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REVIEW ARTICLE

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Carcinomas of the breast showing myoepithelial cell differentiation

A review of the literature

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Abstract Myoepithelial cells are normally located between the epithelial cells and the basal lamina of secretory elements of exocrine glands. Their role in the histogenesis of breast tumours has been studied extensively, and a definite differentiation towards myoepithelial cells has been demonstrated in adenoid cystic carcinoma, adenomyoepithelioma, low-grade adenosquamous (syringomatous) carcinoma, pure malignant myoepithelioma and poorly differentiated myoepithelial-rich breast carcinoma. All these tumours are of low malignancy, with the exception of malignant myoepithelioma and poorly differentiated myoepithelial-rich carcinoma. When a low-grade tumour is associated with a spindle cell component, distant metastases must be expected. Pure malignant myoepithelioma shows morphological and clinical features similar to those of monophasic sarcomatoid carcinomas, and it is possible that this last tumour is linked histogenetically to sarcomatoid carcinomas.

Key words Myoepithelium · Adenoid cystic carcinoma · Low-grade adenosquamous carcinoma · Myoepithelioma · Sarcomatoid carcinoma

Introduction

Myoepithelial cells (MC) are normally located between the epithelial cells and the basal lamina of acini and ducts of breast and sweat glands of the skin, but are found mostly in the acinar component of salivary glands. These flat, elongated cells [2, 13, 34]. are characterized by immunoreactivity with smooth muscle actin, myosin, cytokeratin 14 [13, 34], S-100 protein [34], calponin, caldesmon [63] and GFAP [13, 62] antibodies. At the ultrastructural level MCs are characterized by filaments located at the basal site and pinocytotic vesicles. Most of the filaments consist of actin, tropomyosin and myosin [34], and well-developed desmosomes and bundles of cytokeratin filaments are present.

MC differentiation is commonly encountered in carcinomas of salivary glands, where neoplastic cells express vimentin, which is not expressed in normal myoepithelium [13]. In addition, GFAP, although reported in benign breast lesions [13], is rarely present in breast carcinomas.

In a comprehensive review of MC, Hamperl [24] drew attention to MC proliferation in the breast, and numerous papers describing MC in or accompanying neoplastic conditions of the breast have since been published [1, 4, 25, 52]. These same studies failed to reveal MC differentiation in the neoplastic population of "ordinary" ductal and lobular carcinomas of the breast [1, 4, 25, 52]. However in the last two decades tumours showing MC differentiation have been reported progressively in increasing numbers [5–7, 12, 14, 17, 20, 22, 26–33, 35–41, 44–48, 51, 53–55, 57–61, 64–66].

The aim of the present article is to summarize the features of these tumours.

Adenoid cystic carcinoma

Adenoid cystic carcinoma (ACC) of the breast is very rare, accounting for 0.1% of all breast carcinomas [2, 30]. Nevertheless, its recognition is extremely important as it has very good prognosis; diagnostic criteria should therefore be very stringent, as otherwise the diagnosis of ACC of the breast would lose much of its significance [2]. Although, morphologically, its salivary gland counterpart is similar, the latter entity is far more aggressive than the form affecting the breast.

ACC usually affects women, in whom it is most more frequent in the sixth decade of life, but in rare instances it has been documented in men and in children [45]. In

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more than 50% of the cases, ACC of the breast arises below or adjacent to the areola [2, 26, 39]. It can present as a painful or tender, well-circumscribed but not encapsulated nodule. Sometimes it appears as a cystic lesion [37]. The size ranges from 0.7 to 10 cm, with an average of 3 cm [37]. Bloody discharge from the nipple is unusual.

Histology of ACC of the breast reveals a cribriform, trabecular-tubular or solid pattern of growth (Figs. 1, 2) [30] similar to that in analogous tumours of the salivary glands. The size of the cribriform spaces varies, the largest being referred to as microcysts. Two cell types are visible in routinely haematoxylin-eosin (H&E)-stained sections. The first is composed of basaloid elements, characterized by scanty basophilic cytoplasm. These elements are grouped in nests or outline the cribriform spaces. The second cellular component is a minority of the total neoplastic proliferation and has to be carefully sought. It is characterized by abundant eosinophilic cytoplasm and tiny ductule-like structures. The content of the cribriform spaces is usually alcianophilic mucosubstances, while the ductule-like structures contain PAS-positive material [2]. PAS staining and anti-collagen IV immunostaining reveal a thick basal lamina bordering the cribriform and the microcystic structures (Fig. 3) but not the ductule-like structures [14]. EMA and high-molecular-weight keratin antibodies stain the larger cells lining the ductule-like structures [57], while these same antibodies are negative in the basaloid elements [14]. Immunohistochemistry with anti smooth muscle actin antibody reveals a third cell type. It is mainly located at the periphery of the basaloid elements and has been interpreted to be of myoepithelial nature, in keeping with the ultrastructural findings, by Ro et al. [41]. Oestrogen or progesterone receptor positivity has rarely been found [45].

