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CASE REPORT

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Malignant adenomyoepithelioma of the breast with metastasis in the thyroid gland 12 years after excision of the primary tumor

Case report and review of the literature

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Abstract We describe a patient who was admitted to our hospital with an enlarged left lobe of the thyroid gland. Since fine-needle aspiration showed atypical follicular cells, a surgical exploration followed. Owing to extensive tumor infiltration into the surrounding tissues curative surgery was not possible, and only an incisional biopsy was taken. Histological examination of this biopsy revealed a mixed tumor composed of epithelial and myoepithelial cells. A primary thyroid tumor, metastasis of a salivary gland, and a skin appendage tumor could be excluded based on clinical examination, conventional histology, and immunohistochemistry. A tumor of the left breast treated 12 years earlier had originally been classified as an intraductal/intracystic carcinoma with focal invasion, but was re-examined. Using immunohistochemistry, the breast tumor was reclassified as a malignant adenomyoepithelioma. The current tumor was apparently a metastasis from this primary breast tumor. An updated review of the literature is given, including current knowledge on histological and immunohistochemical features of adenomyoepithelioma of the breast, with special attention to the reported pathological characteristics of recurrent and malignant tumors. Based on the reported pathological characteristics of recurrent and metastatic tumors we offer a diagnostic tool for identifying potentially malignant and recurrent tumors.

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Introduction

Adenomyoepithelioma is a rare primary tumor of the breast in women. It consists of epithelial cells accompanied by myoepithelial cells. Both cell types are normally present in glandular tissue of the breast. In 1970, Hamperl [23] became the first to describe a primary breast adenomyoepithelioma. Since then, reported cases have frequently been presented in small numbers or as single case reports [1, 5, 7, 9–14, 16, 18, 22, 24, 26, 28, 29, 31, 33, 34, 36–44, 49, 50, 53, 55, 59, 62, 64–66, 68–70], and occasionally in larger series [20, 32, 45, 48, 60]. The age of the patients so far reported ranges from 24 to 82 years, with a mean of 58 years. Only two cases have been described in men [3, 58].

Although most of the adenomyoepitheliomas reported have been considered to be benign [10, 16, 19, 22–24, 26, 31, 32, 36, 48–50, 55, 58, 60, 62, 63, 66, 68], they can recur locally [7, 20, 28, 32, 37, 42, 45, 48, 53, 60, 64, 69], progress subsequently to a (more) malignant state [20, 28, 32, 42, 45, 53, 60], and give rise to metastases [9, 20, 32, 37, 45, 53, 60, 64]. Morphological features of malignancy that could predict the potential for local recurrence and/or metastasis are not well established.

We describe a 64-year-old woman with the very rare presentation of metastasis in the thyroid gland from a malignant adenomyoepithelioma of the breast 12 years after excision of the primary tumor.

Case report

Clinical presentation

A 64-year-old woman was admitted to our hospital with complaints of palpitations, perspiration, loss of weight, and intolerance to heat. She had felt a tumor in the left lobe of her thyroid gland. Modified radical mastectomy had been performed for an invasive carcinoma of the left breast 12 years earlier.

