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An immunohistochemical study of the breast using antibodies to basal and luminal keratins, alpha-smooth muscle actin, vimentin, collagen IV and laminin

Part II: epitheliosis and ductal carcinoma in situ

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Summary. A detailed immunohistochemical study has been carried out on 63 breast lesions with epitheliosis, ductal carcinoma in situ and clinging carcinoma (lobular cancerization), using antibodies directed against keratins 5/14 and 14, 15, 16, 18, 19, vimentin, smooth muscle actin, collagen IV and laminin. The results have shown that epitheliosis on the one hand and ductal in situ and clinging carcinoma on the other are immunohistochemically different epithelial lesions. Epitheliosis appears to be epithelial hyperplasia with keratin 5/14 *and* keratin 14, 15, 16, 18, 19-positive cells. Compared to epitheliotic cells tumor cells of clinging carcinoma, lobular cancerization and ductal carcinoma in situ expressed only luminal keratins 14, 15, 16, 18, 19 in 85% of the cases studied; whereas in 15% there was a basal keratin expression. From our results we conclude that the clinging carcinoma (lobular cancerization) represents the initial morphological step in the development of ductal carcinoma in situ and thus may be interpreted as a minimal ductal neoplasia. With the immunohistochemical demonstration of basal and luminal keratins it may be possible in individual cases to differentiate between benign and malignant in situ lesions of the breast.

Key words: Hyperplastic breast lesions – Anti-keratin antibody – Anti-smooth muscle actin antibody – Anti-vimentin antibody – anti-collagen IV antibody – Immunohistology

Introduction

Although there are excellent studies on the frequency and distribution of ductal carcinoma in situ and its biological meaning (Gallager and Martin 1969; Lagios et al. 1989; Ober and Tulusan 1985; Page et al. 1978), viewpoints concerning the development of cancer remain controversial (Azzopardi 1979; Bässler 1978; Fechner and Mills 1990; Millis 1984; Rosai 1991; Stegner 1975). One concept, favoured among others by Black and Kwon (1980), Wellings et al. (1975) and Prechtel (1972, 1974) suggests a transition from benign proliferative to malignant lesions, reflected by a terminology with a numerical grading system, similar to the one used in cervical intraepithelial neoplasia (Ferenczy and Winkler 1987). The second view draws a sharp line between benign proliferating lesions and and carcinoma in situ. This theory, however, implies a de novo carcinogenesis from non-proliferative breast tissue as suggested by Azzopardi in his monograph (1979). In this context he has introduced the term "clinging carcinoma" (Azzopardi 1979), referring to a thin layer of neoplastic cells in ducts or lobules (Eusebi et al. 1989). The involvement of lobules by neoplastic epithelium of ductal type was first described by Fechner (1971), who coined the term "lobular cancerization".

Against this background, we have recently performed immunohistochemical studies of keratin profiles in benign and malignant lesions of the breast (Böcker et al. 1986; Jarasch et al. 1988; Nagle et al. 1986). The most important result, confirmed by Raju and co-workers (1990), was that epitheliosis and ductal carcinoma in situ show a clear and consistent antigenic difference. We undertook the present immunohistochemical evaluation with the objectives of analysing further the histogenetic relationship between epitheliotic lesions and ductal carcinoma in situ (including lesions with lobular cancerization and clinging carcinoma in the terminology of Azzopardi (1979)). Lesions of borderline type of atypical ductal hyperplasia as defined by Page and Anderson (1987) or Fechner and Mills (1990) were not included. We further wished to examine the potential value of immunohistochemistry in the diagnosis of these lesions and to