In ACC of the breast foci of DCIS and of squamous differentiation can be present [30], as can sebaceous differentiation [38, 57]. Invasion of nerves, mitoses and necrosis are occasionally encountered.

One differential diagnosis is collagenous spherulosis (CS) [20], which is generally limited to a few ductules or lobules and only occasionally forms a mass [23]. It is associated with epitheliosis [9].

Prognosis

Ro et al. [41] are of the opinion that it is important to apply the same grading system for ACC, as is used for tumours of the salivary glands. According to their data all their patients with grade I ACC were alive without evidence of disease or had died of unrelated causes at the last follow-up. Recurrences and metastases occurred in two of the six patients with grade II ACC and in the only patient with grade III ACC of the breast. The same grading system was applied by Lamovec et al., who found it of limited value [30]; none of their six patients experienced recurrences or metastases. Recurrences or metastases from ACC of the breast are reported very rarely [32, 37, 45], as are deaths caused by the tumour [45].

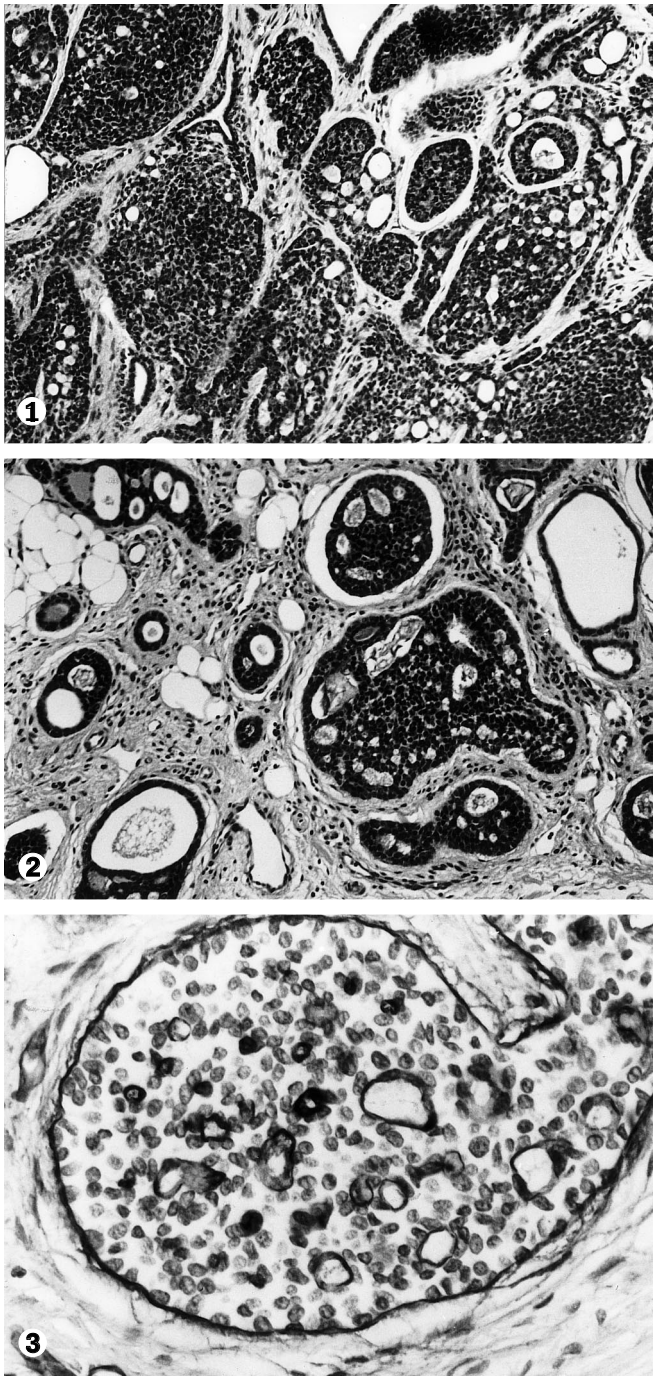


Fig. 1 Low-power view of adenoid cystic carcinoma (ACC) showing cribriform and solid architecture. H&E, ×25

