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ORIGINAL ARTICLE

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Adenomyoepithelioma of the breast with malignant features

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Abstract The clinico-pathological features of 7 cases of adenomyoepithelioma of the breast with features suggestive of malignancy are presented. There was a high incidence of local tumour recurrence, in 2 cases as high-grade infiltrating carcinoma of the breast of no special type ("ductal", grade III). One patient died as the result of a clinically diagnosed cerebral metastasis. Histological examination of the primary breast tumours reveals two main patterns: (1) tumours consisting in part of typical adenomyoepitheliomas but which merge with areas of obviously invasive malignant cells and (2) neoplasms that have the overall architecture of an adenomyoepithelioma but which, on close examination, are found to contain foci of cellular atypia and increased mitotic activity. The two patterns of tumour exhibit the same clinical behaviour and should be distinguished from adenomyoepitheliomas, which are cytologically bland throughout.

Key words Adenomyoepithelioma · Breast · Malignancy

Introduction

Adenomyoepitheliomas are uncommon breast tumours, which have as their defining feature a prominent component of myoepithelial cells in addition to glandular elements lined by epithelial cells. There have been several recent publications concerning this entity. A paper by Tavassoli [8] proposes a new classification of myoepithelial lesions into adenomyoepitheliosis, adenomyoepithelioma (subdivided into tubular, lobulated and spindle cell variants) and pure myoepithelial carcinoma. As defined in that paper, the histology of adenomyoepitheliomas overlaps with several other well-recognised entities within breast pathology, in particular, sclerosing adenosis and ductal adenoma and papilloma, where the proportion of myoepithelial cells is quantitatively different although the architecture of the lesions is similar.

One of the strongest arguments for the identification of adenomyoepitheliomas as a separate group is their biological behaviour, which is characterised by local recurrence in a proportion of cases. Metastases arising from malignant variants of such tumours also occur rarely, and several such cases have recently been reported [1, 3, 8, 9]. Review of the literature reveals that malignant lesions appear to fall into two broad groups: those that are readily identified as consisting of areas of obvious malignancy arising in conjunction with an otherwise typical adenomyoepithelioma [1, 2, 4, 8, 10] and those with the overall appearance of an adenomyoepithelioma but seen on close examination to contain foci of cellular atypia and increased mitotic activity [3, 5, 8, 9]. Recurrent tumours and distant metastases have been reported in association with both groups. Loose et al. [3] suggest guidelines for the identification of malignancy in the second group, based largely on the features of a case in which a distant metastasis was observed.

We have seen several tumours in which myoepithelial cells formed a major component of the neoplasm and the overall appearance of the neoplasm did not significantly overlap with those of other well-defined entities, where we considered the diagnosis of adenomyoepithelioma to be appropriate. Some of these had features that were identified as possibly predictive of an increased risk of malignant behaviour or contained areas of frank malignancy. We report herein the pathological features of these latter tumours and their clinical behaviour over a follow-up period of 12–210 months (median 40 months).

Materials and methods

We traced all cases diagnosed as adenomyoepithelioma in the Guy's Hospital Breast Unit between 1975 and 1994 and found 14 examples; the majority of these cases were received in the unit for a second opinion. We reviewed the haematoxylin and eosin (H&E)-stained sections and identified 7 tumours that we considered to

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Table 1 Antibody used for immunhistochemical studies

Antibody used	Source	Polyclonal/ monoclonal	Dilution
CAM 5.2	Imperial Cancer Research Fund, Fields, London	Monoclonal 44 Lincoln's Inn	1: 2
Anti-smooth muscle actin	DAKO Hughenden Avenue, High Wycombe, Bucks. HP13 5RE	Monoclonal	1: 500
Polyclonal anti-S100	DAKO Hughenden Avenue, High Wycombe, Bucks. HP13 5RE	Polyclonal	1: 800

Table 2 Clinical features of the patients with adenomyoepithelioma, group 1 comprises cases 1–4 and group 2 comprises cases 5–7 (*WLE* wide local excision, *A/W* alive and well)