Dedicated to Prof. Dr. E. Grundmann on the occasion of his 70th birthday

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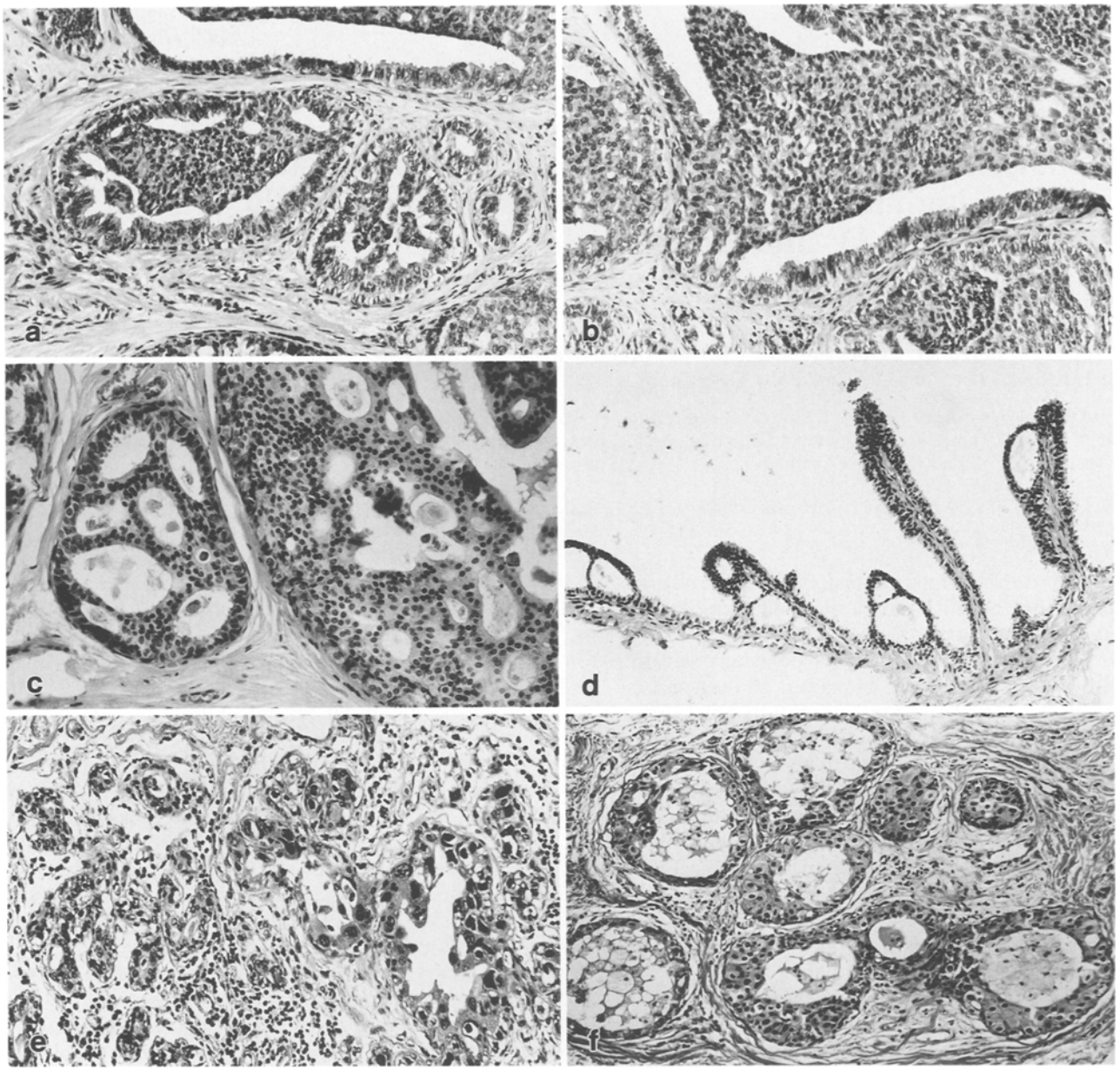

Fig. 1 a–f. Haematoxylin-eosin photographs of epitheliosis (**a, b**), ductal carcinoma in situ (**c**), clinging carcnoma (**d**), lobular cancerization (**e–f**). **a–c** ×200, **e–f** ×250, **d** ×400

discuss the practical and conceptual implications of our results.

Materials and methods

A series of cases of epitheliosis ($n=37$), ductal carcinoma in situ ($n=26$) and lobular cancerisation ($n=6$) were compared immunohistochemically. Mammary tissue from biopsies or lumpectomies of frozen sections was used. The material was snap-frozen in liquid nitrogen and stored at −70° C until used. In all instances, slides of formalin-fixed, paraffin-embedded "counterparts" of the lesions were critically reviewed. The lesions were classified according to the criteria by Azzopardi (1979), Haagensen et al. (1981), Page and Anderson (1987) and Carter (1990). Typical examples of epitheliosis, lobular cancerization and ductal carcinoma in situ are shown in Fig. 1 a–f.

