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ORIGINAL ARTICLE

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Adenomyoepithelioma of the breast associated with low-grade adenosquamous and sarcomatoid carcinomas

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Abstract Six cases of invasive breast carcinoma with unusual morphological features are reported. The ages of the female patients ranged from 46 to 79 years (mean 60.5). All tumours had areas typical of an adenomyoepithelioma. In three cases adenomyoepithelioma gradually merged with low-grade adenosquamous carcinoma. In the other three patients a sarcomatoid carcinoma was associated with adenomyoepithelial areas. A common origin is proposed for these neoplasms, which extends the morphological spectrum of epi-myoepithelial cell tumours.

Key words Breast · Adenomyoepithelioma · Myoepithelium · Carcinoma

Introduction

Myoepithelial cells (ME) are a normal constituent of the mammary gland and occasionally give rise to hyperplastic and neoplastic lesions [11, 26]. Pure ME carcinomas have rarely been reported in the breast [2, 4, 7, 16, 22–24, 27]. In contrast, tumours, consisting of a proliferation of both epithelial cells (ECs) and ME are more frequently encountered and represent a spectrum of morphologically and biologically distinct tumours [1, 11]. Adenomyoepithelioma (AME) is included among the latter [1, 9, 13, 14, 19, 21, 31]. AME is a low-grade tumour; it can recur and, rarely, metastasize [14, 15, 28].

The purpose of the present paper is to report on six cases of AME associated with other types of carcinoma. These widen the spectrum of epi-myoepithelial tumours.

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Materials and methods

The cases were retrieved from the consultation files of two of us (V.E., J.L.P.). Tissues were formalin-fixed and routinely processed for paraffin. For each case 2–10 blocks were available (mean 4). Consecutive sections were cut from selected blocks. Immunostaining was performed according to the method described by Hsu et al. [12], slightly modified for streptavidin – biotin complex (Enzo). The sources and dilution of antibodies are reported in Table 1.

Results

Clinical data

The patients' clinical data are briefly summarized in Table 2. All were women, ranging in age from 46 to 79 years (mean 60.5). One of the patients had a family history of breast carcinoma (case 4). Three patients had undergone a previous ipsilateral biopsy for a palpable

Table 1 Sources and dilutions of the antibodies used (*M* monoclonal, *LWK* low-molecular-weight keratin, *HWK* high-molecular-weight keratin, *EMA* epithelial membrane antigen, *GCDFP-15* gross cystic disease fluid protein 15, *SM Actin* smooth muscle actin)

Antibody		Source	Dilution
LWK	M	Dako, MNF 116	1:100
HWK	M	Ortho Diagnostic System, EAB 903	1:200
EMA	M	Dako, E29	1:200
GCDFP-15	M	DBA, D6	1:500
SM Actin	M	Dako, 1A4	1:100

Table 2 Clinical data (*CA %* percentage of component A, *UOQ* Upper outer quadrant, *SA* subareolar region, *IIQ* Internal inferior quadrant, *R*, right, *L* left, *Q* quadrantectomy, *AxL* axillary dissection, *RM* radical mastectomy, *Lu* lumpectomy, *FU* follow up, *AW* alive and well, *AWD* alive with disease, *rec* recurrence, *CT* chemotherapy, *LuM* lung metastases)

Case no.	Sex	Age	Site	Size (cm)	CA%	Treatment	Follow up
1	F	46	UOQ-R	1.5	5	Q+AxL+CT	AW, 7 months
2	F	79	SA	2	30	RM	AW, 16 months
3	F	65	UOQ-L	2	30	RM+AxL	AW, 11 months
4	F	57	UOQ-R	4	10	RM+AxL	AW, 5 months
5	F	55	IIQ-R	2.5	50	RM	AW, 7 years
6	F	60	UOQ-L	4	50	Lu	Local rec 5 months AWD, 3 years, LuM

breast lesion, which proved to be fibrocystic changes in two (cases 4 and 5) and an intraductal papilloma in one (case 1).