Fig. 2 ACC showing prevalent cribriform pattern. H&E, ×40

Fig. 3 Anti collagen IV antibody clearly outlines the cribriform structures in ACC. ABC, ×250

Metastases can develop after 10–20 years, which makes it imperative to follow up these patients for a long period [2]. Lungs are the most frequent sites of metastases. Other organs can be involved, such as liver, bone and kidney. Metastases from ACC of the breast have been recently reviewed by Colome et al. [11].

Treatment

Since simple excision of the tumour may lead to local recurrence and as lymph node metastases are known to be very rare [41, 65], it seems that the best treatment for ACC is wide excision with adequate histopathological examination of the excisional margins.

Low-grade adenosquamous carcinoma (syringomatous carcinoma)

This tumour, originally described in the breast by Rosen and Ernsberg in 1987 [46], is the breast counterpart of similar tumours arising in the skin and known by various names, such as syringomatous carcinoma, microcystic adnexal carcinoma, sclerosing duct carcinoma or sweat gland carcinoma [47], and in salivary glands, where they are referred to as syringomatous carcinomas by Johnstone and Toker [28] and Bondi and Urso [3].

Low-grade adenosquamous carcinomas (LGASC) affect adult patients, with a peak incidence in the sixth decade of life [46, 61]. The tumour presents as a palpable nodule, commonly located in the upper lateral quadrant, ranging from 1.5 to 8 cm in diameter [46, 61]. One patient had bilateral asynchronous LGASC [61]. On macroscopic examination it presents as a firm lesion, with infiltrative margins, and its cut surface is yellow [46, 61].

Histology

Histologically LGASC is composed of solid cords and/or glandular structures with angulated profiles (Fig. 4). The stroma is very exuberant, containing abundant fibroblasts with plump, elongated, tortuous nuclei. Inflammatory infiltration, composed of mature lymphocytes, is seen either clumped in pseudofollicles or dispersed through the lesion.

The neoplastic glandular structures and solid cords are surrounded by a layer of myoepithelial cells [22, 61] (Fig. 5). Some of the elements present in the solid cords are reminiscent of squamous cells, which are occasionally aggregated in squamous pearls. Microcalcifications can be present [61]. LGASC can also be associated with other lesions, adenomyoepithelioma (AME) being the most frequently encountered (Fig. 6) [22, 61]. It has been suggested that this entity is linked to both AME and sarcomatoid carcinomas [22].

No oestrogen or progesterone receptor positivity was found by Van Hoeven et al. [61] in LGASC.

On histology, LGASC is easily distinguished from tubular carcinoma, as the latter lacks squamous differentiation and a myoepithelial layer. However, differential diagnosis against syringomatous adenoma of the nipple [43] is very difficult, as this latter lesion is probably the equivalent tumour arising in the skin.

LGASC can recur locally [46, 61], and metastases have been reported on rare occasions [61]. Only in one case was the death of the patient attributable to LGASC [61].