Antibodies (Abs) KA1 and KA4 were kindly provided by R.B. Nagle. KA1 is directed against keratins 5/14 and KA4 against keratins 14, 15, 16 and 19[1] (for characterization of the Abs see Nagle et al. 1986 and Jarasch et al. 1988). The following monoclonal antibodies (mAbs) applied were commercially obtained: anti-vimentin (clone V9, Boehringer, Mannheim, FRG), anti-α-smooth muscle (sm) actin (HHF-35, Boehringer), anti-collagen-IV Abs (Dianova, Hamburg, FRG) and anti-laminin (Dianova). For double stainings, additional polyclonal Abs against keratins 8/18 (TPA) (Sangtech Medical Co., Bromma, Sweden) were used. The reactivity of the mAb was visualized using fluorescein conjugated secondary Abs. Fluorescein-isothyocyanate (FITC)-coupled or tetrameth-

[1] KA4 reacted preferentially with keratin 19

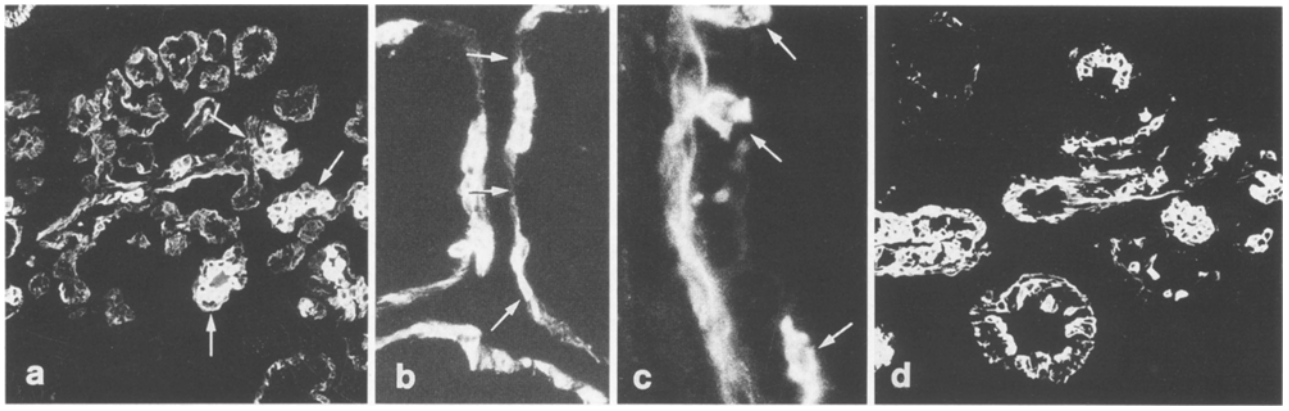

Fig. 2a–d. Normal breast stained with K5/14 mAb KA1: **a** Myoepithelial cells of terminal ducts and acini are clearly stained. Note intensive staining of cells in luminal position of some acini and terminal ductules (*arrows*). ×400. **b, c** Parts of acini with staining of most, but not all myoepithelial cells (*arrows*). Intensive staining of luminal cells, most of them in contact with the basal cells (*arrows*). **b** ×1000, **c** ×1300. **d** Adenosis. Strong K5/14 mAb KA1 reaction of myoepithelial and many luminal cells. ×400

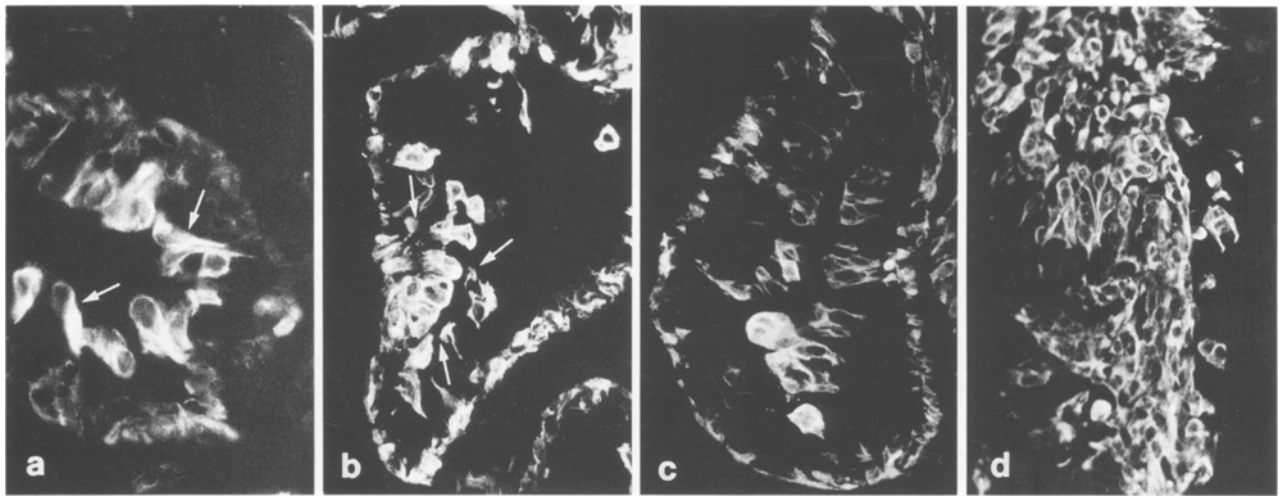

Fig. 3a–d. Epitheliosis with different degrees of intraluminal hyperplasia, increasing from **a** to **d**, immunostained with K5/14 mAb KA1. Note intensive staining of polygonal to tadpole-shaped cells (*arrows*). With increasing proliferation the K5/14 mAb KA1-positive cells form clusters (*arrows* in **b**) basally located cells of which are still in contact with the myoepithelial cells. The clustered K5/14 mAb KA1-positive cells may be located in the lumen (**c**). In fully developed lesions the K5/14 mAb KA1-positive cells may fill much of the lumen (**d**)

