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Adenomyoepithelial adenosis and low-grade malignant adenomyoepithelioma of the breast

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Summary. Adenomyoepithelial adenosis of the breast is a form of adenosis not previously described. It is similar in several ways to microglandular adenosis, but one significant difference is the presence of myoepithelial cells. The present case originated as adenomyoepithelial adenosis in a 46-year-old woman. In the course of 18 years it proliferated and changed into a low-grade malignant adenomyoepithelioma. Electron microscopy confirmed the presence of myoepithelial cells in the adenosis, and immuno-histochemical study demonstrated cells containing actin (representing myoepithelial cells) in the adenosis as well as in the adenomyoepithelioma.

Key words: Breast – Adenosis – Myoepithelium – Myoepithelioma

Hyperplasia of myoepithelial cells is encountered in many benign conditions in the breast (Hamperl 1970), but it is rarely the main component of a tumour (Gaudier et al. 1931; Hamperl 1970; Toth 1977; Bässler 1978; Azzopardi 1979; Erlandson and Rosen 1982; McClure et al. 1982; Zarbo and Oberman 1983). Adenosis very similar in appearance to the fairly rare microglandular adenosis but with widespread myoepithelial cell proliferation does not appear to have been described previously. We, therefore report one such case which proliferated for 18 years and showed transition into low-grade malignant adenomyoepithelioma.

Case report

In April 1962 a 46-year-old woman had an approx. 2 cm large piece of tissue removed from the upper lateral quadrant of the right breast. The morphological changes were interpreted as "breast tissue with adenomatous hyperplasia of a type which could not be accurately classified". A recurrence, about 1 cm, in December of the same year exhibited a "peculiar adenoma with a somewhat haphazard mixture of the glandular elements".

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During the subsequent years there was, periodically, a palpalbe mass in the upper lateral quadrant of the right breast. Mammography in 1968, 1970, 1971, and 1976 showed non-specific density of varying size.

In December 1977 mammography showed definite progression. Now, there were several, small, well-defined masses in the upper lateral quadrant. Two pieces of tissue were excised, measuring in all 5 × 4 × 3 cm. The larger specimen contained a firm area measuring 10 mm. On the basis of Hamperl's studies from 1970 on myoepithelial cells in the breast, the tumour-like infiltrate was interpreted as an adenomyoepithelioma, without evidence of malignancy. In early 1978 the patient could again feel a mass at the biopsy site, but did not consult her doctor until April 1980. At that time, mammography exhibited an approx. 1 cm irregular tumourous infiltration deep to the old scar. A segmental resection of 9 × 5 × 3 cm was performed. The cut surface showed nodular adipose tissue and an 8 mm greyish-yellow, firm tumourous infiltration.

Microscopic examination revealed, in principle, the same changes as in the 2 previous biopsies, but because of accentuated proliferations and the tendency to recurrence the tumour was interpreted as a low-grade malignant adenomyoepithelioma.

The patient has attended annual follow-up, including clinical investigation and mammography, most recently in August 1983, without signs of recurrence. The left breast has been normal on all occasions.

Material and methods

All tissue specimens have been fixed in a 4% formaldehyde solution, embedded in paraffin, cut into 4–6 μ sections, and stained with haematoxylin-eosin, PAS, and alcian blue.

In August 1983 all biopsies were stained by the immunoperoxidase method for actin.

From paraffin-embedded tissue 6 μm thick sections were cut, deparaffinized with xylene and alcohol, treated with 0.5% H_2O_2 in methanol and a 0.05% trypsin solution. After rinsing in phosphate-buffered saline (PBS), the sections were incubated with porcine serum at room temperature. This was followed by incubation with specific antibody to smooth muscle actin (from rabbit, titre 1:40). After another rinsing in PBS, the sections were incubated with peroxidase-bound anti-rabbit immunoglobulin, rinsed in PBS, stained with carbazol, anew rinsed in distilled water, and counterstained with Mayer haematoxylin. (Positive and negative controls were used).

Tissue for electron microscopy was cut from formalin-fixed material, post-fixed for one h. at room temperature in cacodylate-buffered 1% osmium tetroxide, dehydrated in ethanol, and embedded in Epon. Semi-thin sections for light microscopic orientation were stained with toluidine blue. Ultra-thin sections were mounted on Formwar-coated copper grids and stained with uranyl acetate and lead citrate.