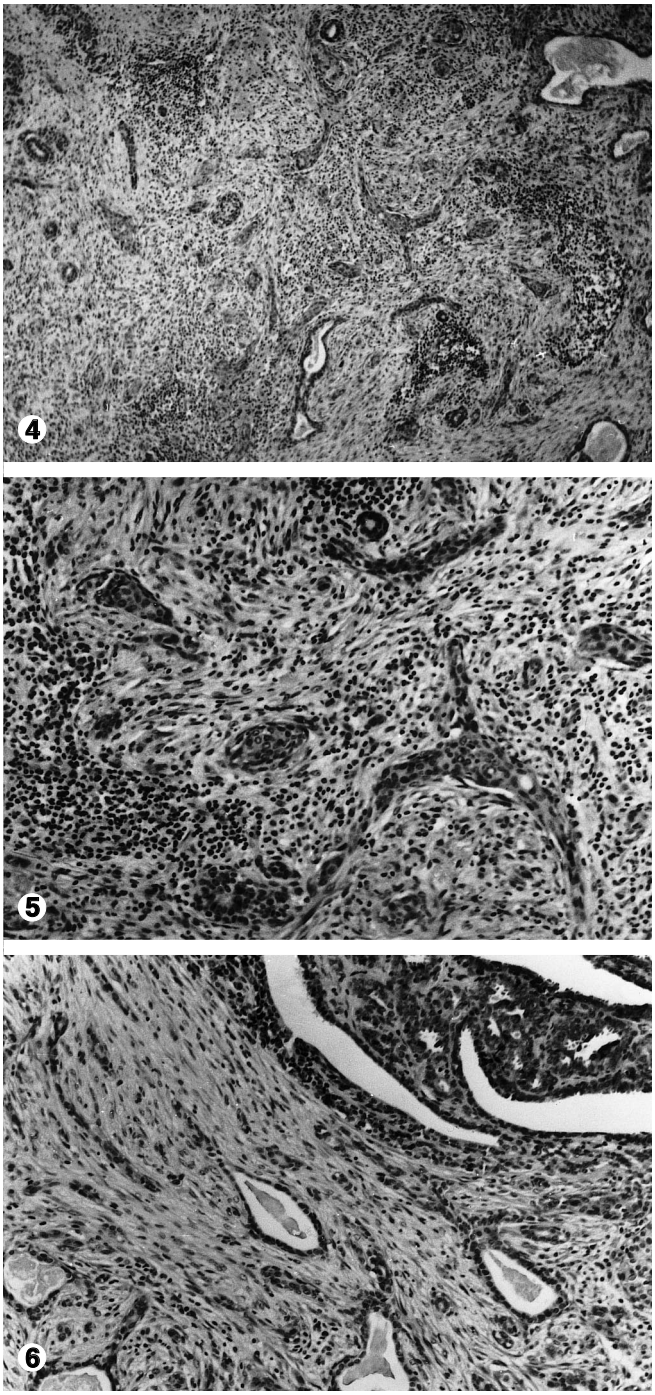


Fig. 4 Syringomatous carcinoma, or low-grade adenosquamous carcinoma (LGASC) is composed of glandular structures with angular profiles. H&E, ×25

Fig. 5 In syringomatous carcinoma (LGASC) the neoplastic glands are surrounded by a double layer of epithelial and myoepithelial cells. H&E, ×40

Fig. 6 Syringomatous carcinoma (LGASC) associated with adenomyoepithelioma (AME), tubular type. H&E, ×40