yl/rhodamine-isothyocyanate (rhodamine)-coupled Abs (Dianova), raised to either mouse or rabbit IgG, were used.

Immunofluorescence microscopy was performed on cryostat sections (5 μm) air-dried and fixed in acetone at −20° for 10 min as described (Moll et al. 1982). For double immunofluorescence microscopy, both primary Abs were applied simultaneously, as were the specific secondary Abs. With each staining, a negative control was obtained by omitting the primary Ab and replacing it with non-immune serum. In addition, some sections were stained using the alkaline phosphatase anti-alkaline phosphatase method (Cordell et al. 1984).

Results

Staining results of the *normal breast* for all Abs used have already been described in a previous paper (Böcker et al. 1992). For the understanding of epitheliotic lesions, however, the K5/14 mAb KA1 staining of the normal gland must be briefly reviewed (Fig. 2a–c). K5/14 mAb KA1 reacted with most of the myoepithelial cells of ducts and lobules in a similar way as did α-sm actin mAb. In addition, however, some luminal cells reacted brightly with K5/14 mAb KA1. These cells were arranged in single cells or in small groups, most of them being in contact with the basal myoepithelial cells. Some occasional cells had clearly lost their contact to the basal cells (Fig. 2c). Occasionally, all luminal cells of an acinus were stained with K5/14 mAb KA1. All these K5/14-positive luminal cells did react neither with K8/18 TPA Ab nor with actin (Fig. 2a).

All samples of epitheliosis ($n=37$) immunoreacted with the mAbs to basal keratin 5/14 (mAb KA1) *and* luminal keratins 8, 18, 19 (mAb KA4 and TPA Ab). In addition, the myoepithelial layer of epitheliotic lesions almost always exhibited a positive reaction with K5/14