Each of the six patients presented with a palbable breast lump that had rapidly increased in size in the months immediately before presentation. In four cases the nodules were located in the upper outer quadrant, in one in the internal inferior quadrant (case 5) and in the remaining patient (case 2) in a subareolar site. In three cases the tumour affected the right, and in two the left breast. In one case the laterality was not recorded. On the mammographs the tumours appeared as ill-defined densities; granular type calcifications were detected mammographically in one case (case 5). In one case (case 1), the mammography could not be evaluated because the surrounding tissues were too dense. Four patients underwent modified radical mastectomy and axillary dissection; in one case (case 1) quadrantectomy with axillary dissection was followed by chemotherapy. The lymph nodes were free of metastases in all these five patients, who are alive without disease 5 months to 7 years after surgery (mean 27 months). One patient (case 6) was treated by lumpectomy only. She developed a local recurrence after 5 months, which was treated by radical mastectomy and axillary dissection. The axillary lymph nodes were free of metastases. At the time of mastectomy chest radiography, liver echography, and bone scintigraphy failed to reveal any distant metastases. Nevertheless, 21 months after the first appearance of the tumour the patient developed multiple lung metastases. At present, 3 years after the lumpectomy, the patient is alive but has pulmonary metastases.

Pathology

Macroscopy

All six tumours had invasive margins. In cases 4 and 6 these were partially cystic. The tumours ranged from 1.5 to 6 cm (mean 2.3) in their greatest axis.

Histology

Each tumour consisted of two components. One was common to all cases (component A), while the other varied from case to case (component B).

The common component (component A) displayed features similar to those seen in AME, as previously described elsewhere [9, 14, 19, 27, 32]. Accordingly, the lesions consisted of nests or sheets of two cell types: spindle or cuboidal cells with clear cytoplasm surrounded and encircled cuboidal or columnar elements with eosinophilic cytoplasm (Figs. 1, 2). Nuclei were round to

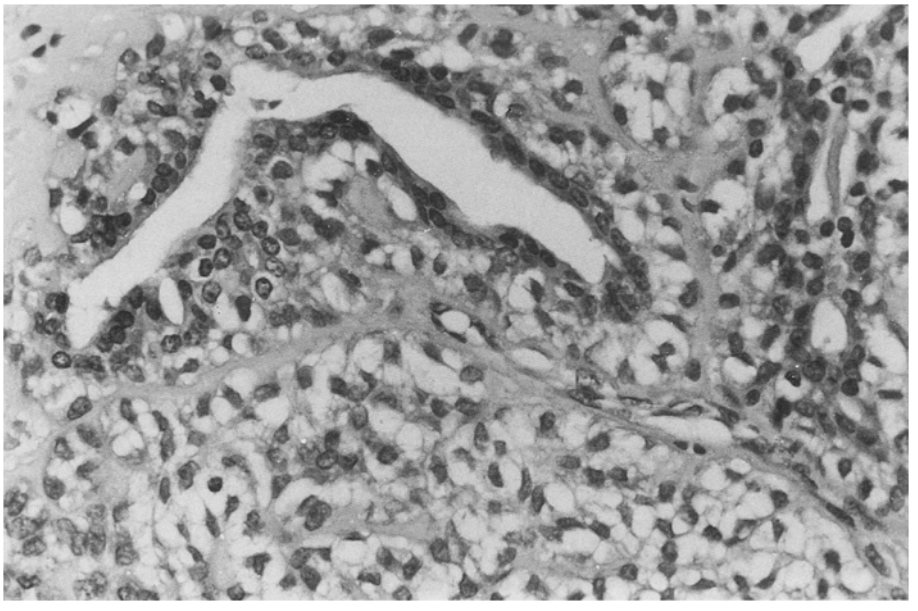

Fig. 1 Case 4: component A with typical features of AME. The outer cell layer is visible. HE, ×350