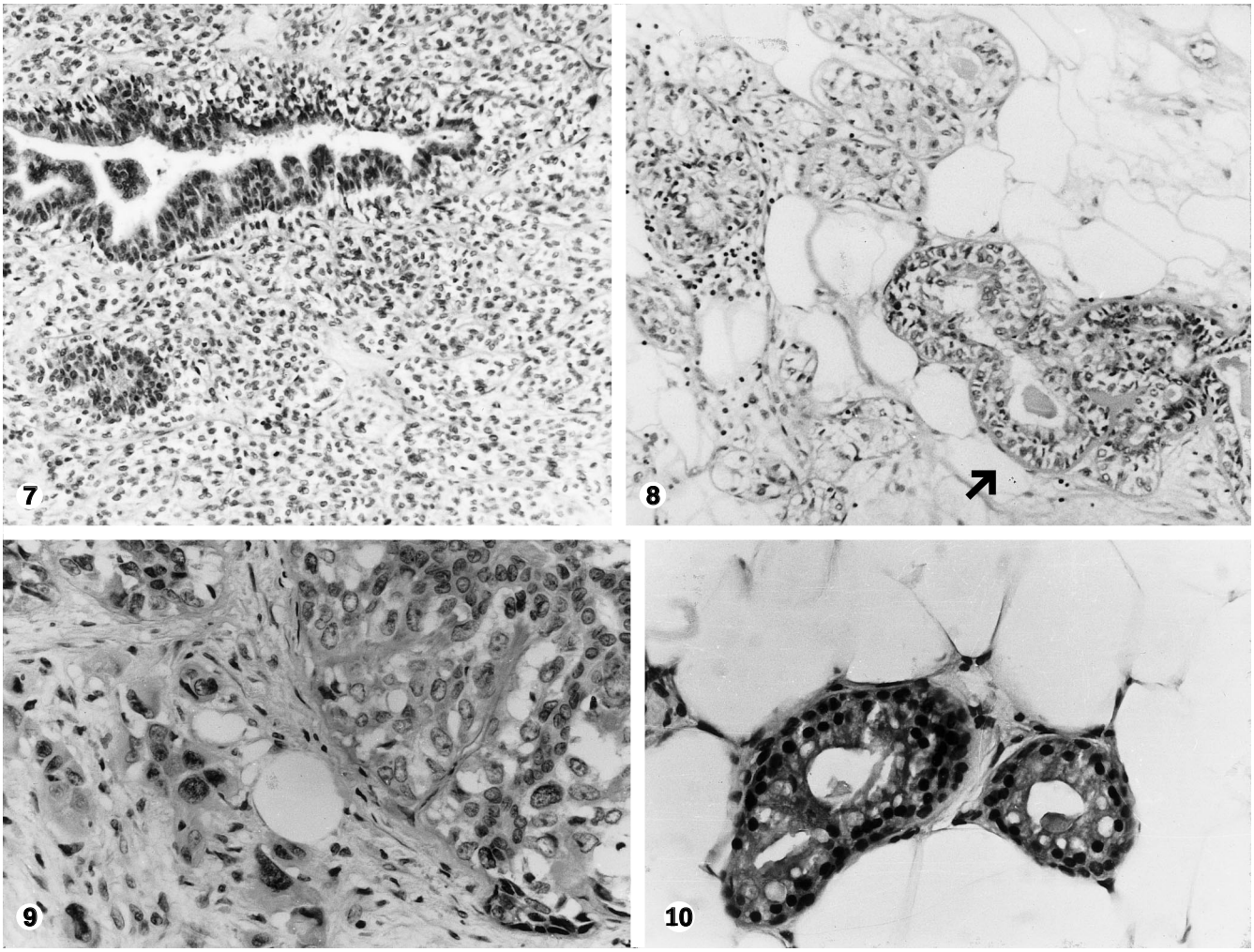


Fig. 7 AME with a predominantly solid type of growth. H&E, ×40

Fig. 8 AME tubular type, associated with apocrine adenosis. H&E, ×40

Fig. 9 AME associated with a proliferation of markedly atypical neoplastic cells. H&E, ×250

Fig. 10 AA: glands are lined by two layers of cells, epithelial and myoepithelial. H&E, ×125

Terminology

As these lesions are morphologically identical to cases occurring in salivary glands, the unifying term syringomatous carcinoma is probably the most appropriate, describing this entity in a way we prefer.

Adenomyoepithelioma

AME is a biphasic tumour that can affect the skin, salivary glands and breast [10, 17, 24], and it is called epimyoepithelial carcinoma when it occurs in a salivary gland [50]. AME was first illustrated by Hamperl [21], and first fully documented by Kiaer et al. [27] and Eusebi et al. [17]. Subsequently numerous cases have been reported in the literature [44, 55, 66]. Minute AME are seen increasingly in screening materials (J.L. Peterse, personal comunication).

AME usually affects adult patients older than 50 years, with a range from 27 [44] to 82 years [55]. To date only one case has been observed in a male patient [54]. AME presents as a palpable tumour [17, 44, 55], present on average for about 1 year. One of the cases reported by Tavassoli [54] had been present for 18 years.

On macroscopy the nodules are well circumscribed and range in size from 1 to 7 cm in greatest diameter.

On histology AME are found to be predominantly solid, but they can show tubular (Figs. 7, 8) or papillary features [54]. Irrespective of the growth pattern, two cell types are seen regularly. One cell type is predominantly basaloid or spindle-shaped, with cytoplasm varying from clear to eosinophilic. Nuclei are roundish with minute nucleoli. These cells constitute the majority of the neoplastic population, especially in the solid areas. In glandular areas they constitute the outer layer. These same cells are rich in glycogen [17] and contain smooth muscle. In addition, immunoreactivity for S-100 protein has been reported. These same cells are constantly negative for epithelial membrane antigen (EMA). The second cell type is columnar to cuboidal, having finely granular eosi-

nophilic to foamy cytoplasm, globoid nuclei and prominent nucleoli. These cells line the lumina of the glandular structures. This second type of cell is strongly stained for EMA and shows immunological and ultrastructural evidence of apocrine differentiation in most cases [17]. In about 40% of the cases showing a solid pattern, necrosis is extensive. Mitoses usually do not exceed three mitotic figures per high-power field.

Recently cases of otherwise typical AME associated with areas composed of markedly atypical cells (Fig. 9), most frequently spindle-shaped, have appeared in the literature [7, 22, 35, 36]. In addition, Rosen [45], reviewing the morphological spectrum of AME, has described areas of cartilaginous or myoid differentiation.