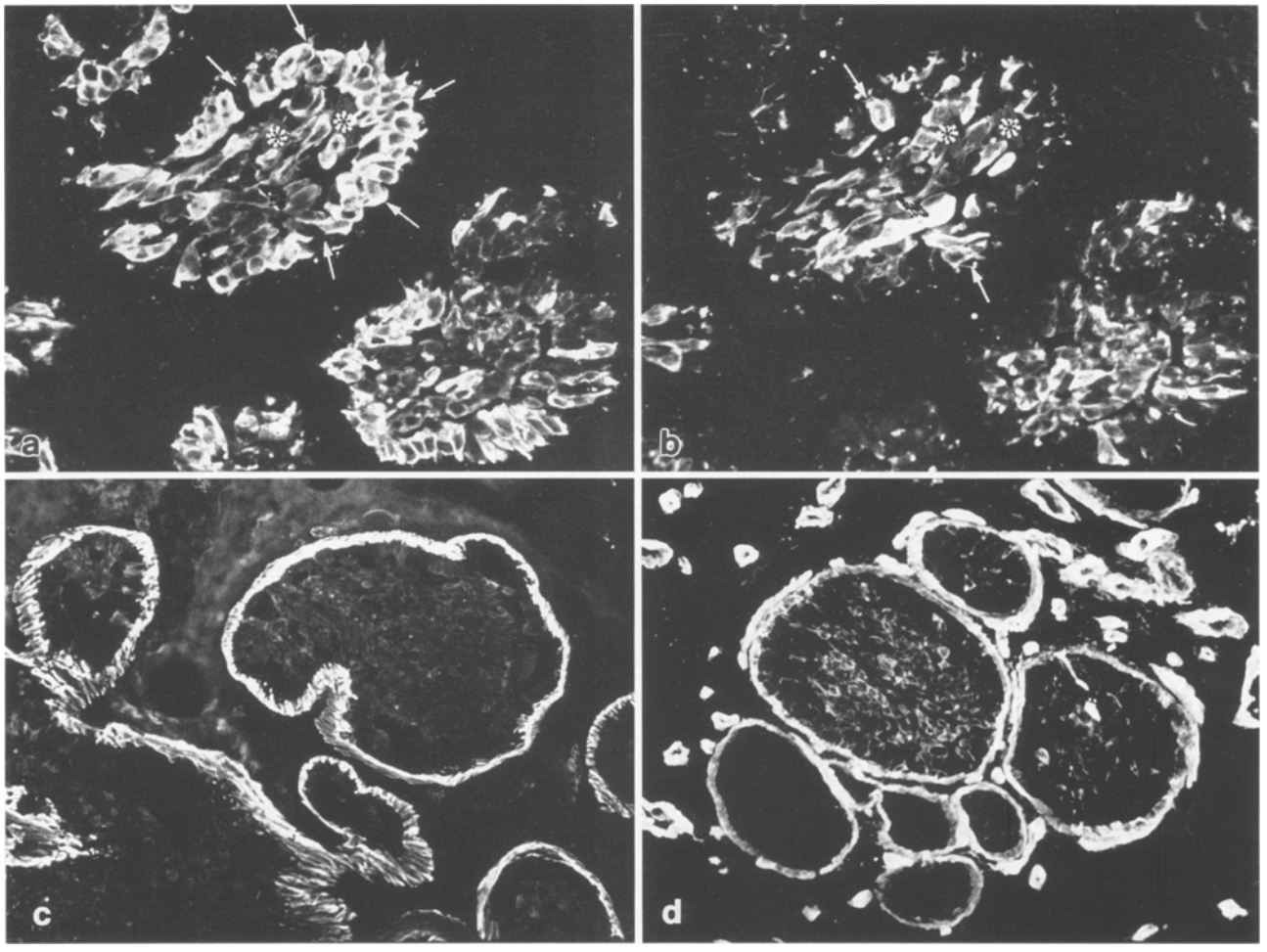

Fig. 4a–d. Epitheliosis: **a, b** Double staining of an epitheliotic lesion with K8/18 TPA (**a**) and K5/14 mAb KA1 (**b**). Note that the epithelial cells in "normal position" are intensively stained with K8/18 TPA (*arrows* in **a**) with occasional unstained cells. In addition, many proliferating cells in the lumen show a keratin 8/18 expression. K5/14 mAb KA1 immunostaining shows a reverse reaction. Only occasionally do cells show a double staining with both K8/18 and K5/14 mAbs (*cells between asterisks* in **a** and **b**). **c** Epitheliosis immunostained with actin mAb. There is only a myoepithelial reaction. Note that intraluminal cells are negative. ×400. **d** Epitheliosis immunostained with collagen IV mAb. Note intensive staining of basal lamina of glands and surrounding vessels. ×400

mAb Ka1 (Fig. 3). In lesions with discrete intraluminal hyperplasia there were scattered brightly K5/14 mAb KA1 stained luminal cells, some of them with a tadpole appearance, the small tail of the cells being obviously in contact with the basal cells (Fig. 3). In other cases, clusters of proliferating K5/14 KA1-positive cells projected into the lumen (Fig. 3). These cells often had spindle-shaped or plump cytoplasmic bodies. In fully developed epitheliotic lesions, these cells filled much of the lumina (Fig. 3).

The two luminal keratin Abs (mAb KA4 and Ab TPA) used disclosed results which were the opposite of the mAb KA1 reactions. In early lesions K19 mAb KA4 stained the luminal cell layer continuously, leaving myoepithelial cells and single or clustered "luminal cells" unstained. In most advanced cases, variable numbers of K19 KA4-positive cells could be found among the intraluminal cell proliferations. Compared to the peripherally located K19 mAb KA4-positive cells, the intraluminal cells seemed to be small and sometimes even spindle-shaped (Fig. 4). Double-label immunofluorescence showed negative staining for K8/18 TPA-Ab and K19 mAb KA4 in the K5/14 mAb KA1-positive cells and vice versa (Fig. 4), although this reaction pattern was not found exclusively and intermediate immunophenotypes were also seen (Fig. 4). α-sm actin mAb strongly reacted as a continuous layer with the basal myoepithelial cells, while the intraluminal cells showed no reaction. Collagen IV and laminin mAbs yielded a bright reaction with the basal lamina of epitheliotic lesions and capillaries (Fig. 4).