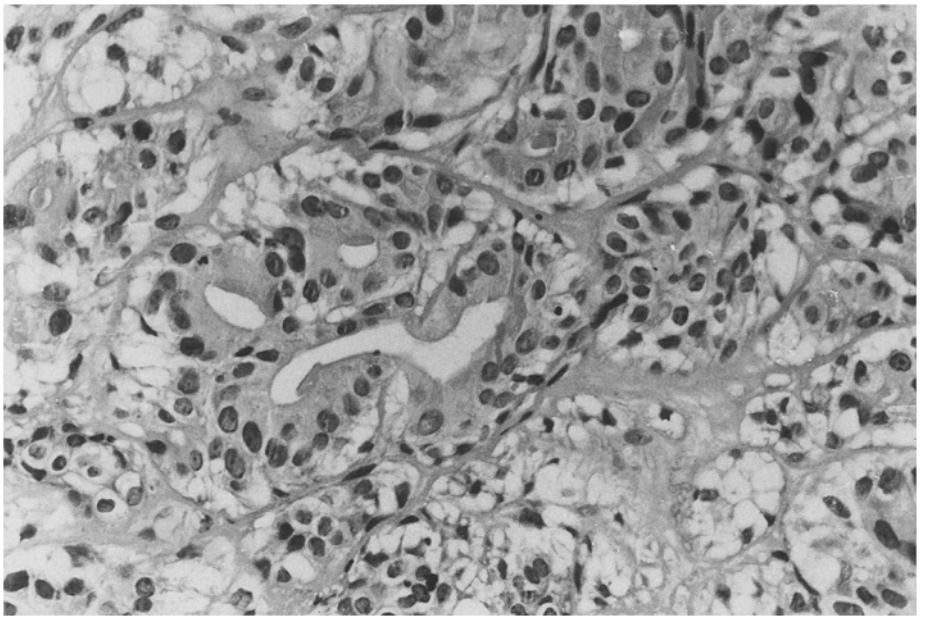

Fig. 2 Case 6: component A. The inner epithelium shows an apocrine phenotype. Nuclei are irregular. HE, ×350

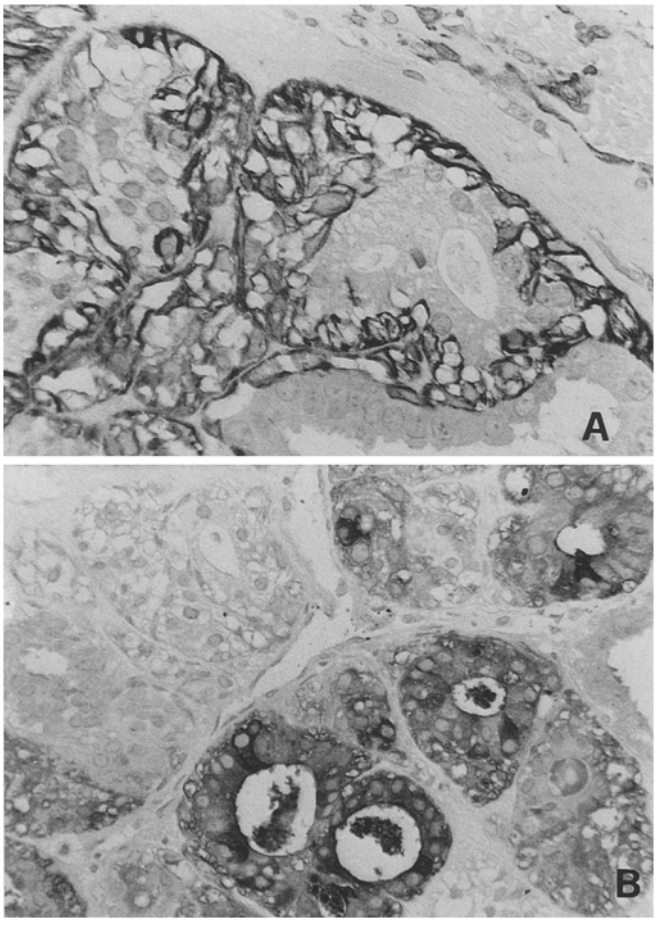

Fig. 3 **A** Case 3: numerous myoepithelial actin-rich cells outline the glands in the AME area. ABC peroxidase, ×250. **B** Case 6: the inner epithelium of numerous glands is positive with GCDFP-15 antiserum. ABC peroxidase, ×250

ovoid in most cases, and mitoses were rare. The pattern of growth was variable in different cases, being vaguely papillary, resembling a ductal adenoma, in case 1 to solid, as seen in case 6. In case 3 the clear cells showed marked nuclear pleomorphism. In all cases, the outer clear cell layer stained with actin (Fig. 3a). Low-weight keratins, EMA and GCDPF-15 antisera stained the eosinophilic cells (Fig. 3b).

