelial carcinoma).

In our study we describe the different types of myoepithelial or basocellular hyperplasia associated with florid epithelial hyperplasia in cases of fibrocystic disease. These cells lie between the luminal epithelium and the basement membrane and show a selective and intense expression of S100 protein. This staining pattern correlates with the staining of the myoepithelial (basal) compartment in benign breast disease and in tumours (Nakajima et al. 1982; Egan et al. 1987; Hijazi et al. 1989; Tavassoli 1991). The staining patterns for S100 protein described in our study differ from the results in the papers cited above in their focal, segmental and bud-like patterns in extra- and intralobular ducts and in non-sclerosing adenosis. Local hyperplasia forms basal solid buds arranged like a string of pearls which bulge against the basement membrane and displace the normal myoepithelium (Figs. 1B, D, 2A). Glandular transformation of these basal buds together with circumferential exophytic hyperplasia in terminal ducts form a basal circumductal adenosis (Figs. 1C, 2B). Tanaka and Oota (1970) studied the microarchitecture of fibrocystic disease and described a similar budding of abnormal ducts and ductules. In forming these adenomatous structures the cells alter their immunohistochemical reactivity (Moll 1991). Their staining with antibodies against S100 protein becoming weaker. More cytokeratins are present as demonstrated by reactivity with the antibody KL1. The cells in circumductal adenosis have thus lost some of the properties of MEC (Fig. 2B).

Equivalent but more regularly differentiated and arranged solid and acinar buds in a juvenile adenofibroma are shown in Fig. 2D. This basocellular hyperplasia also expresses S100 protein and the component cells do not react with antibodies against actin and desmin. The various types of staining patterns of S100 protein within epithelial hyperplasias are shown in Fig. 4.

Intraductal epithelioses show heterogeneous staining patterns immunohistochemically as far as myoepithelial cytokeratins (Ck 5, 14) and S100 protein are concerned (Nagle et al. 1986; Jarasch et al. 1988; Raju et al. 1990). This confirms observations by Hamperl (1970) and Azzopardi (1979) using conventional staining techniques. They believed that the cells of epitheliosis were of an indeterminate type, possibly incompletely differentiated MEC. The cells of epitheliosis contain the cytokeratins 1, 5, 10, 14 in 70–100% and in about a half of the cases S100 protein (Raju et al. 1990). This was confirmed by Egan et al. (1987) as well as by our own investigations, where the cells expressing S100 protein form a mosaic-like pattern within fenestrated epitheliosis in 30–60% (Fig. 3A, B). With conventional staining these labelled cells show a paler and more voluminous cytoplasm than the normal epithelial cell of the duct and some of the immunohistochemical results explain the interpretation as a myoepithelial hyperplasia. These cells, however, do not express actin or desmin just like the basal buds. Therefore they are not identical with typical actin-positive MEC as they demonstrate only some immunohistochemical features of MEC. Solid epithelial hyperplasia in terminal ducts often exhibits a strong and homogeneous staining of S100 protein in all cells. These cells are in continuity with the basal cell compartment, which is the origin of epithelial hyperplasia expressing S100 protein (Figs. 2C, 3A).

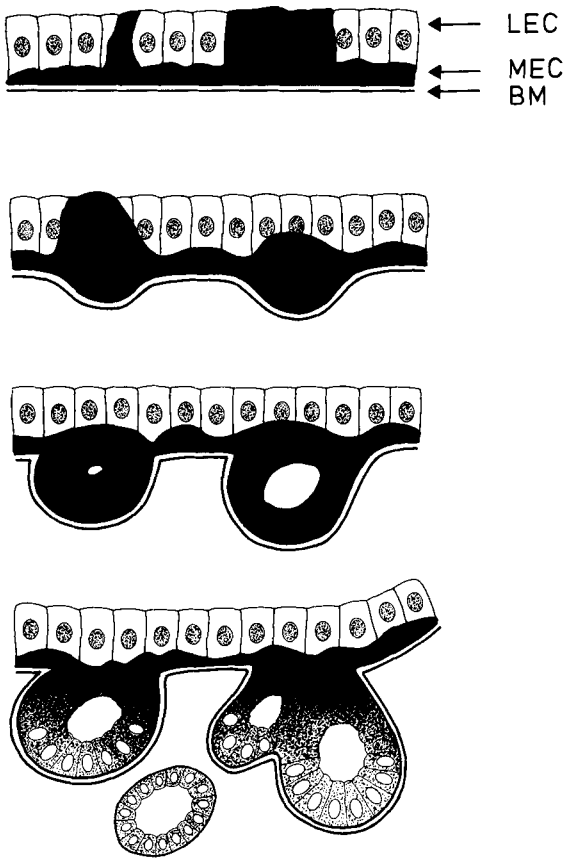

Fig. 4. Drawing of different types of the S100-protein-positive basocellular hyperplasias with segmental, bud-like, acinar proliferations and glandular transformation. *LEC*, Luminal epithelial cells; *MEC*, myoepithelial cells; *BM*, basement membrane

Ductal and lobular carcinoma in situ give no reaction with antibodies against the myoepithelial cytokeratins (Ck 5, 14) (Jarasch et al. 1988) or Ck 1, 5, 10, 14 (Raju et al. 1990). The labelling of the often atrophic myoepithelium can therefore be achieved more reliably by antibodies against actin than against S100 protein. Egan et al. (1987) did not show reactivity of tumour cells with antibodies against S100 protein. Our investigation revealed a few reactive cells in three intraductal carcinomas, either within the group of tumour cells or on the luminal surface. A mosaic-like heterogeneous staining pattern with S100 protein was not detected in carcinoma in situ. Further studies will evaluate the importance of the expression of S100 protein in intraductal epithelial hyperplasia as a tool in differential diagnosis.

In a few cases of invasive carcinoma cells that were stained by an antibody against S100 protein could not be differentiated from ordinary tumour cells by electron microscopy (Lunde et al. 1987). A greater frequency of S100-protein-positive cells was reported by Dwarakanath et al. (1987), who found 48% positive cells, and by Stroup and Pinkus (1988), who found more than 50% in primary tumours and 20% in metastases.

The morphological and immunohistochemical behaviour of cells partially expressing S100 protein show MEC features. These cells either form solid or acinar buds between the luminal epithelium and the basement membrane alongside the normal myoepithelium or they are part of intraductal epithelioses. This 'third cell type' of the breast has been described as basal or clear cell (Toker 1967; Stirling and Chandler 1976; Bässler 1978; Smith et al. 1984) or as indeterminate cell (Ozzello 1971; Stegner 1986). In electron microscopic investigations of the normal human breast Smith et al. (1984) describe a variant of basal clear-like cells with hemi-desmosomes and myofilaments showing characteristics of a transition between these clear cells and the MEC in addition to the basal clear cells of the lobulo-alveolus. The authors suggest that the basal clear cell is a precursor of the MEC but not epithelial cells. Without discussing the concept of stem cells (Bennett et al. 1978; Rudland et al. 1980; Nagle et al. 1985) Joshi et al. (1986) found that the basal clear cells were, together with the ductal and lobular luminal epithelial cells, the compartment with the highest proliferative capability. Our investigations show that the cell compartment identified by staining with antibodies against S100 protein and cytokeratins but not with antibodies against smooth muscle actin, expresses incomplete features of the fully differentiated MEC. In our opinion these cells not only represent a pool of precursor cells but are able to form basal cell hyperplasia and types of basal cell adenosis of the ductulo-lobular units beside normal MEC. To our knowledge these forms and transformations in fibrocystic disease have not yet been investigated.

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