Light microscopy

All specimens exhibited fundamentally the appearance of adenosis, consisting of multifocally, disorderly arranged glands of slightly varying shape and size (Figs. 1 and 2). In places the glandular epithelium was flattened, cuboidal, in other places was simple columnar. Elsewhere there was a peripheral layer of flattened cells and focal squamous epithelial metaplasia. In general, the cytoplasm was clear, but in places eosinophilic, and there were foci of luminal snouts. Several glands, moreover, exhibited peripheral, localized proliferation of uniform cells with a pale cytoplasm (Fig. 3). A few glandular lumina contained eosinophilic, PAS-positive material. The luminal part of the glandular epithelium was in places PAS-positive, but all the pale cells were PAS-negative.

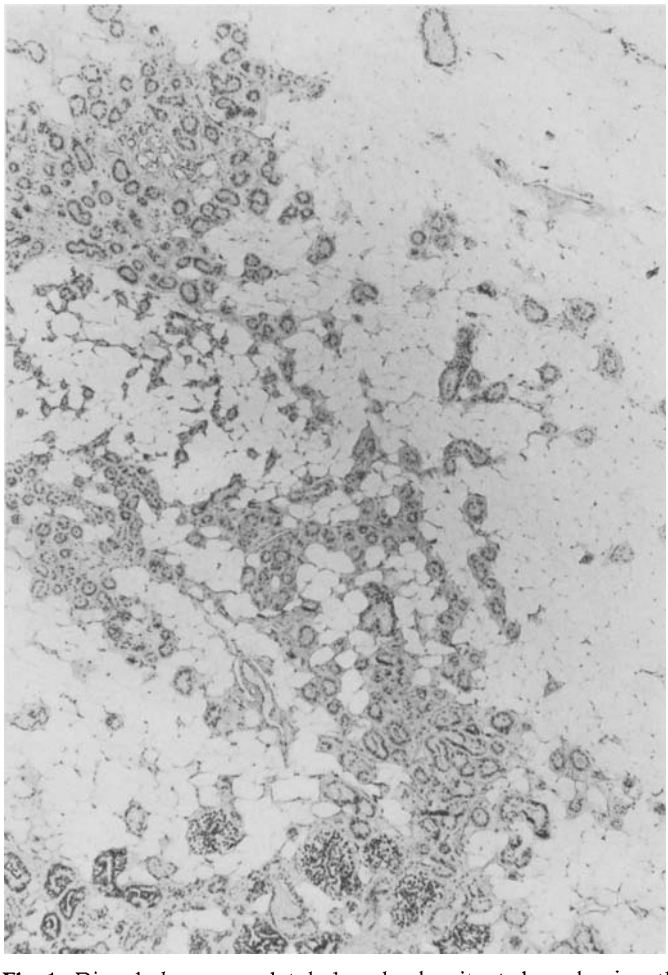

Fig. 1. Disorderly arranged tubular glands, situated predominantly in adipose tissue. H & E ×25

Sections from the tumour-like infiltrates in the last three biopsies (from 1962, 1977, and 1980) showed ill-defined tumour tissue made up of densely arranged glands of varying size and of fundamentally the same appearance as in the surrounding adenosis (Fig. 4). Within the infiltrates there were, in places, slightly dilated glands lined with a simple layer of apocrine epithelium. Cellular proliferation was most pronounced in the biopsy from 1980 in which there was also intraluminal, trabecular epithelial bridging, but no cribriform structure and no necroses (Fig. 5). In the sparse stroma there were small areas of adipose tissue, but no myxoid areas, cartilage, or bony tissue and no elastosis or microcalcifications.

In all specimens there were smooth transitions between tumour infiltrates and the surrounding adenosis (Fig. 6).