This component was admixed in various proportions (5–50% of the complete lesion) with the second component (component B), which displayed variable features. In cases 1–3 AME areas were surrounded by elongated, angular tubules diffusely invading the breast stroma (Figs. 4, 5). These neoplastic glands consisted, like AME, of two cell types. The outer cell layer was made up of flattened actin-positive spindle cells (Fig. 6). The lumina of the tubules in these three cases were lined with cuboidal cells with eosinophilic, granular cytoplasm and round to avoid, regular nuclei. Squamous metaplasia was found (Fig. 7), in some glands. The squamous epithelium stained with high-molecular-weight keratin only (Fig. 8). In contrast, low-molecular-weight keratin and EMA decorated the luminal epithelial cells when squamoid pearls were not seen. GCDFP-15 antiserum gave consistently negative results in all cells of this second, component. Mitoses were rarely encountered. The stroma surrounding the tubules was "desmoplastic", being characterized by a proliferation of fibroblasts with plump, elongated, tortuous nuclei. Lymphocytes, either clumped or diffusely dispersed, were an additional feature. In case 3, single neoplastic cells were seen in the stroma. These cells had eosinophilic cytoplasm and irregular nuclei and reacted with both low- and high-molecular-weight keratin.

In case 2, component B showed a multinodular growth pattern within one quadrant. One of these foci blended with a small area (0.5 cm) of type B mucoid carcinoma [3].

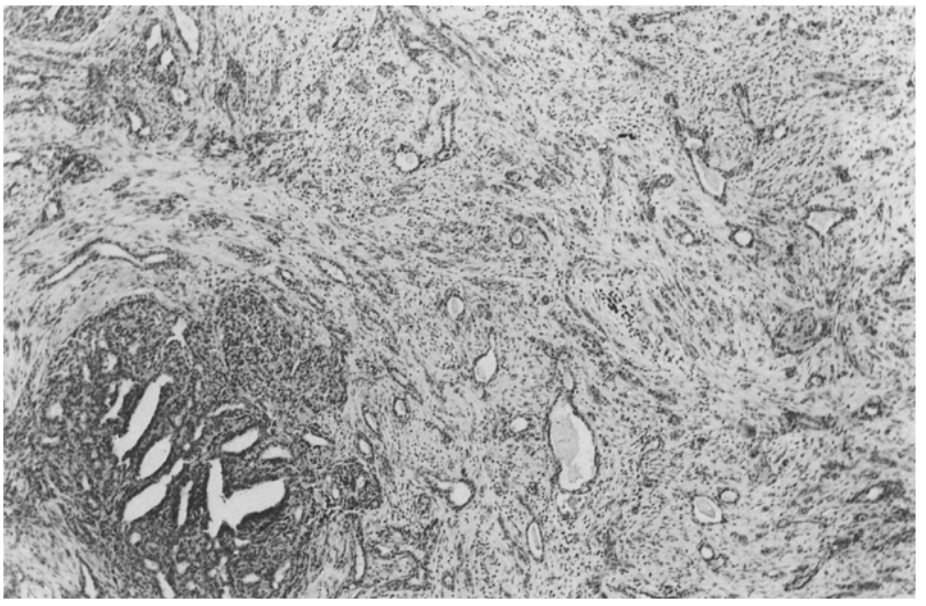

Fig. 4 Case 2: AME (*lower left*) blends with LGASC. Numerous glands and chords are intermigled together in a desmoplastic stroma. HE, ×100