Case No	Age (years)	Site	Clinical size of tumour (cm)	Presentation	Treatment	Time to recurrence	Present status
1	64	Right breast	3	Lump	WLE	None	A/W 12 months
2	43	Left breast	4	Mobile lump	WLE×2 Mod. radical mastectomy + 1 cycle CMF	2 months 4 months	A/W 36 months
3	76	Left breast	1.7	Mobile lump	WLE Simple mastectomy	12 months	A/W 60 months
4	72	Right breast	4.5	Lump	Mod. radical mastectomy	None	A/W 12 months
5	39	Left breast	1.3	Lump	WLE×2 simple mastectomy	180 months 210 months	A/W 210 months
6	81	Right breast	3	Lump	WLE×2	6 months	A/W 6 months
7	76	Unknown	15	Lump	WLE	36 months	Died of cerebral tumour at 36 months

show overt features of malignancy or foci of cellular atypia and prominent mitotic activity. Mitotic counts were carried out in 10 consecutive high power fields (hpf; 1 hpf = 0.17 mm^2 on the microscope used) in the area of highest mitotic activity identified at lower magnification.

An immunohistochemical study was then carried out using the antibodies listed in Table 1. Cells were considered to be of epithelial phenotype if they stained for CAM 5.2 and were not stained by antibodies to α-actin. The immunophenotype of myoepithelial cells was that of staining for α-actin and S100 protein but not for the cytokeratins detected by CAM 5.2. Although staining for S100 protein was originally thought to be restricted to myoepithelium, it also occurs to a variable extent in epithelial cells and so does not differentiate between the two cell types; it can, however, still be useful in distinguishing myofibroblasts (α-actin positive; S100 negative) from myoepithelial cells (α-actin and S100 positive).

Follow-up information was obtained by contacting the pathologist or clinician concerned with each case, who kindly obtained the relevant information from the patient's hospital notes. We were able to get this information in all cases, and the clinical histories of the patients are summarised in Table 2.

Results

The histological features of the cases are summarised in Table 3. The tumours fell into two main groups as follows. Group 1 (cases 1–4) comprised lesions in which the tumours showed a biphasic pattern, with some areas of typical adenomyoepithelioma merging with other areas of obviously malignant tumour (Figs. 1, 2). Group 2 (cases 5–7) consisted of lesions in which the tumour had the overall architecture of an adenomyoepithelioma but there were focal areas of atypicality detectable only on close examination (Fig. 3).

In both types, the adenomyoepithelial component was composed of multiple, glandular structures lined by an inner layer of epithelium surrounded by prominent myoepithelial cells. Focally both elements showed evidence of hyperplasia, but this was more frequent and more pro-

Fig. 1 **a** Case 1. The tumour consisted of an adenomyoepithelioma composed of regular glandular structures lined by a two cell population which blended in its deeper portion with a highly cellular area of atypical epithelioid and spindle cells. H&E, ×25. **b** Within the highly cellular areas there was pleomorphism and abnormal mitotic activity. A few residual tubular structures were present. H&E, ×200. **c, d** Immunohistochemistry **c** for CAM 5.2 and **d** for α-actin shows that the atypical cells have both an epithelial immunophenotype (×200) and a myoepithelial immunophenotype (×100) ▶