In 22 of the intraductal carcinomas we found a strong and identical reaction for K19 mAb KA4 and K8/18 Ab TPA (Fig. 5). In contrast, K5/14 mAb KA1 decorated most of the basal myoepithelial cells, usually with a few unremarkable luminal cells (Fig. 5). α-sm actin mAb gave an almost identical immunoreaction as K5/14 mAb KA1 and often these two immuno-staining pat-

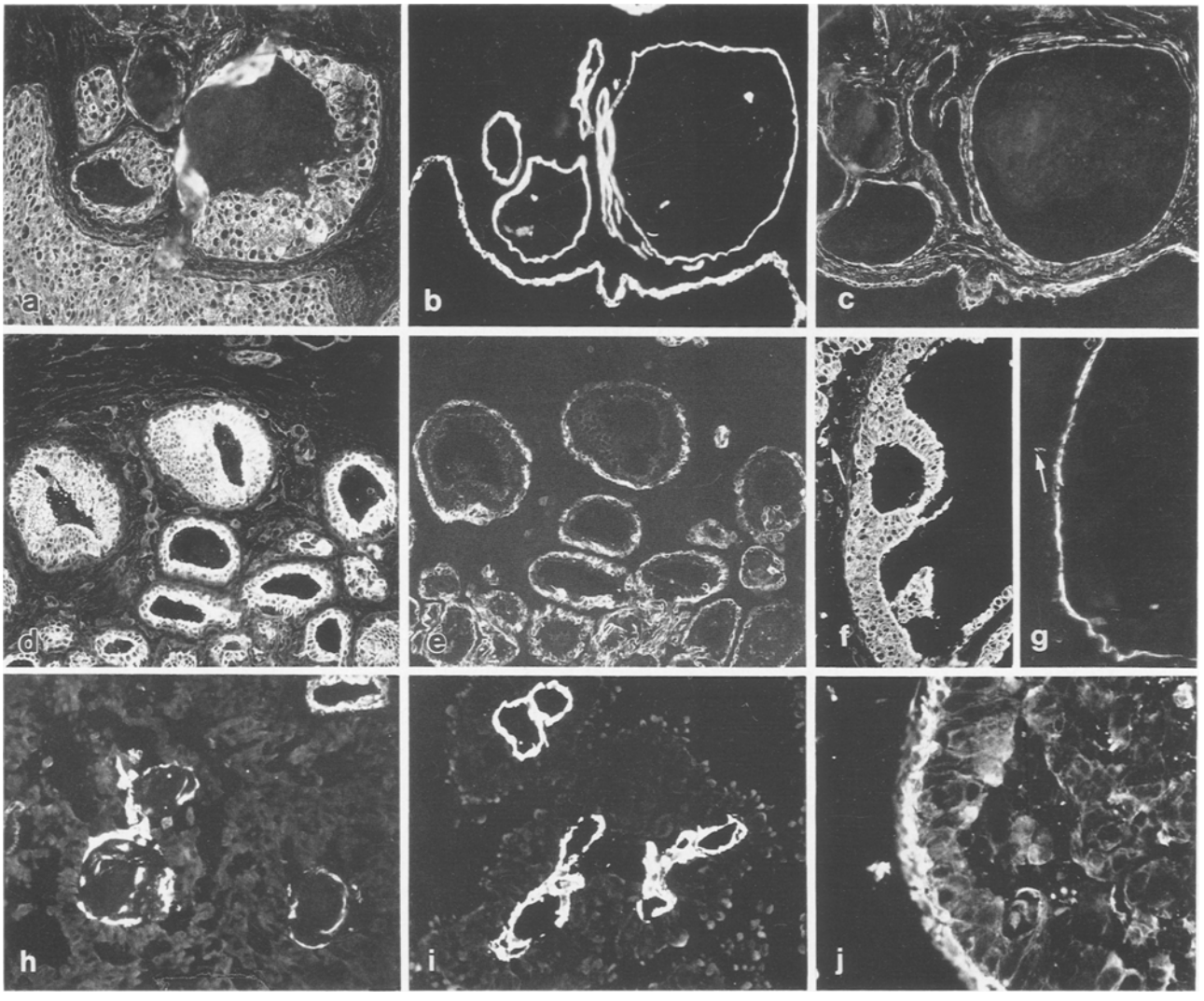

Fig. 5. Ductal carcinoma in situ, lobular cancerization, and clinging carcinoma. **a–c** Step section of ductal carcinoma in situ, immunostained with K8/18 Ab TPA (**a**), K5/14 mAb KA1 (**b**) and actin mAb (**c**). Note intensive staining of neoplastic luminal cells with K8/18, while myoepithelial cells are stained with K5/14 and actin. The neoplastic cells are non-reactive with K5/14 mAb. **d, e** Step section of lobular cancerization immunostaining with K8/18 Ab TPA (**d**) and K5/14 mAb KA1 (**e**). Note the same staining pattern as in ductal carcinoma in situ. ×350. **f, g** Step section of clinging carcinoma stained with K8/18 Ab TPA (**f**) and K5/14 mAb KA1 (**g**) with identical staining pattern. Note in (**f**) a small portion of an invasive ductal carcinoma that shows no myoepithelial layer (**g**). ×400. **h, i** Papillary carcinoma in situ stained with K5/14 mAb KA1 (**h**) and actin mAb (**i**) with staining of myoepithelial cells in a papillary stalk. ×300. **j** Ductal carcinoma in situ immunostained with K5/14 mAb KA1. Note intensive staining of myoepithelial cells and weak reaction of neoplastic intraluminal cells. ×500