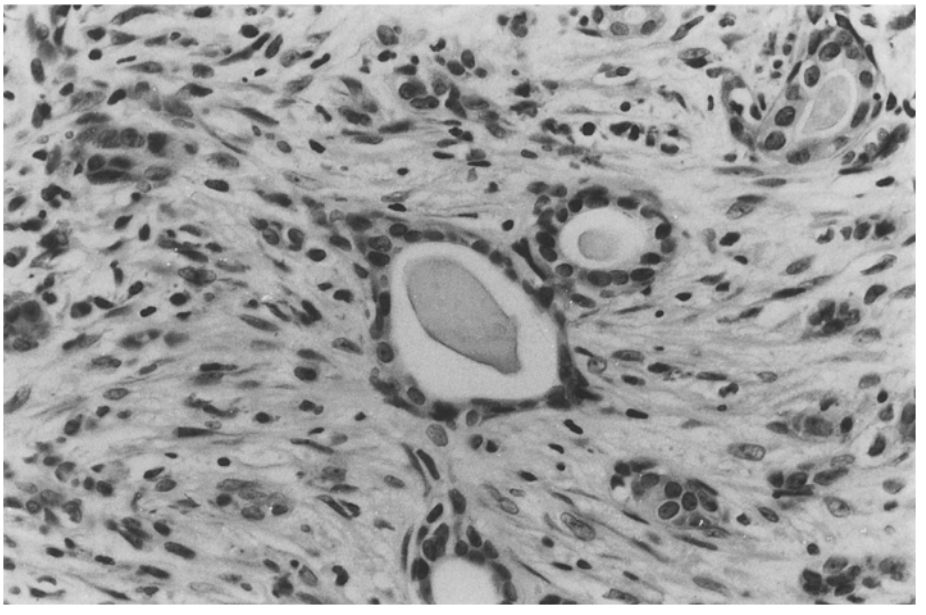

Fig. 5 Case 2: angular tubules lie within a desmoplastic stroma where numerous lymphocytes are visible. HE, ×250

In cases 4–6, the second component consisted of a neoplastic proliferation of atypical spindle cells (Fig. 9). These gradually merged among clustered epithelial sheets, showing squamous differentiation. In other areas the neoplastic elements invaded and dissected the stroma, forming vascular-like spaces (Figs. 10, 11) as previously described in acantholytic squamous cell carcinoma [8]. Mitoses, some of which were atypical, were frequent in all these three cases, and areas with necrosis were seen in case 6. Clusters of multinucleated osteoclast-like giant cells were present focally in case 4. Multinucleated neoplastic cells were seen in case 6. In this case, the primary tumour consisted of a pure AME proliferation. However, the recurrence showed, in addition, a second component formed of spindle-shaped neoplastic cells; these made up at least 50% of the lesion, having the features of an acantholytic squamous cell carcinoma. The neoplastic spindle cells reacted positively with high-molecular-weight keratin only; staining with any of the other antisera was consistently negative.

Discussion

All six tumours had features in common, consistent with those of AME as described by several authors [9, 14, 19, 26, 31]. These included an outer cell layer composed of cuboidal clear elements encircling secretory type glandular epithelium [31]. AME areas were intermingled, in the present cases, with two different patterns of neoplastic proliferations. One was characterized by angulated glands in a desmoplastic lymphocyte-rich stroma. The

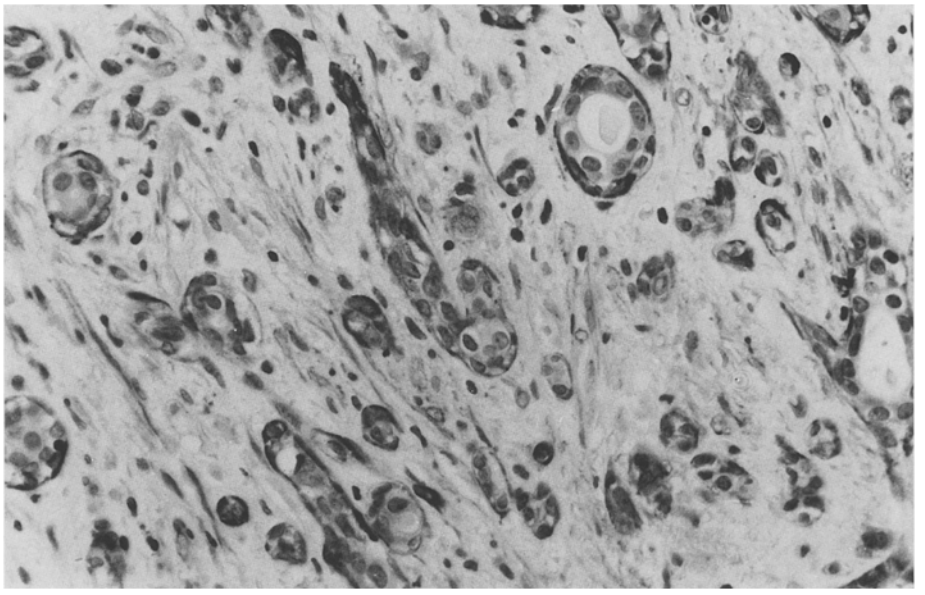

Fig. 6 Case 2: flattened myoepithelial cells constantly surround the neoplastic tubules and chords. ABC anti-actin peroxidase, ×250