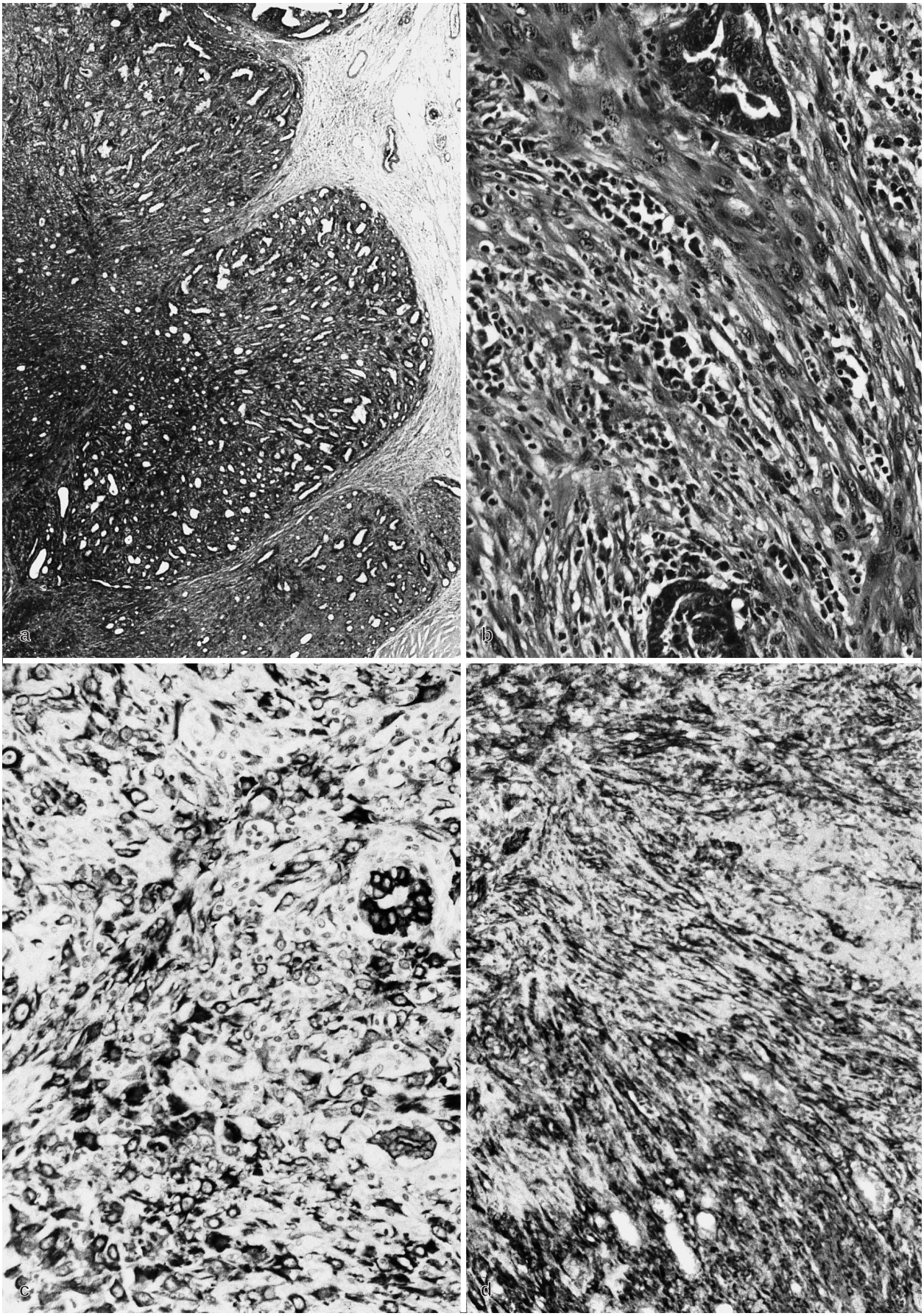
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Table 3 Summary of histopathological features

Case no.	Mitotic index (mitoses per 10 high power fields)	Phenotype of malignant cells	Pattern of recurrent tumour
1	7	Both myopeithelial and epithelial	None
2	10	Epithelial	Adenomyoepithelioma with malignant features, then invasive ductal carcinoma
3	13	Both myopeithelial and epithelial	Adenomyoepithelioma with malignant features
4	9	Both myopeithelial and epithelial	None
5	6	Both myopeithelial and epithelial	Adenomyoepithelioma with increasing cellular atypia
6	16	Epithelial	Invasive ductal carcinoma
7	13	Both myopeithelial and epithelial	Cerebral metastasis, unknown histology