terns could not be distinguished. Collagen IV and laminin mAbs always showed a continuous basal lamina surrounding the neoplastic cells (Fig. 5b). In two cases of papillary type of carcinoma in situ a pattern basically similar to that seen in normal ductal carcinoma was recorded with all Abs used, with the exception of K5/14 mAb KA1 and α-sm actin mAb. These reacted in a significantly smaller, albeit variable number of myoepithelial cells (Fig. 5h–i). Interestingly, all of 6 cases of lobular cancerization/clinging carcinoma showed an identical immunophenotype (Fig. 5d–g).

In a minority of ductal in situ carcinomas (4/26; 15%) a different immunophenotype was observed with K5/14 KA1 mAb-positivity. It is noteworthy that the tumour cells showed weaker reaction than the surrounding myoepithelial cells (Fig. 5j).

Discussion

The morphological criteria for florid hyperplasia as used by Page and Anderson (1987) and Fechner and Mills (1990) seem to be identical to those for epitheliosis used by Azzopardi (1979). It is defined by an intraluminal epithelial proliferation of polygonal, oval to spindle-shaped cells with a swirling or subtle streaming pattern, showing irregular collapsible (fenestrated) spaces. Recent immunohistochemical studies with staining for bas-

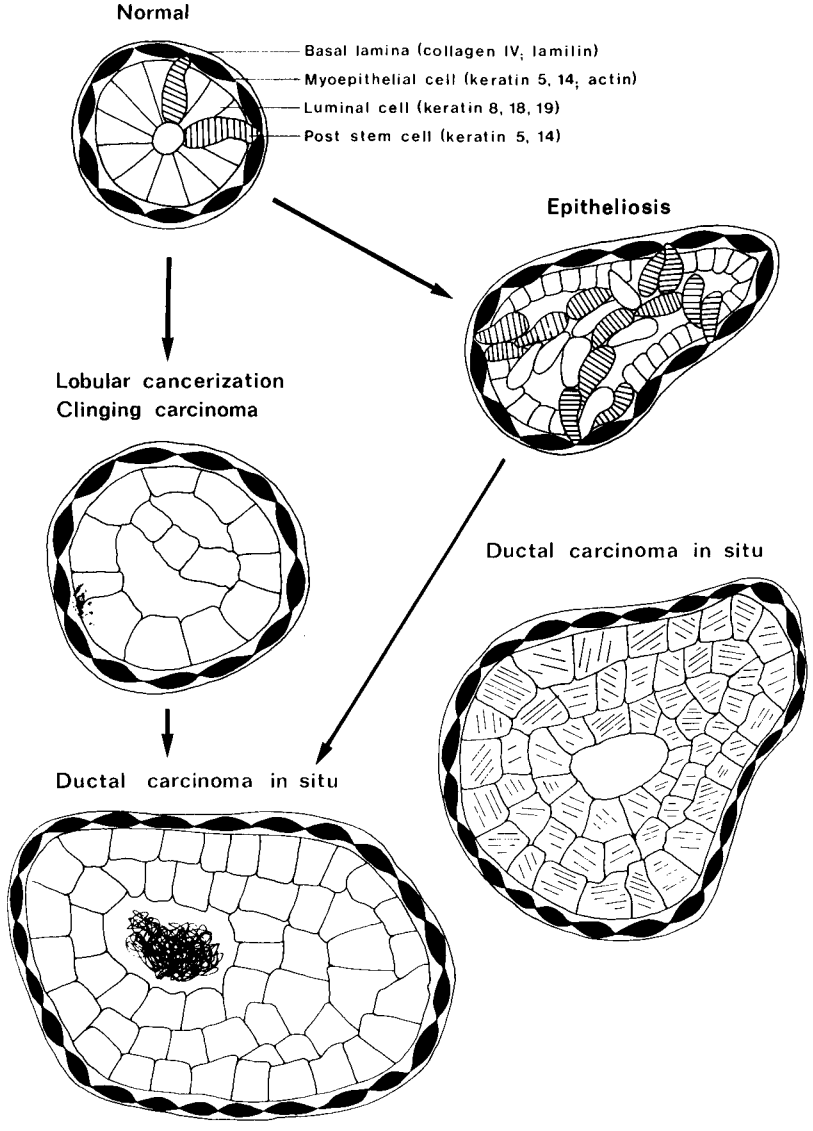

Fig. 6. Schematic illustration of our most important immunohistochemical findings and their conceptual implications for the development of ductal carcinoma in situ (for details see text)