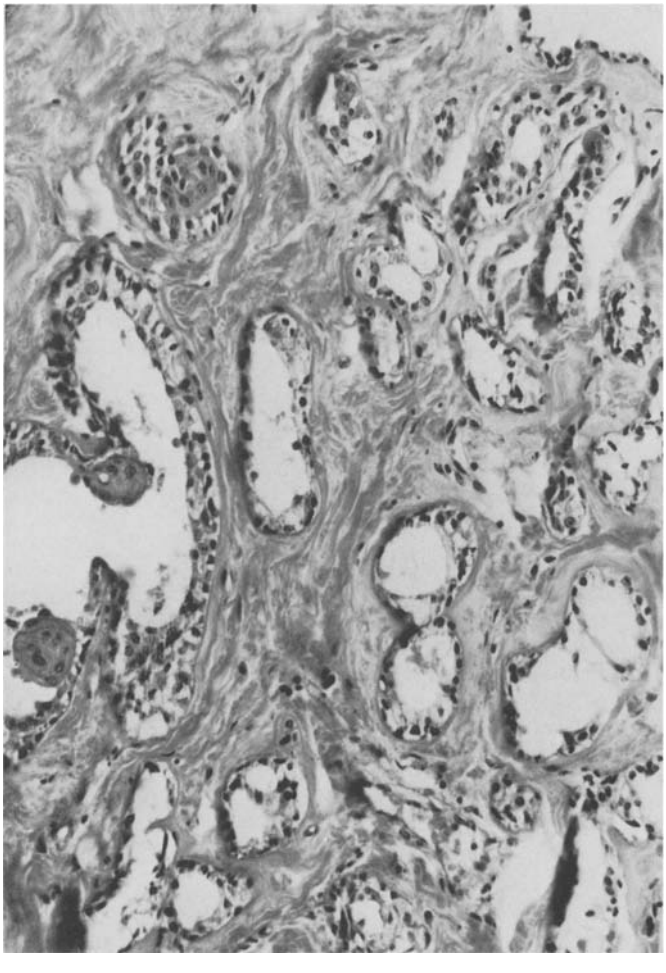

Fig. 2. Glands of varying size with focal squamous epithelial metaplasia in fairly acelluar, fibrous stroma. H & E ×100

Immuno-histochemistry

Anti-actin staining was positive at the site of the peripherally localized cells in most of the adenosis areas in all biopsies and showed a varying intensity of positivity in the proliferating pale cells in the tumour areas (Fig. 7).

Electron microscopy

The tubules of the adenosis were surrounded by a basal lamina and had a centrally placed lumen. Epithelial cells with few microvilli at the free margin bordered the lumen. At the apical boundaries adjacent epithelial cells were united by tight junctions, and along the lateral cell border desmo-

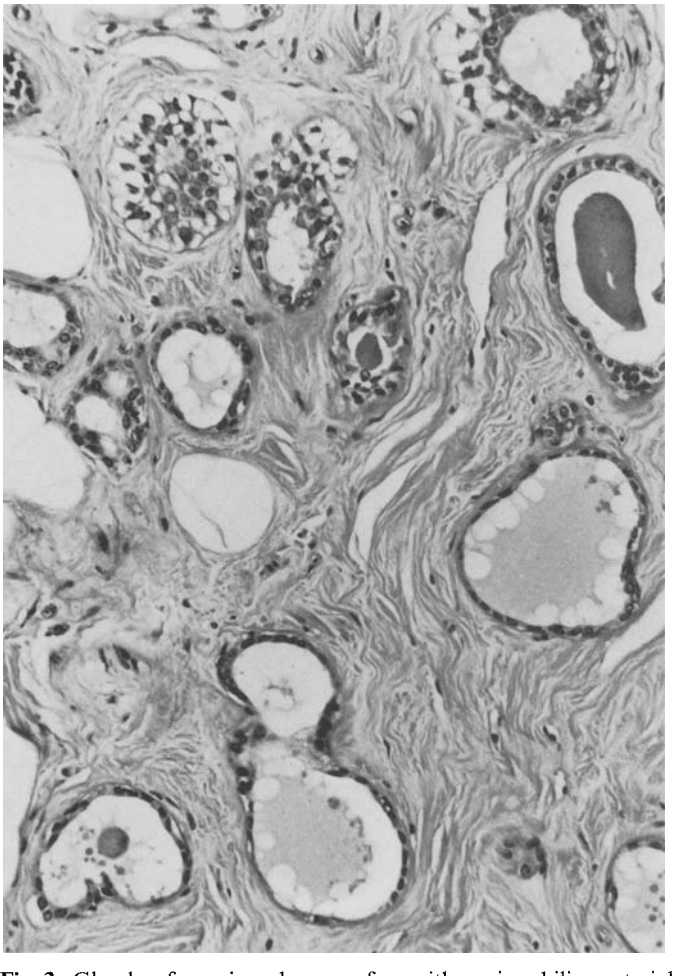

Fig. 3. Glands of varying shape, a few with eosinophilic material in the lumina. In three of the glands peripheral proliferation of pale cells, in part partially and in part throughout the circumference, occluding the glandular lumen. Stroma fairly acellular and fibrous. H & E ×100

somes were seen. Along the epithelial side of the basal lamina there were many myoepithelial cells (Fig. 8), showing numerous microfilaments with dense bodies in the cytoplasm. The microfilaments were attached to plaques at the cell membrane (Figs. 9 and 10).