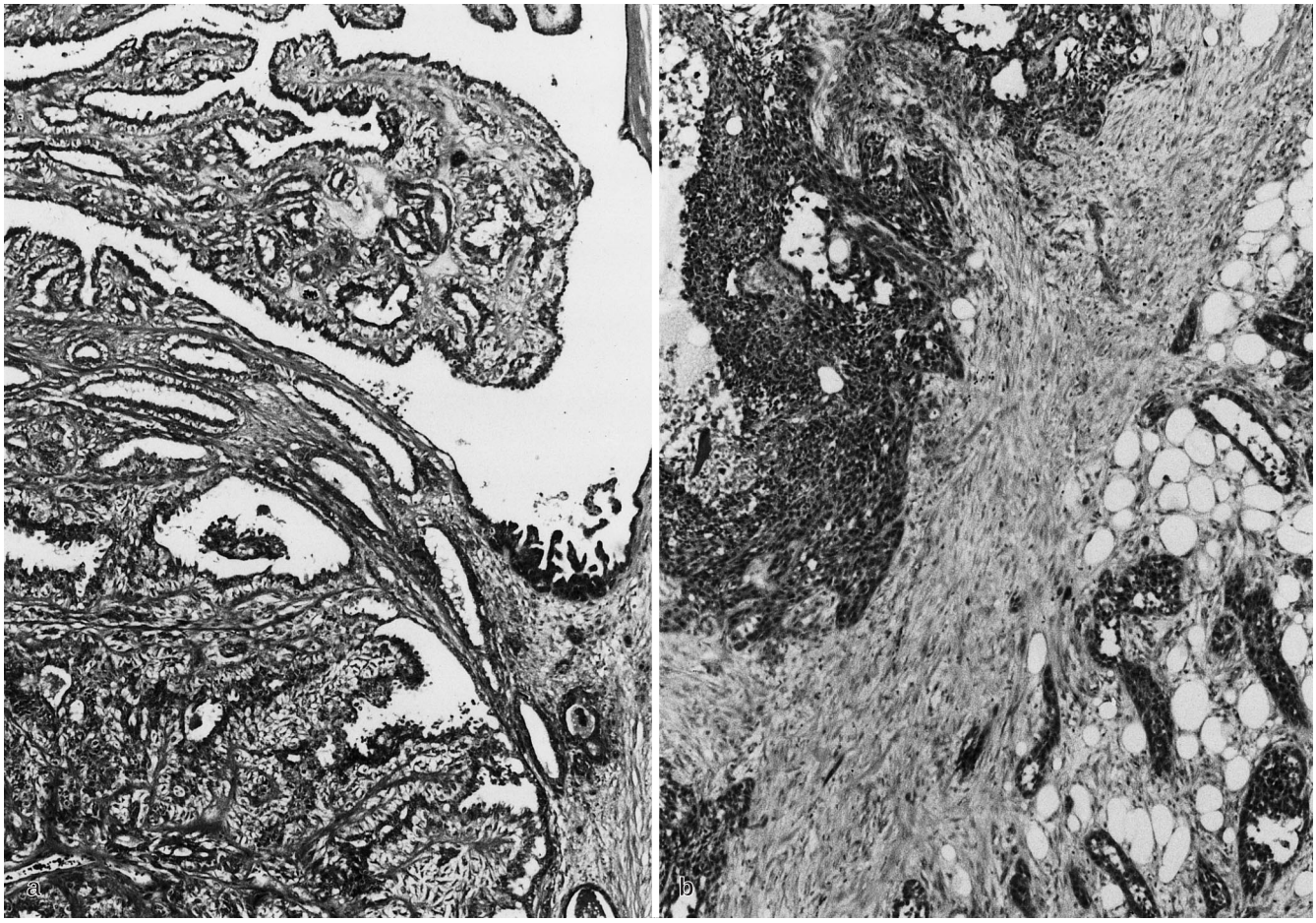