AME can be associated with other types of neoplastic proliferation, such as syringomatous carcinoma (LGASC) and sarcomatoid carcinoma [22, 61]. In one case [22] AME preceded the appearance of sarcomatoid carcinoma, which manifested as the only local recurrence. This association supports the hypothesis of myoepithelial cell origin for sarcomatoid carcinomas [21, 22, 48].

Apocrine adenosis (AA)

Eusebi et al. [17] used this term for a glandular proliferation present in association with both their cases of AME. It was histologically similar to the glandular proliferation called adenomyoepithelial adenosis in the report of the case before that of Kiaer et al. [27]. Apocrine adenosis is composed by roundish glands (Fig. 10) with large lumina containing faintly eosinophilic granular material, and surrounded by a thick basal lamina. Glands are lined by two cell layers (Fig. 6). The outer cell layer is formed by cuboidal cells with clear cytoplasm, which is usually strongly immunoreactive for smooth muscle actin antibody. The cells lining the lumina are columnar, have granular cytoplasm, and show immunohistochemical and ultrastructural evidence of apocrine differentiation; hence the descriptive term apocrine adenosis [17]. The lesion must be incorporated in the spectrum of AME.

Whether apocrine adenosis is hyperplastic or neoplastic has been matter of debate. In one case it preceded AME [27]. In one other case it was associated with a frank carcinoma [60]. In the 12 cases seen by the writers, AA was adjacent to typical areas of AME, with zones of transition. Therefore it is very likely that this glandular proliferation is part of the spectrum of AME.

Apocrine adenosis should be distinguished from microglandular adenosis [8, 42, 56] and tubular carcinoma [19]. At variance from apocrine adenosis, microglandular adenosis is characterized by smaller glands lined by a single layer of epithelial cells lying on a continuous ring of well-formed basal membrane [19]. MC and apocrine differentiation are not present in microglandular adenosis [19]. Tubular carcinoma is constituted by angulated glands lined by a single layer of epithelial cells, lacking myoepithelial elements and basal lamina. In addition, no apocrine differentiation is present and the stroma of tubular carcinoma is rich in elastic tissue and perivascular elastosis is the rule [19].

Prognosis

From the data offered from the literature it appears that AME is a low-grade malignancy. Local recurrence is frequent if a local excision is performed. In contrast, with only one exception, recurrences have not been described in patients treated with mastectomy [31]. Local or distant metastases have rarely been reported [59], and only one fatal case has been described [31]. However, when AME is associated with anaplastic areas [7, 35, 36] distant metastases (often involving the lungs) have to be expected.

Pure malignant myoepithelioma

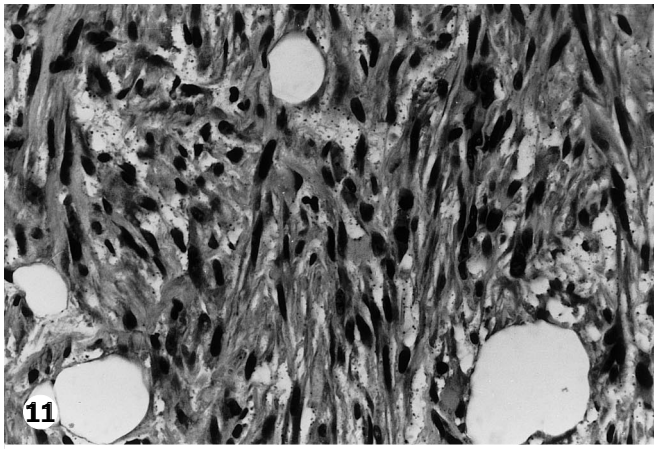
If we exclude those cases of AME that are associated with anaplastic areas [7, 22, 35, 36, 55] only 12 cases of pure malignant myoepithelioma (MM) of the breast, that is a tumour composed exclusively of malignant myoepithelial cells, have been reported so far [6, 15, 16, 29, 33, 40, 48, 49, 51, 53, 58]. These cases occurred in adult patients, most of whom were older than 50 years (range 25–81 years, mean 54 years) [33, 58]. The nodules varied from 0.9 cm to 21 cm in size [40, 58].