Discussion

In four biopsies from the same area of the same breast taken at wide intervals – 18 years between the first and the most recent biopsy – we found an unusual adenosis resembling microglandular adenosis in many respects (Ro-

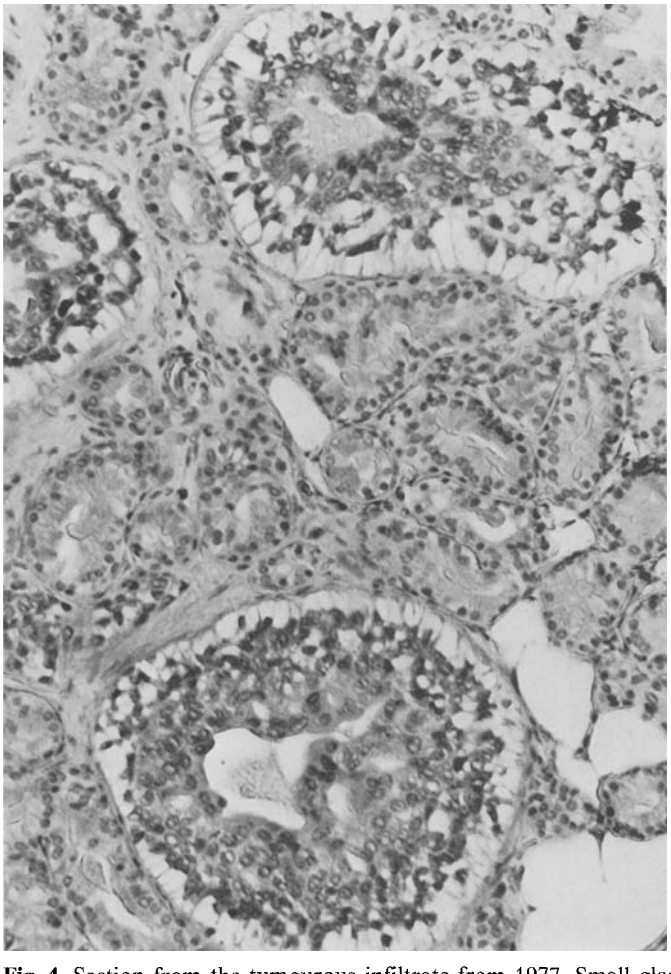

Fig. 4. Section from the tumourous infiltrate from 1977. Small glands with simple columnar epithelium are disorderly mixed with larger glands showing peripheral proliferation of uniform, pale cells and a luminal epithelium with eosinophilic cytoplasm. H & E ×250

sen 1978; Linell et al. 1980; McDivitt et al. 1982; Clement and Azzopardi 1983; Rosen 1983; Tavassoli and Norris 1983). The case has been referred to in Rosen's paper on microglandular adenosis (1983).

In 1983 all preparations from this case were revised. Electron microscopy and anti-actin examination disclosed changes which distinguish this adenosis in essential respects from typical microglandular adenosis: In several places the irregularly arranged glands were more varying in shape and size than described in microglandular adenosis, and in a number of places the glands were lined with simple, tall, pale columnar epithelium. In a number of the tubular glands there was an even transition from a simple layer of cells with eosinophilic, granular cytoplasm to cells with a clear cytoplasm resembling the "clear-cell" changes found by Barwick et al. in lobules and