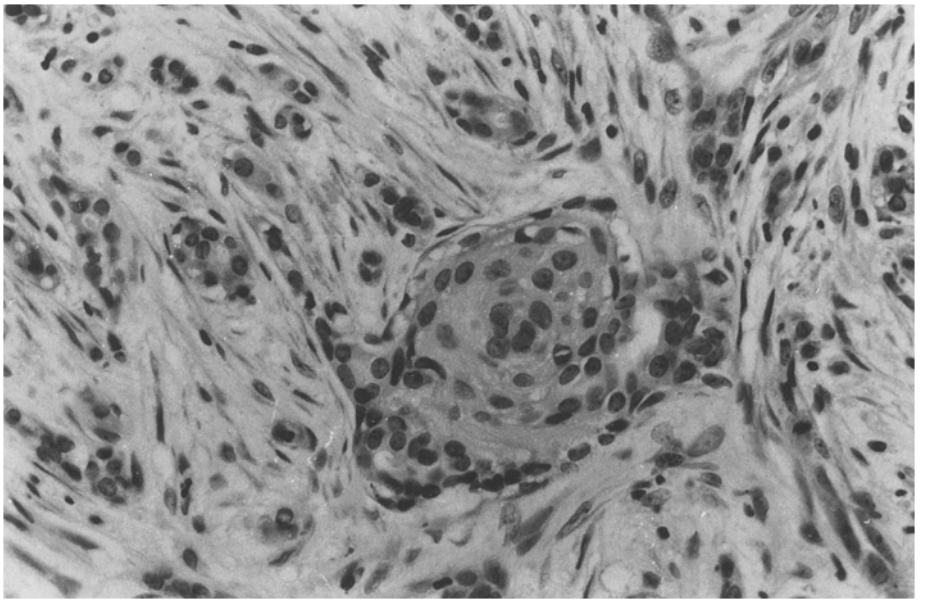

Fig. 7 Case 2: a squamous pearl fills the lumen of a gland. HE, ×250

glands had an outer myoepithelial layer encircling epithelial secretory cells; squamoid metaplasia was present in varying degrees. These features are similar to those described by Rosen et al. [20] as low-grade adenosquamous carcinoma (LGASC).

The outer myoepithelial cell layer demonstrated in the present cases has previously been mentioned in LGASC and illustrated with one photograph by Van Hoeven et al. [29]. Nevertheless, it was constantly present in the three cases reported here, and myoepithelial cells are visible outlining the tubules of the cases illustrated in the literature, as well as in the eight cases of pure LGASC obtained from the consultation files of one of us (V.E.). Therefore, it seems that LGASC and AME constitutes a notable exception to the widely accepted rule [1] that there is no myoepithelial cell outer layer in invasive carcinoma of the breast.

The other pattern associated with AME consisted in an atypical spindle cell proliferation. These cells stained positive with anti-high-molecular-weight keratin. Occasionally spaces of vascular appearance were formed, making these cases in all respects similar to a variant of sarcomatoid carcinoma previously described as acantholytic squamous cell carcinoma [8].

The combination of AME with LGASC and acantholytic squamous cell carcinoma might be coincidental. However, the close association and gradual transition of the different components makes this hypothesis difficult to accept. In addition, the association between AME and LGASC appears more than fortuitous, as in no fewer than three cases in the series reported by Van Hoeven et