al (myoepithelial) keratins 5/14 and simple keratins 8/18/19 disclosed the generally biphasic appearance of proliferating cells of epitheliosis (Jarasch et al. 1988). Additional immunohistochemical stainings by Raju et al. (1990) and by ourselves in a recent study (Böcker et al. 1992) clearly showed that these luminal cells with the keratin 5/14 pattern lack the myoepithelial differentiation marker actin.

As far as keratin 5/14-positive cells in the normal breast are concerned, we and others have identified two subsets of cells (compare Fig. 6). The first is the myoepithelial cell which expresses in addition to keratin 5/14 α-sm-actin as the most important differentiation antigen, vimentin and in a minor subpopulation glial fibrillary acidic protein, nerve growth factor receptor and common acute lymphoblastic leukaemia antigen (Viale et al. 1991; Gould et al. 1990; Gusterson 1986). The second subset of K5/14-positive cells comprises luminal cells that are negative for almost all differentiation antigens, including actin. Only extremely rarely did K5/14-positive cells exhibit a positive reaction for simple keratins 8/18/19.

By analogy with the situation in the epidermis, where 10% of basal K5/14-positive layer cells are thought to be stem cells or transit amplifying (post-stem cells) (Potten 1979) one may speculate that in the breast the K5/14-positive cells in a luminal position might comprise committed post-stem cells or cells in transition to luminal-type cells, as suggested by Purkis et al. (1990). Against this background, there seems to be some logical reason to believe that epitheliosis represents a proliferation of post-stem cells with a gradual differentiation to luminal cells. This suggestion is based on the observation of early epitheliotic lesions which nearly always disclose focal proliferation of K5/14-positive cells with communication of some of these cells to the basal layer. In more advanced lesions occasional cells with both basal K5/14 and luminal keratins 8/18/19 are found, a finding consistent with the transformational state to luminal cells. Supporting data are derived from the immunohistologi-

cal evaluation of adenotic lesions, which in comparison with normal glands show an increased number of K5/14-positive cells in a luminal position. Thus we conclude that epitheliosis represents an epithelial hyperplasia of the breast imitating the physiological regeneration of luminal breast epithelium.

Ductal carcinoma in situ, however, represents a proliferation of cells with a purely luminal keratin 8/18/19 expression (Fig. 5) in 85% of our cases. In only 15%, there is a very faint basal keratin 5/14 expression, which is very weak when compared with the external myoepithelial cells. Immunophenotypically, lobular cancerizations and clinging carcinomas, which Azzopardi (1979) believes to be early stages of ductal carcinomas in situ, reveal the same immunophenotypic behaviour as typical ductal carcinoma in situ.

In our opinion, our results suggest that clinging carcinoma/lobular cancerization and ductal carcinoma in situ display the same set of phenotypic traits (Fig. 6), a finding conistent with a de novo carcinogenesis as suggested by Azzopardi (1979). Nevertheless, there are some indications that a ductal carcinoma in situ may also develop in an epitheliotic lesion (Fig. 6). However, from our own preliminary results this route of carcinogenesis seems to be rare.

Some earlier studies (Page et al. 1978; Dupont and Page 1985) have correlated a higher cancer risk of patients with epitheliosis when compared with those with scleradenosis and adenosis. This is not surprising in view of the experimental data of Russo and Russo showing (1980) that more differentiated breasts are less prone to cancer, and of our own study, revealing different immunohistochemical patterns of differentiation in both lesions with a higher maturation in scleradenosis.

Although the primary objective of this study was to assess the histogenetic relationship of lobular cancerization/clinging carcinoma, ductal carcinoma in situ and epitheliosis, we also sought to assess the utility of immunohistochemistry in differential diagnosis. Staining for keratins 5/14 and 8/18/19 accentuated the biphasic appearance of epitheliosis and the monophasic proliferation of lobular cancerization, clinging carcinoma and ductal carcinoma in situ. This approach may thus be useful in distinguishing these lesions, especially the early in situ carcinomas. In routine pathology, however, careful morphological examination should suffice for proper diagnosis in most cases (see Azzopardi 1979). Further immunohistochemical evaluation of lesions that are summarized, for instance, under the term of atypical ductal hyperplasia (Azzopardi 1979; Page and Anderson 1987; Fechner and Mills 1990) will give us more information about the rare transformation process of epitheliosis to cancer.

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