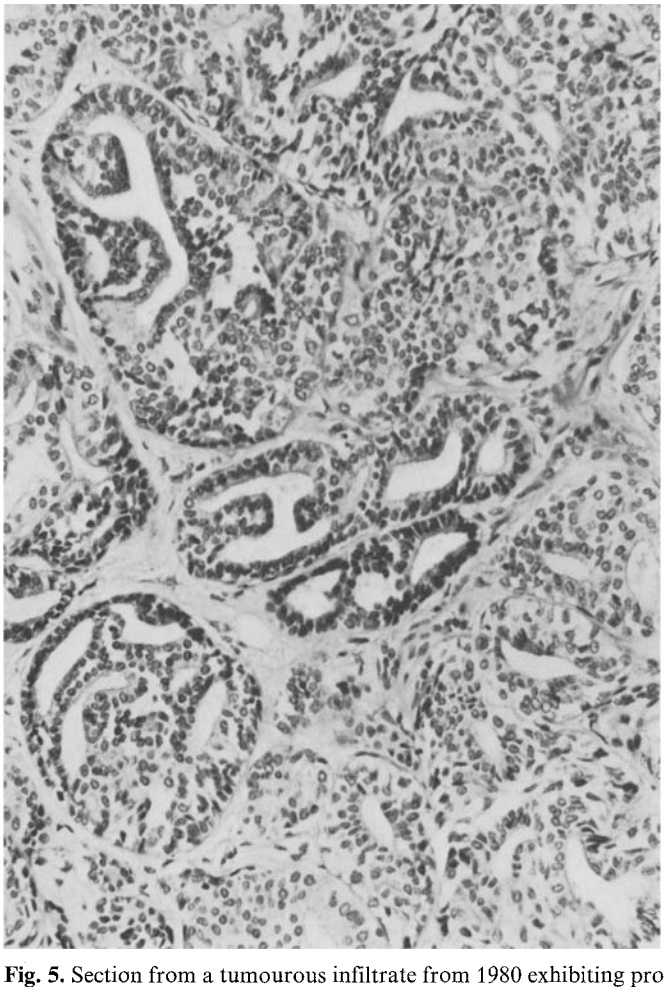

Fig. 5. Section from a tumourous infiltrate from 1980 exhibiting pronounced epithelial proliferations, focally with intraluminal bridging. In some glands solid proliferations of pale, uniform cells. H & E ×100

terminal ducts (1982). Barwick et al. (1982) observed these clear-cell changes partly in epithelium and partly in myoepithelium. Similar clear-cell changes have been described by Skorpil (1943) and by Theele and Bässler (1981) who call them metaplasia, whereas Hamperl (1970) interpreted similar changes as glycogen-filled myoepithelial cells.

In a number of glands there was a peripheral layer of cells, in some places flattened, but in others proliferating double or pseudostratified (Figs. 3 and 4) similar to the focal and partly to the diffuse myoepithelial cellular hyperplasia described by Hamperl (1970). The cytoplasm of these cells stained positively with anti-actin, indicating a myogenic origin. Electron microscopy also confirmed the occurrence of myoepithelium which is absent in microglandular adenosis (Clement and Azzopardi 1983; Rosen 1983).

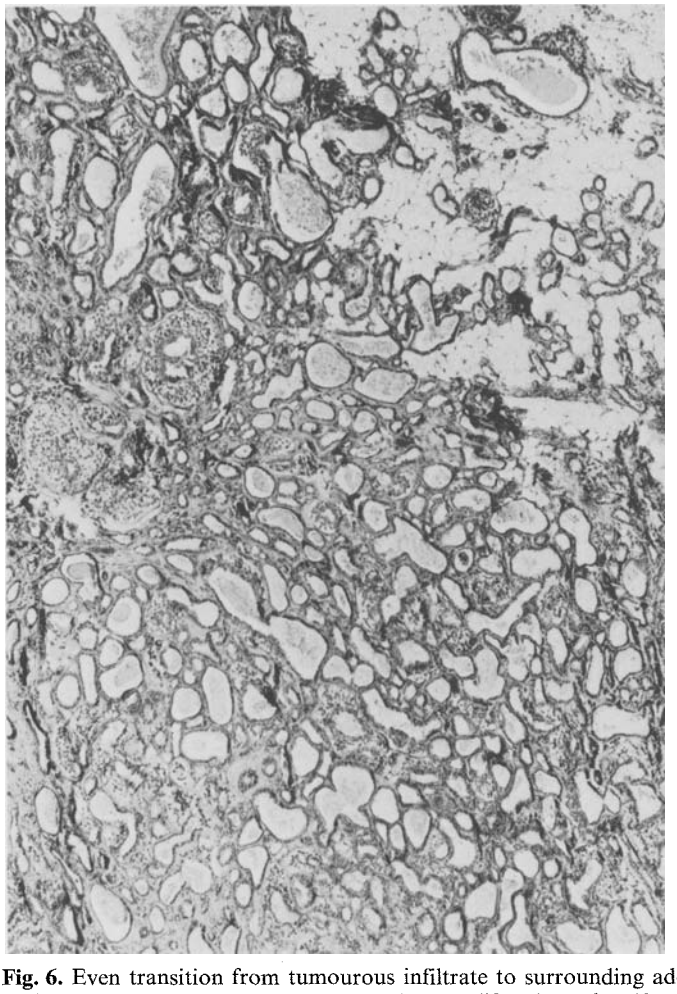

Fig. 6. Even transition from tumourous infiltrate to surrounding adenosis. In the tumourous infiltrate there is in several places marked proliferation of uniform, pale cells peripherally in the glands. H & E ×25

In some glands there was squamous-cell metaplasia, which has not been described in microglandular adenosis. In some areas the changes were reminiscent of tubular carcinoma, but the glands were not in a stellate pattern, there were few angular glands, no elastosis, and no foci of intraductal cribriform/micropapilliferous carcinoma (Rosen 1978; McDivitt et al. 1982). Unlike sclerosing adenosis, the present lesion was not of lobular structure.