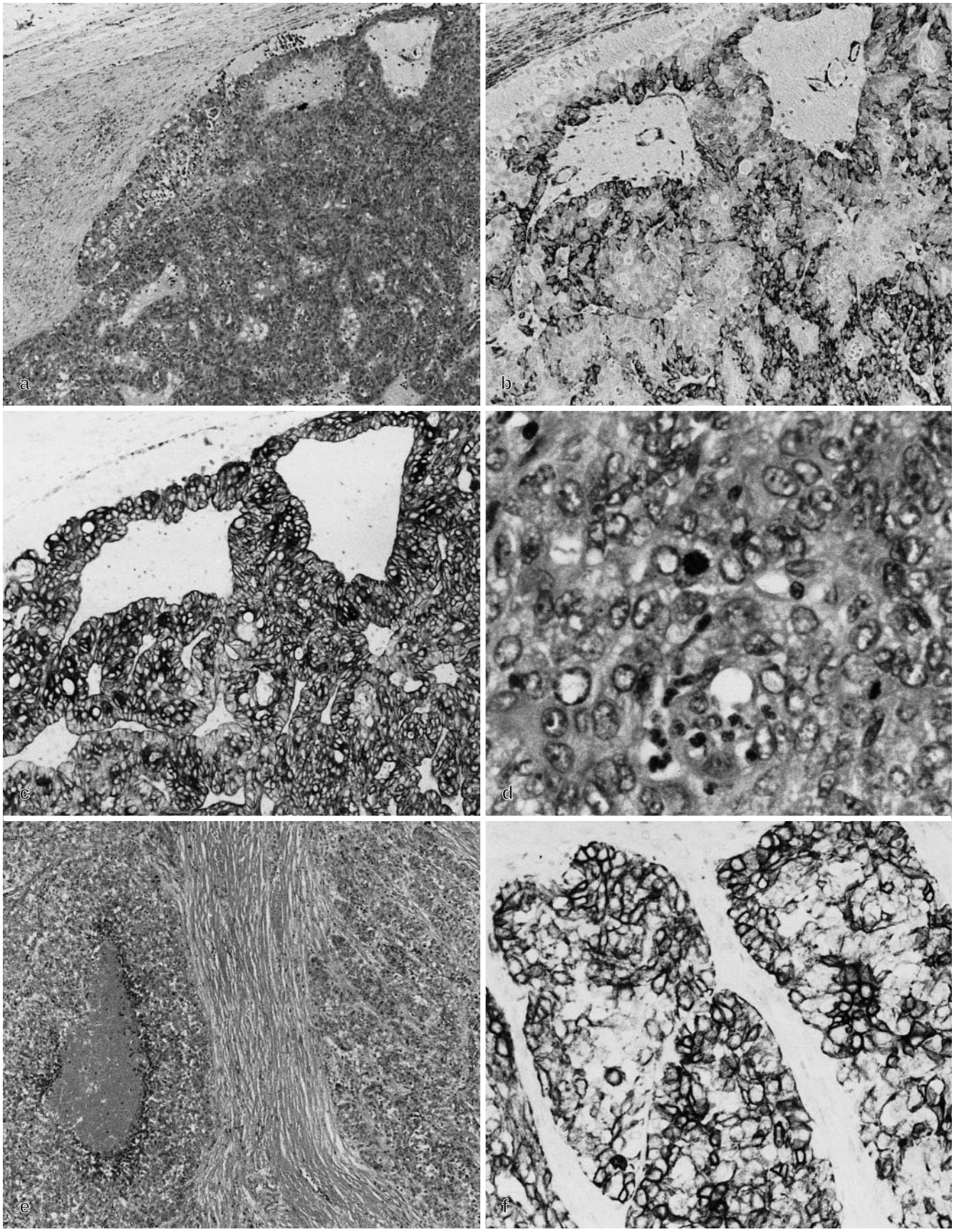