Histology of these cases is heterogeneous. Seven cases were composed of atypical spindle cells (Figs. 11, 12) showing intensely eosinophilic cytoplasm. In one instance [6] the neoplastic cells had clear cytoplasm. In one further case a predominantly intraductal component was also present [53]. In two cases [51] the tumours were also intralobular. Finally, one case showed a poorly differentiated in situ and invasive duct carcinoma colliding with a spindle-cell myoepithelial component [48].

All cases showed immunohistochemical and\or ultrastructural features of myoepithelial cell differentiation. In one case [15] squamous cell differentiation was also present.

Follow-up information was available in eight cases of invasive MM. Local recurrences or distant metastases have been documented [29, 48, 49, 58] in four cases. In three cases death eventually occurred 6 months, 32 months and 6 years after presentation [28, 48, 49]. The remaining four patients were free of disease, but the follow-up periods were still very short (varying from 3 to 32 months). In summary, about 50% of reported malignant myoepitheliomas had an aggressive clinical behaviour similar to that described for sarcomatoid carcinomas [18, 21].

On morphology it appears extremely difficult, if not impossible, to separate MM from the monophasic variant of sarcomatoid carcinoma (SC) [21], especially as no fewer than 10 of the 14 cases of SC studied by us [18] displayed actin-positive cells in the “sarcoma-like” component. In addition, cases of AME showing adjacent ar-



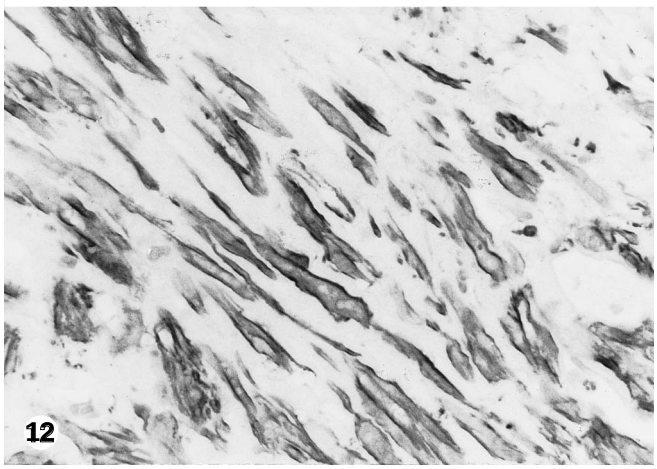


Fig. 11 Pure malignant myoepithelioma (MM), composed of markedly atypical spindle cells. H&E, ×250

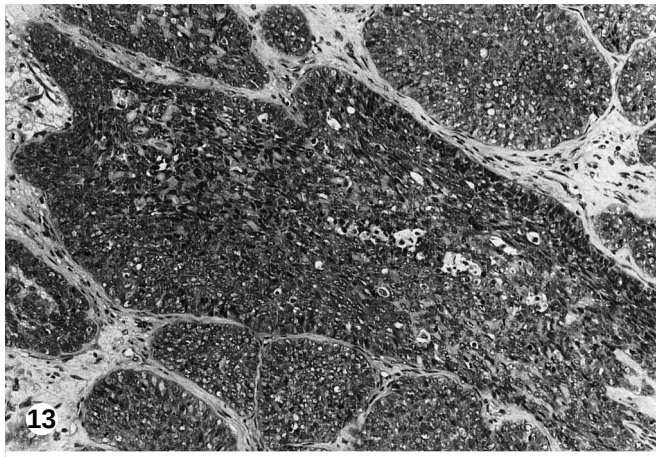
Fig. 12 Pure MM: smooth muscle actin is strongly positive in the neoplastic cells. ABC, ×250

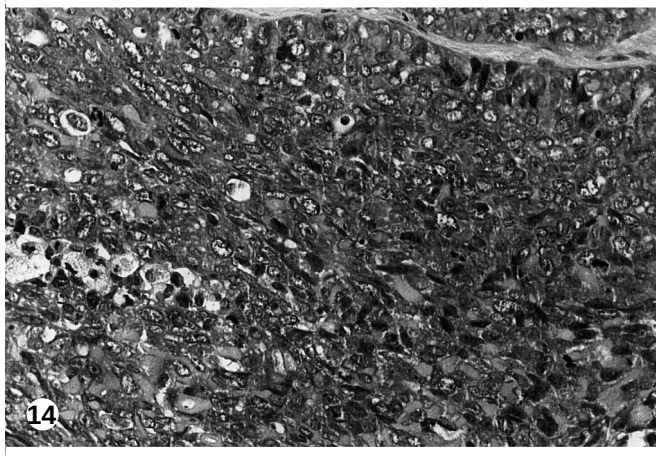
eas composed of spindle-cell actin-rich malignant tumour [35, 36] indicates that transitional forms exist between classical AME and spindle-cell pure myoepithelioma.