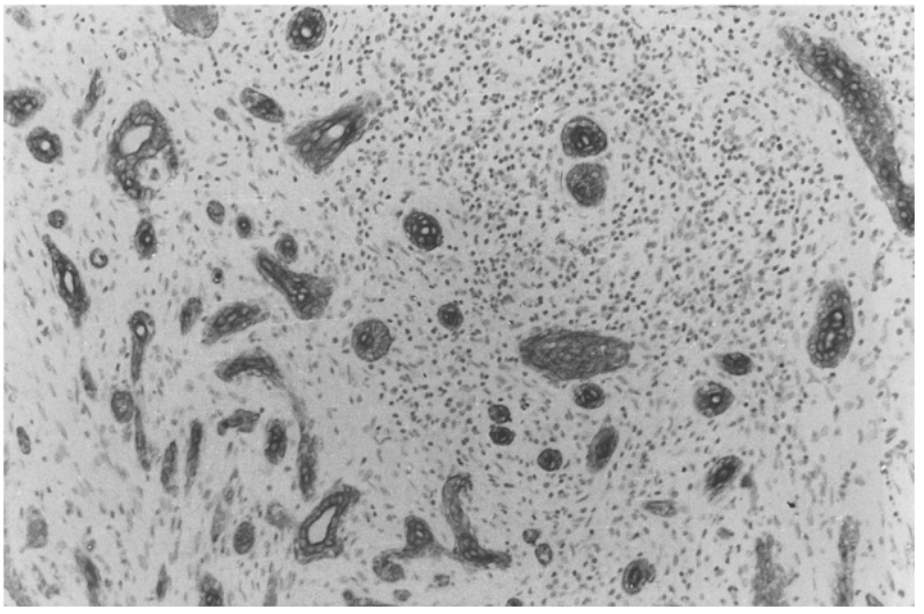

Fig. 8 The epithelium of the glands and chords reacts with anti-high molecular-weight keratin antiserum. ABC peroxidase, ×150

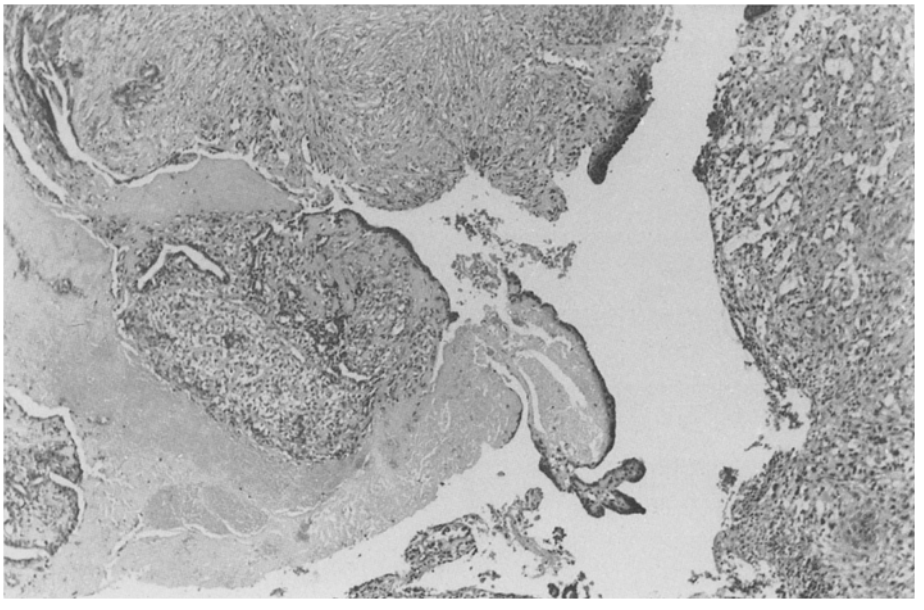

Fig. 9 Case 4: an AME area blends with a neoplastic proliferation of atypical spindle cells. HE, ×100

al. LGASC was intermingled with AME [29]. Furthermore, cases of AME intermingled with a spindle cell neoplastic proliferation very similar to that seen in our cases 4–6 have been previously reported [2, 5, 17, 18, 25, 29]. This probably indicates that the two components represent a single neoplastic process.

While LGASC is phenotypically close to AME, being formed by a dual epi-myoepithelial proliferation, acantholytic squamous cell sarcomatoid carcinoma appears more difficult to relate to an epi-myoepithelial origin. However, increasing evidence indicates involvement of myoepithelial cells in the genesis of sarcomatoid carcinomas [10]. The relationship between myoepithelial cells and squamous cell metaplasia is well established [6], as cases have been described of myoepithelial cell carcinomas with squamous cell differentiation [6, 7].

As discussed elsewhere [10], the development of sarcomatoid carcinomas may follow metaplasia of myoepithelial cells, as also suggested by Hamperl [11]. The intimate association of a sarcomatoid carcinoma with an epi-myoepithelial proliferation and the fact that AME has preceded sarcomatoid carcinoma occurring as a relapse (case 6) suggest a myoepithelial origin for the former.