Fig. 2a, b Case 3. This tumour had the architecture of an adenomyoepithelioma with focal papillary areas in parts (**a**), but elsewhere (**b**) there were islands of spindle-shaped tumour cells infiltrating fat and fibrous connective tissue with only a few epithelial lined spaces. On immunohistochemistry the spindle cells stained with the myoepithelial markers α-actin and S100 and staining for epithelium with CAM 5.2 was seen in the epithelial-lined spaces. H&E, ×50

Fig. 3a–f Case 6. **a** The first tumour removed from this patient had the pattern of an adenomyoepithelioma throughout (H&E, ×50), and was found to contain both **b** epithelial and **c** myoepithelial components on immunostaining for CAM 5.2 and α-actin. Immunohistochemistry, ×100. **d** However, at higher magnification, areas of cellular pleomorphism and atypia were apparent within the hyperplastic epithelial cell population. H&E, ×400. **e** The subsequent tumour excised from this patient was an infiltrating ductal carcinoma grade III. H&E, ×50. **f** It stained only with CAM 5.2. Immunohistochemistry, ×200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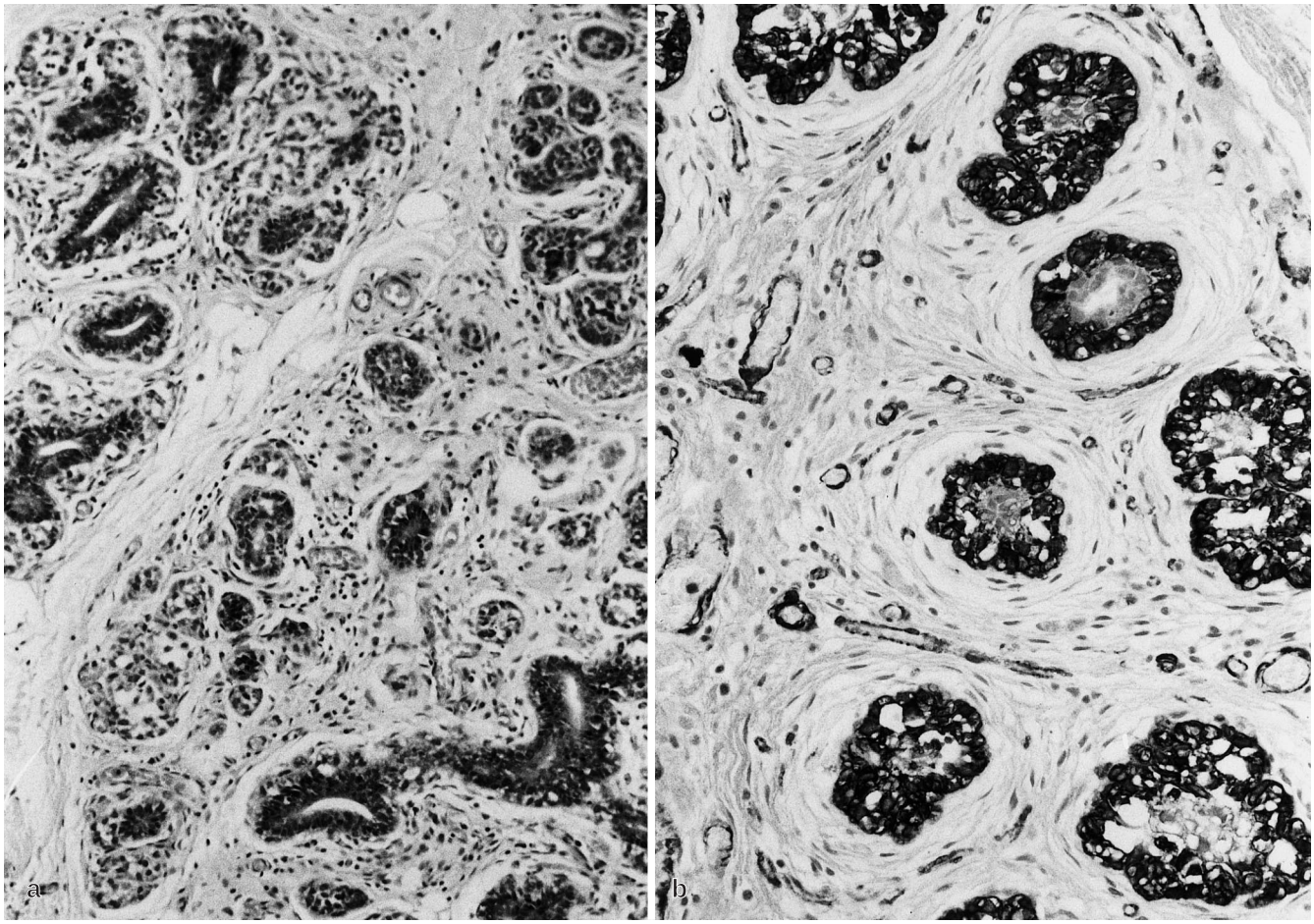

Fig. 4a, b Case 5. Breast tissue immediately around the adenomyoepithelioma in this case was remarkable, **a** as a prominent layer of myoepithelium with abundant clear cytoplasm was present within otherwise normal breast lobules. H&E, ×100. **b** This clearly stained for α-actin. Immunhistochemistry, ×200

nounced in the myoepithelial element. The growth pattern was somewhat reminiscent of ductal adenoma in some (cases 1 and 3); in case 3 there was also a partly papillary pattern; in others (cases 5 and 6) the growth pattern was more solid, with sheets and clumps of cells, some with abundant clear cytoplasm and some spindle shaped. In this pattern the epithelial element sometimes consisted of scattered, frequently compressed, epithelial-lined structures. In cases 2, 4 and 7 both patterns were present and the appearance varied from area to area. Foci of squamous metaplasia were present in cases 2, 3 and 5. The adenomyoepithelial element had a rounded, pushing border but in group 2 this component had an irregular margin focally, although no definite invasion of surrounding breast tissue around the tumour was seen.

In group 1 (cases 1–4), within the tumour mass the adenomyoepitheliomatous areas blended with malignant foci composed of islands of large, pleomorphic and polygonal cells, which infiltrated the adjacent breast tissue (Fig. 1b). In cases 1 and 2 the atypical cells had a largely epithelioid morphology, but in case 1 there were also atypical spindle-shaped cells. In cases 3 and 4 the spindle cells predominated, and there were scattered osteoclast-like multinucleated giant cells. Within the sheets of spindle cells in case 3 there were some scattered epithelium-lined spaces. Mitotic activity, including abnormal mitoses, and occasional small foci of necrosis were present in the areas of malignancy in all the tumours. The immunophenotype of the malignant cells was epithelial in case 2 and both epithelial and myoepithelial in the rest (see Table 3, Fig. 1c, d).