Poorly differentiated myoepithelial-rich carcinoma of the breast

Poorly differentiated myoepithelial-rich carcinoma of the breast (PDMC) is a recently recognized variant of breast carcinoma [12] characterized by a proliferation of "ordinary" secretory epithelial cells intermingled with myoepithelial cells. In sections the neoplastic cells are arranged in sheets (Fig. 13), showing focal central necrosis. The neoplastic cells are polygonal to spindle shaped, and their nuclei appear elongated with plump nucleoli (Fig. 14). Atypical mitoses are numerous. Immunohistochemistry using epithelial and smooth muscle markers is helpful in distinguishing the dual population (Fig. 15).

PDMC presents as a palpable nodule in elderly female patients (mean age: 63 years). In two cases metastases to the axillary lymph nodes have been detected. As





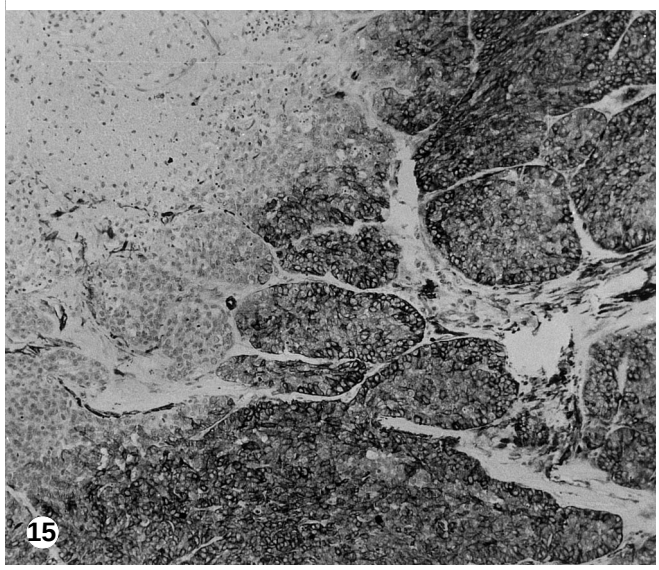


Fig. 13 Poorly differentiated myoepithelial-rich carcinoma (PDMC) is composed of sheets of neoplastic cells. H&E, ×40

Fig. 14 PDMC: neoplastic cells are polygonal to spindle shaped; nuclei are irregular and each has a prominent nucleolus. H&E, ×125

Fig. 15 PDMC: anti-smooth muscle actin antibody is positive in some cells, while others are not immunoreactive. ABC, ×40

all the three patients reported were alive and well 12–69 months after surgery, it has been suggested that such cases have a more favourable prognosis than "ordinary" poorly differentiated invasive ductal carcinoma [12].

Conclusions

MC are clearly involved in several neoplastic processes, ranging from benign to malignant. Malignant lesions show a spectrum of morphological features, which correspond to different clinical behaviours. At one end of the spectrum ACC, syringomatous carcinoma and AME are low-grade malignant tumours, which progress slowly and rarely give rise to metastases. A more aggressive course should be expected when these lesions are associated with proliferation of atypical cells showing the immunohistochemical and/or ultrastructural features of MC differentiation. The other end of the spectrum includes malignant myoepithelioma, which is morphologically and clinically similar if not identical to monophasic sarcomatoid carcinoma, with PDMC located between the two extremes in terms of prognosis.

It appears that tumours with MC differentiation can have well or poorly differentiated features that parallel those seen in ordinary invasive carcinomas. As elaborated elsewhere [21], it is possible that tumours showing MC differentiation are the result of neoplastic transformation from a stem cell capable of dual differentiation. This is suggested by the presence of both types of neoplastic elements intermingled in PDMC, and also by the fact that most of the tumours made up of neoplastic myoepithelial elements consist phenotypically of two types of cells: secretory epithelial and myoepithelial neoplastic elements.

The characterization of MC depends on the immunophenotypic and ultrastructural findings. It is likely that studies at gene level will broaden the spectrum of MC tumours. Some of the so-called undifferentiated stem cell invasive carcinomas may be shown to have the genetic information allowing the development of contractile proteins.

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