LGASC are morphologically closer to AMEs, being composed of an epi-myoepithelial proliferation. Nevertheless, these lesions are characterized by a prominent stromal "desmoplasia", are diffusely invasive and also show conspicuous squamous metaplasia. In this respect this type of lesion might be the missing link between well-differentiated AME and sarcomatoid carcinomas. Most sarcomatoid carcinomas are biphasic and, in this

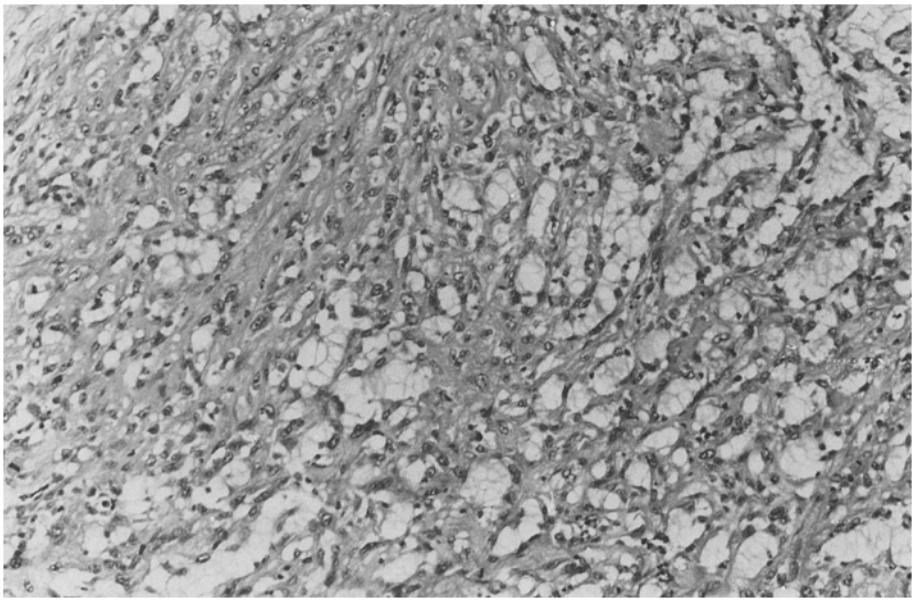

Fig. 10 Case 4: a spindle cell malignant proliferation is visible showing a spongiform reaction. HE, ×175

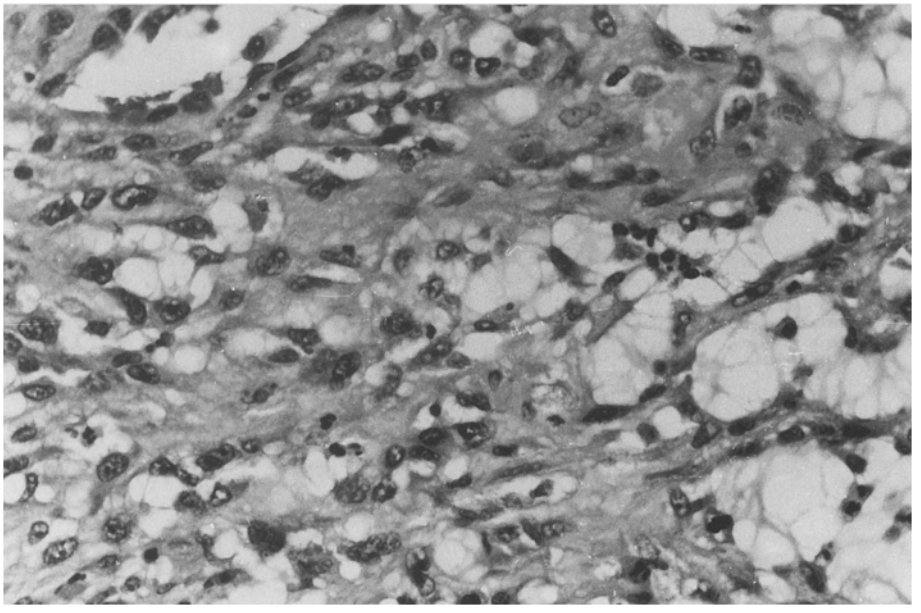

Fig. 11 Case 4: vascular-like spaces are prominent. HE, ×350

respect, can be interpreted as the anaplastic counterpart of the less aggressive epi-myoepithelial tumours, such as AME and LGASC.

Although both AME and LGASC are considered to be tumours of low-grade malignant potential, acantholytic squamous cell carcinomas are highly malignant lesions [8]. It is not yet possible to be certain about the biological behaviour of the tumours described, in view of the short follow-up.

It seems reasonable to accept that features observed in our six cases can be regarded as different phenotypic expressions of a single neoplastic process. Therefore, a common origin is proposed for these neoplastic lesions, which widens the morphological spectrum of epi-myoepithelial cell tumours.

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