The tumour in case 2 was incompletely excised initially and underwent progressive enlargement requiring re-excision at 2 months, when the tissue removed had features similar to those in the first biopsy specimen. In a subsequent mastectomy after a further 2 months, however, an infiltrating carcinoma of no special type (“ductal”, grade III) and without a myoepithelial component was apparent. Case 3 recurred at 1 year, the recurrence showing similar features to the original tumour in that patient (Fig. 2a, b).

In group 2 (cases 5–7) only on examination of the tumour at high magnification were foci of cellular atypia identified. These were characterised by cells with enlarged, pleomorphic, vesicular nuclei containing prominent nucleoli and showing a higher level of mitotic activity than the remainder of the tumour (Fig. 3d). In cases 5 and 7 these atypical cells were predominently spindle shaped and appeared to merge with the myoepithelial cells surrounding the glandular structures of the adeno-

myoepithelioma. In case 7, foci of atypical epithelioid cells were also present, but in both these cases the atypical cells had both an epithelial and a myoepithelial immunophenotype. In case 6 the malignant cells were entirely epithelial, both morphologically and immunophenotypically (see Table 3, Fig. 3).

Case 5 was noteworthy for the presence of focal squamous metaplasia within the tumour and, in addition, a proliferation of prominent clear myoepithelial cells around otherwise normal breast structures adjacent to the main tumour mass in each excision specimen (Fig. 4). This tumour recurred at 15 years and again at 17.5 years after removal of the primary mass. The first recurrence had a similar histological appearance to the original tumour but the second recurrence showed an increased degree of cellular atypia and an increase in mitotic count from 6/10 hpf to 16/10 hpf. Case 6 recurred after 6 months as an infiltrating carcinoma of no special type ("ductal", grade III) without a myoepithelial component, and its cytological features resembled the epithelial component of the original adenomyoepithelioma (Fig. 3e, f). In case 7 the patient died of a solitary intracerebral mass, which was clinically diagnosed as a secondary tumour deposit, presumably from the breast tumour as no other primary site was identified. Unfortunately no histological confirmation of the diagnosis was obtained.

Discussion

Adenomyoepithelioma of the breast is an uncommon diagnosis if strict criteria are used in its definition. Removal of the primary tumour may occasionally be followed by local recurrence, but metastasis is very rare. In our series 1 patient died of an intracerebral mass clinically diagnosed as a secondary deposit from her breast tumour, and 4 others had at least one local recurrence. The 2 cases without recurrence have been followed-up for only a year (and 1 of them is now lost to follow-up). This is a much higher recurrence rate than has been reported for series of unselected adenomyoepitheliomas: combining the two largest series published so far, 6 of 45 (13%) patients have developed recurrent lesions [6, 8]. Some of the variation may be due to differences in the definition of an adenomyoepithelioma, but the clinical behaviour of our cases is consistent with the identification of a more aggressive form of the neoplasm.

Histological malignancy arising in relation to an adenomyoepithelioma seems to adopt one of two patterns: either as an area of overtly malignant tumour or as diffusely scattered foci of cellular atypia. Within our small number of cases, no real difference in clinical behaviour was apparent between the two patterns, which may well represent different stages in the evolution of "malignant adenomyoepithelioma". The former pattern has previously been identified in one of Tavassoli's patients [8] and in other single case reports [1, 4, 10]. Other tumours, also exhibiting metastatic spread, have shown more subtle changes, as in the case reported by Loose et al. [3]. These authors considered features of a high mitotic count throughout the tumour, cytological atypia worsening in recurrences and infiltration beyond the edge of the main tumour mass as indicative of malignancy in the context of an adenomyoepithelial tumour. The cytological atypia was present in both cell types, and the mitotic activity is described as "throughout the tumour", but they did not specify in which cell types. Focal cytological atypia was also seen in 3 of our cases (5–7): in 1 of these the tumour is thought to have metastasised and in 1, to have recurred as an invasive ductal carcinoma. It is difficult to use mitotic activity as the sole criterion for malignancy, since the metastatic tumour reported by Chen [1] showed 5 mitoses/10 hpf whilst Tavassoli records up to 14 mitoses/10 hpf in otherwise unremarkable adenomyoepitheliomas [8].

Until now only 5 cases of metastasis from an adenomyoepithelioma [1, 3, 4, 8, 9], 4 of which were confirmed histologically [1, 3, 8, 9], have been reported in the literature. In 1 patient an axillary metastasis may have represented direct local spread from a primary tumour in the axillary tail of the breast [8]. All 3 cases that spread beyond the axillary lymph nodes have proved fatal [1, 3, 9]. Histological examination of excised metastases in 2 cases has shown a monomorphic population of spindly myoepithelial or undifferentiated carcinoma cells [1, 3]. In 2 other cases the metastases have had a biphasic epithelial/myoepithelial appearance [8, 9].