We call this adenosis – which does not seem to have been described previously – *adenomyoepithelial adenosis*. In some areas it is morphologically compatible with microglandular adenosis which may co-exist with other adenoses (Rosen 1983).

In the biopsies from 1962, 1977, and 1980 there was an even transition

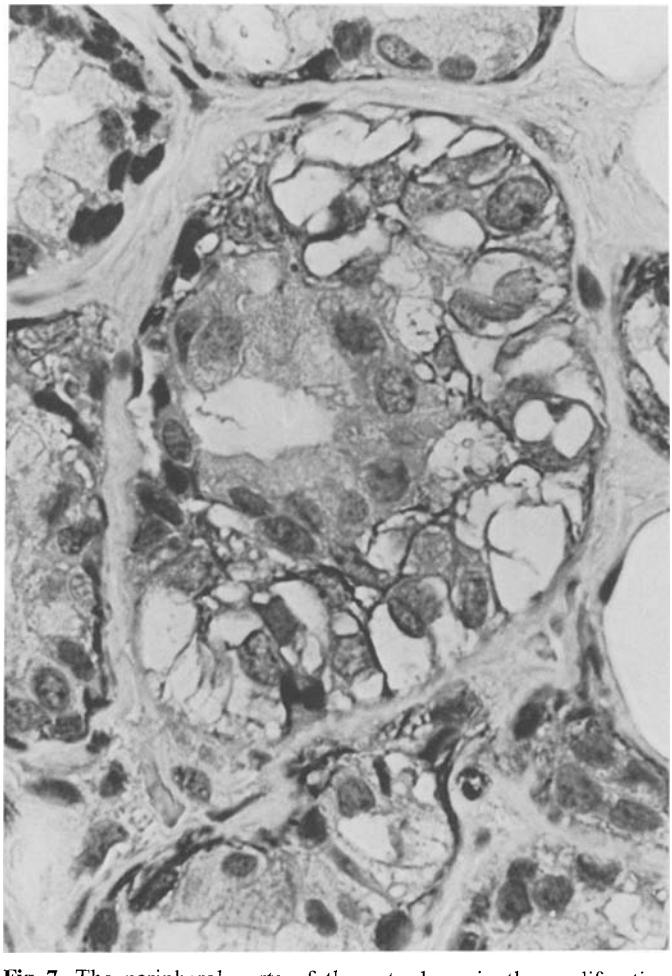

Fig. 7. The peripheral parts of the cytoplasm in the proliferating, pale cells in the central gland and the peripheral cells in the surrounding glands show positive anti-actin staining. ×400

from the adenosis to the more solid, tumour-like infiltrates which were made up of fundamentally the same elements as the adenosis. In some areas these tumourous infiltrates were reminiscent of glycogen-rich clear-cell carcinoma (Hull et al. 1981; Benish et al. 1983), but PAS-staining was negative. Myoepithelium may be seen in intraductal carcinomas as residual, normal myoepithelial cells (Sarkar and Kallenbach 1966; Murad and von Haam 1968; Bussolatti et al. 1980; Papotti et al. 1983), but not as proliferating, myoepithelial cells. Therefore, an intraductal carcinoma is not likely.

No oncocytic transformation of the peripheral proliferating cells was seen as described in oncocytic papilloma of the breast (Nielsen 1981). There were no proliferating spindle cells as in the few published cases of myoepithe-