Tavassoli [8] recognised malignancy in adenomyoepitheliomas as arising within the epithelial or the myoepithelial component, in the former case taking the form of an infiltrating ductal carcinoma and in the latter, which she termed myoepithelial carcinoma, consisting of an infiltration of malignant myoepithelial cells but with persistent epithelial-lined spaces. However, as pointed out by Trojani et al. [9], the term myoepithelial carcinoma has been used for malignant lesions composed entirely of atypical myoepithelial cells without an epithelial component. They, therefore, preferred to call tumours with a persistent biphasic cell population malignant adenomyoepitheliomas. It could be argued that a true "malignant adenomyoepithelioma" is a tumour with a biphasic cell population and that the others are more accurately designated as "carcinoma arising within an adenomyoepithelioma". Thus our cases 2 and 6 could be classified as ductal carcinomas arising in adenomyoepitheliomas and cases 1, 3, 4, 5 and 7 as true malignant adenomyoepitheliomas.

Adenocarcinoma following adenomyoepithelioma appears to be a very unusual occurrence; the only somewhat similar case previously reported was the 1 in Tavassoli's series [8], where an invasive ductal carcinoma arose in the same breast 2 years after an adenomyoepithelioma had been removed; no evidence of malignancy was reported in the adenomyoepithelioma, and it is not known whether or not the infiltrating carcinoma occurred in the same quadrant as the adenomyoepithelial tumour. One of our patients in whom a ductal carcinoma followed an adenomyoepithelioma (case 2) had areas of in-

vasive carcinoma within her original tumour whilst in the second (case 6) the adenomyoepithelioma contained foci of atypical cells that were cytologically similar to the subsequent invasive carcinoma.

Previous reports of the rare entity of mammary low-grade adenosquamous carcinoma [7, 11] have noted a close association with an adenomyoepithelioma in the adjacent breast tissue in 3 cases. Additional evidence of the coexistence of adenomyoepithelioma and adenosquamous carcinoma is provided by a recent report of 6 more cases of invasive carcinoma closely associated with an adenomyoepithelial tumour [2]. In 3 the carcinoma was of low-grade adenosquamous type, and in 3 it was an acantholytic squamous cell sarcomatoid carcinoma. During the course of the present study we were also struck by the similarity between areas within adenomyoepitheliomas containing foci of squamous metaplasia and the entity of low-grade adenosquamous carcinoma. In 3 cases of the latter tumour in our files there was preservation of the myoepithelial layer around a proportion of the infiltrating epithelial islands and cells with the appropriate immunohistochemical staining pattern for myoepithelial cells were present in the stroma. Two of these tumours contained small benign papillary foci with a prominent myoepithelial component, which could have represented part of a pre-existing adenomyoepithelioma. These findings reinforce the possibility that adenosquamous carcinomas, and probably also at least some sarcomatoid carcinomas, represent part of a spectrum of lesions including adenomyoepitheliomas. Although Tavassoli [8] considers sarcomatoid carcinoma to be clearly distinct from malignant adenomyoepithelioma, Foschini et al. [2] suggest that there is increasing evidence of involvement of myoepithelial cells in the genesis of sarcomatoid carcinomas.

The architectural similarity of adenomyoepitheliomas and of some well-defined benign pathological entities suggests that they may fall in the middle of a spectrum of lesions extending from sclerosing adenosis, ductal papillomas and ductal adenomas at one end to adenosquamous carcinomas and sarcomatoid carcinomas at the other. The cases we report here appear to lie towards the malignant end of the spectrum of adenomyoepitheliomas, and in some there is evidence of progression from a more benign appearance to a more malignant appearance in repeated recurrences.

In summary, we report 7 neoplasms in which we conclude that the diagnosis of adenomyoepithelioma is appropriate, and all the tumours showed histological features suggestive of potential malignant behaviour. Local recurrence occurred in 4 cases and probable distant metastasis in 1 other. We believe that it is important to examine adenomyoepitheliomas not only for obvious features of malignancy, but also for foci of cellular atypia and increased mitotic activity. It appears that both these latter features are indicative of tumours that are likely to recur locally, may progress to a more malignant form, and probably have the potential to metastasise. Complete excision and long-term clinical follow-up appear to be the appropriate measure in such cases.

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