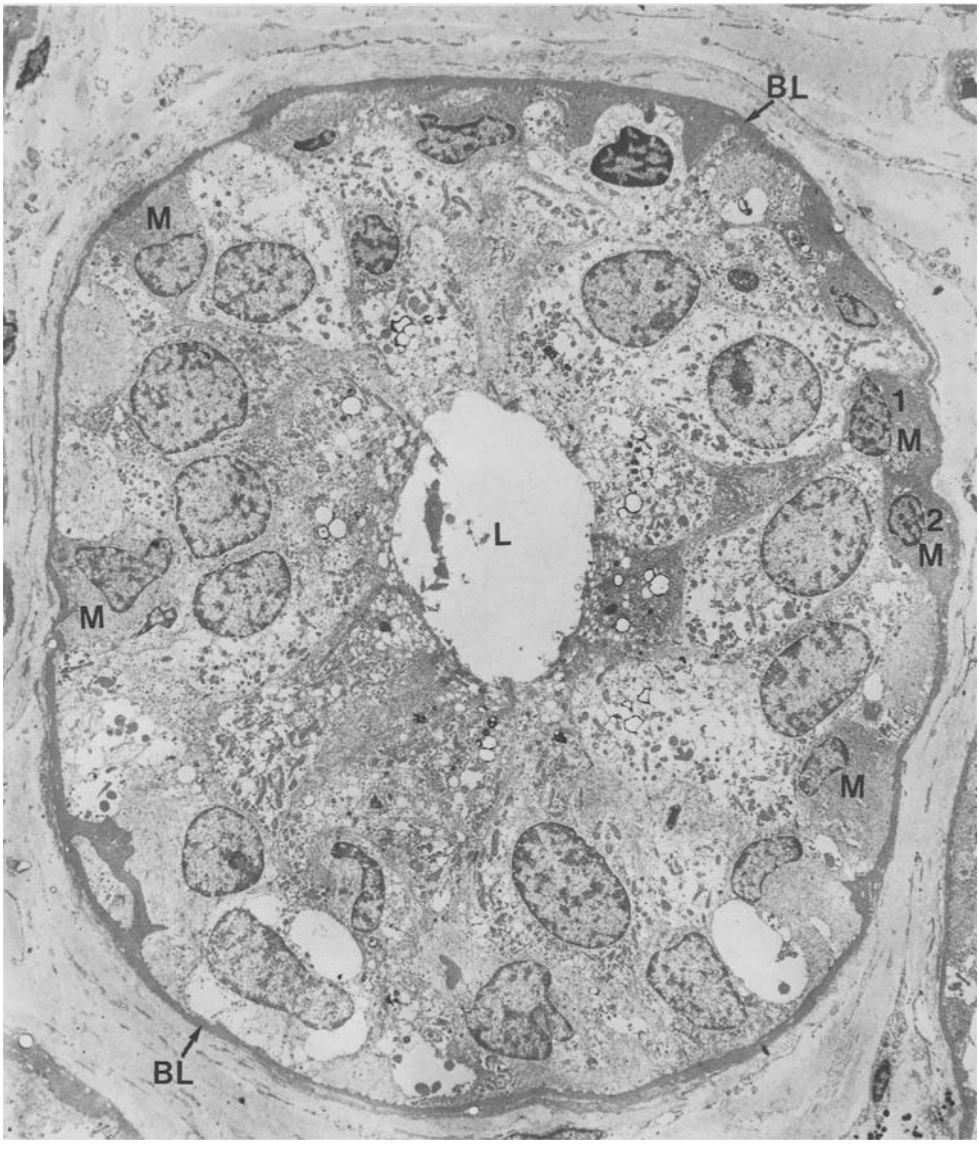

Fig. 8. Tubule with centrally placed lumen (*L*) and surrounded by a basal lamina (*BL*). Along the basal lamina myoepithelial cells (*M*). Those numbered 1 and 2 are illustrated at a higher magnification in Fig. 9. ×2,800

lioma in the breast (Gaudier et al. 1931; Toth 1977; Erlandson and Rosen 1982; Zarbo and Oberman 1983) and only a superficial similarity to the skin adnexa-like adenomas which have been found in the breast (Finck et al. 1968; Hertel et al. 1976).

The glandular elements in the major part of the three tumourous infiltrates consisted of two types of cell: peripherally proliferating myoepithelial

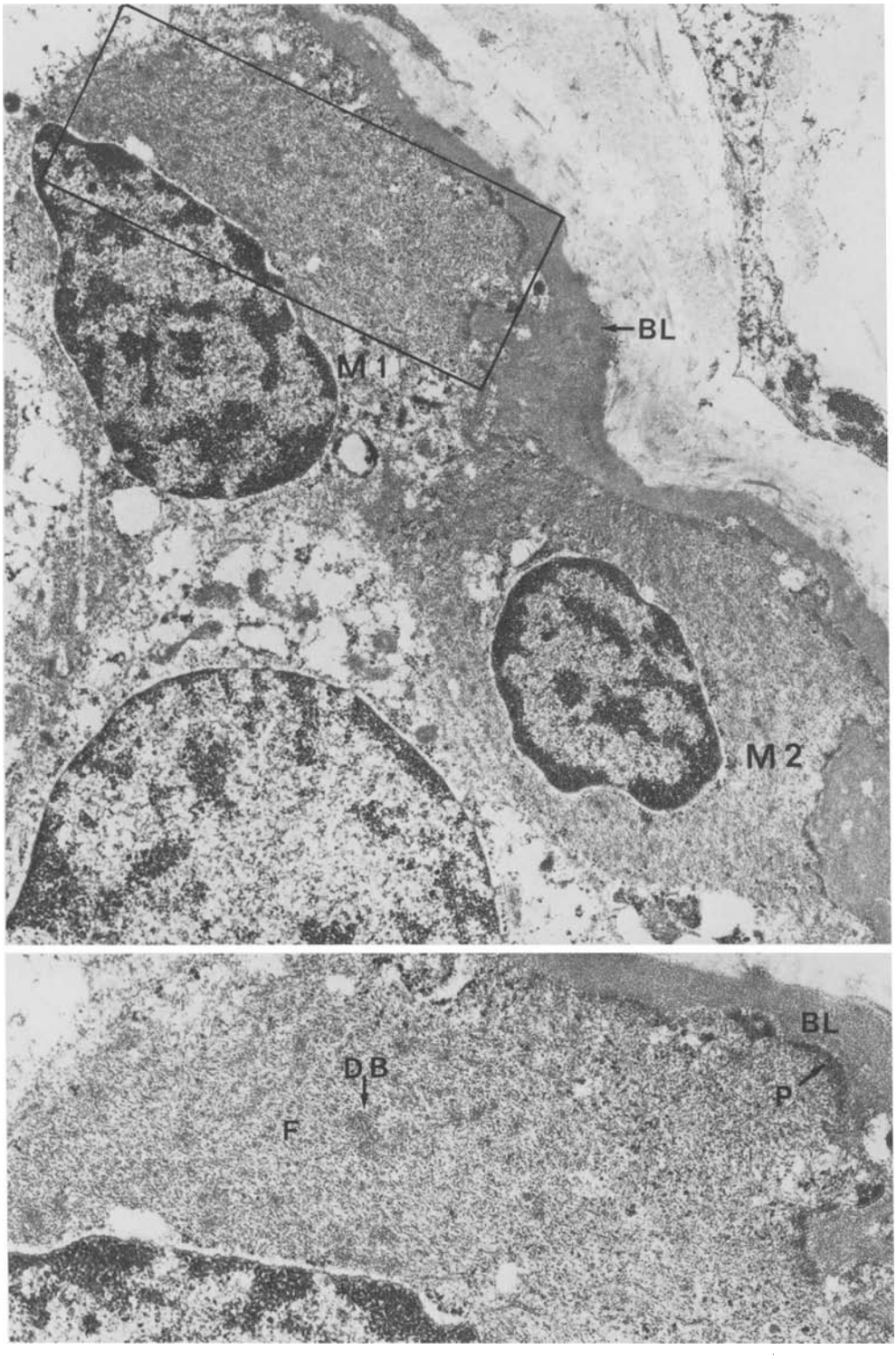

Fig. 9. Two myoepithelial cells resting on a thick fibrillar basal lamina (*BL*). ×15,000

Fig. 10. Boxed area from Fig. 9 illustrating microfilaments (*F*) with dense bodies (*DB*) in the cytoplasm of a myoepithelial cell. Along the plasma membrane attachment plaques (*P*) ×25,000

cells and luminally localized eosinophilic cuboidal and columnar cells. There was a marked similarity to clear-cell adenomas in the salivary glands (Thackray and Sobin 1972; Thackray and Lucas 1974), "mixed" salivary type adenoma of the human female breast (McClure et al. 1982), and adenomyoepithelioma of the breast (Hamperl 1970). Azzopardi JG (personal communication) and Linell F. (personal communication) agree concerning the similarity to adenomyoepithelioma. There were no mesenchymal components as in pleomorphic adenoma of the breast (Sheth et al. 1978; van der Walt and Rohlova 1982).

In the tumour infiltrate from 1980 there was marked epithelial and myoepithelial proliferation. The changes were interpreted as malignant, and there was great likeness to a case of malignant adenomyoepithelioma of the parotid gland illustrated by Azzopardi (1979).

Considering the even transition and the pronounced morphological similarities to the adenosis, the tumour infiltrates must be presumed to have arisen from it. It is difficult to make a statement concerning the degree of malignancy, but the case has been interpreted as a low-grade malignant adenomyoepithelioma and the patient has had no recurrence for 3 years after the most recent excisional biopsy.

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