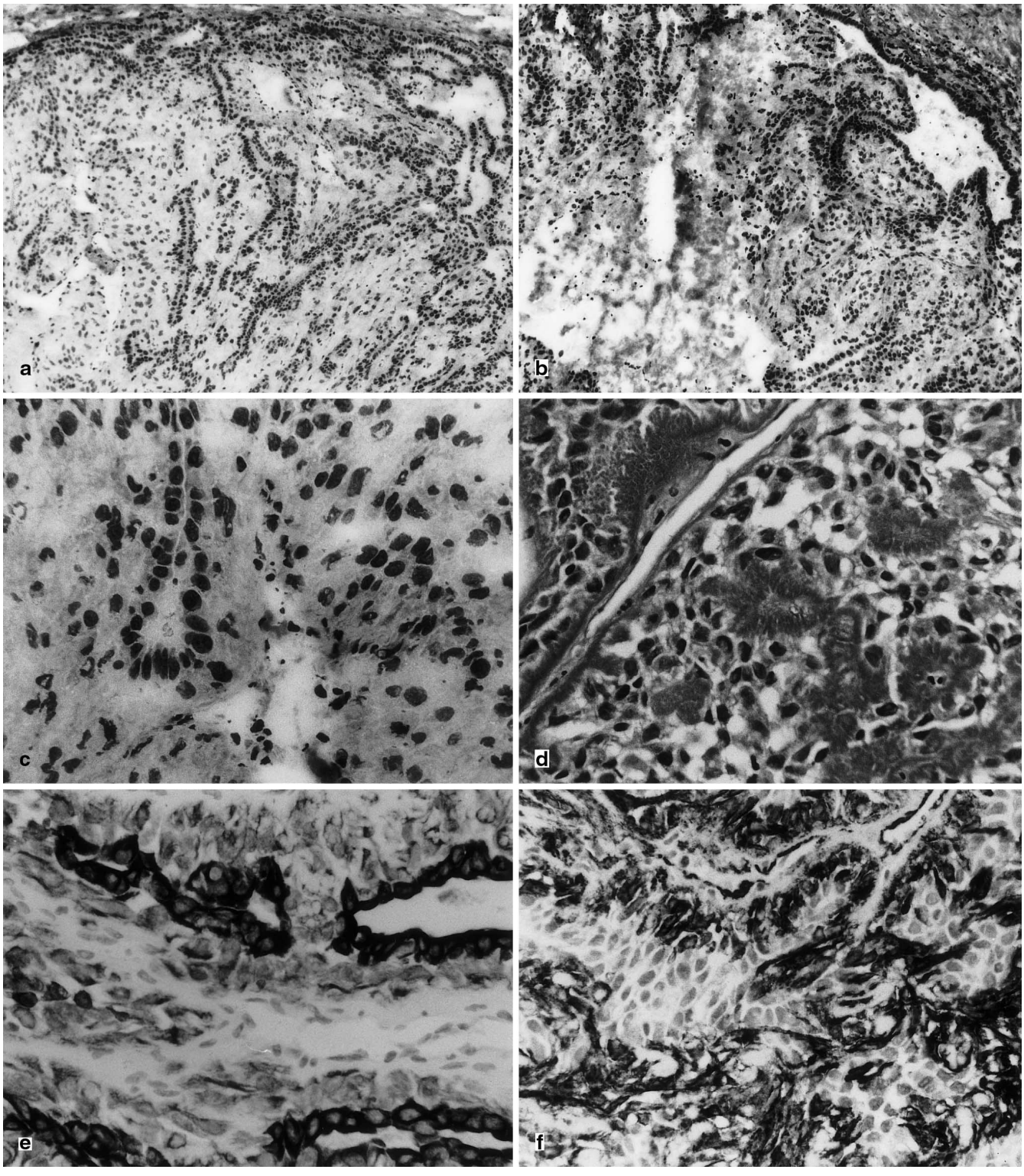

Fig. 1a–f Metastatic tumor of thyroid. **a** The epithelial component displays irregular tubuli, partly dilated with pale moderately cellular areas of the myoepithelial component in between. **b** Extensive necrosis in partly solid and partly papillary tumor. **c** Solid area of pale myoepithelial cells with atypical nuclei surrounding a few tubuli. **d** PAS-positive, diastase-resistant material around and within the myoepithelial component, representing basement membrane material. Immunohistochemistry. **e** The epithelial cells were strongly positive and the myoepithelial cells slightly positive for keratin CAM 5.2. **f** The myoepithelial cells were strongly positive for smooth muscle actin alpha-Sm-1

Table 1 Immunohistochemical characteristics of the thyroid metastasis (*TM*), the primary breast tumor (*PBT*), and the reported adenomyoepitheliomas (*RA*)[a] (*ND* not done, + positive reaction, – negative reaction, *F+* focally positive, +/– positive as well as negative reaction reported, (+) positive reaction in minority of reported cases)

Markers	Epithelial cells			Myoepithelial cells		
	TM	PBT	RA	TM	PBT	RA
EMA	ND	ND	+	ND	ND	–
Cytokeratin	+	+	+	+	F+	+/–
CAM 5.2	+	+	+	+	F+	+/–
Prekeratin	ND	ND	+	ND	ND	–
CEA	+	+	+	+	+	+/–
GCDFP-15	–	F+	+/–	–	F+	+/–
Estrogen receptor	–	F+	+/–	–	–	–
Progesterone receptor	ND	ND	+/–	ND	ND	–
Vimentin	F+	F+	–	+	+	+/–
S100 protein	–	–	–(+)	+	+	+
Smooth muscle actin	–	–	–	+	+	+
Chromogranin	–	–	–	–	–	–
Desmin	ND	ND	–	ND	ND	–

[a] RA based on 43 reported studies

Physical examination revealed an asymmetrical enlarged multinodular palpable thyroid, with an elastic mass on the left side. No palpable lymph nodes were found, and further physical examination, which included the skin and salivary glands, showed no abnormalities.

Histological analysis was required since fine-needle aspiration cytology revealed follicular cells with marked atypical features.

At surgical exploration, a large tumor was found in the left thyroid lobe, infiltrating the surrounding muscles, the esophagus, and the tracheal wall and obliterating the left internal jugular vein. Because curative surgery was not possible, only an incisional biopsy was taken.

Pathological examination

The entire biopsy specimen, 1.5 cm in size, was processed for frozen section. The hematoxylin and eosin (HE)-stained slides revealed an invasive carcinoma infiltrating the muscle. After routine formalin fixation (4% buffered formalin) and paraffin embedding, the tumor was evaluated (Fig. 1a–d). The tumor did not show features of a thyroid carcinoma. Rather, a biphasic structure was seen with two distinct cell types. The first cell type consisted of small cubic or columnar cells with eosinophilic cytoplasm forming ducts, slit-like spaces or slightly cystic structures, and sometimes trabeculae, which suggested an epithelial origin. Within the lumina, a periodic acid–Schiff (PAS)-positive, diastase-resistant, secretion was found, with slightly positive staining of the apical portion of the cytoplasm of the epithelial cells. The epithelial cells also showed some glycogen (PAS-positive, diastase-digestible, granules) in the cytoplasm. Few mitoses were present. The second cell type consisted of larger polygonal cells with clear cytoplasm and pleomorphic nuclei with one or more prominent nucleoli and numerous mitoses. These cells surrounded the former cells or were separated off in solid nests or strands, which suggested a myoepithelial origin. Around and partly within the groups of these myoepithelial cells, PAS-positive and diastase-resistant, eosinophilic hyaline material was found. This suggests basement membrane material. The cells contained a large amount of glycogen. Necrotic areas were also present.

To exclude thyroid carcinoma and to confirm the diagnosis of a mixed epithelial and myoepithelial tumor, immunohistochemistry was performed (Table 1). In summary, the markers for thyroid malignancies (thyroglobulin and calcitonin) were negative. The epithelial component of the tumor was strongly positive for different types of keratins and other epithelial markers. The myoepithelial component of the tumor was strongly positive for (smooth) muscle actin, vimentin, and S100 protein (Fig. 1e, f). Between 10% and 25% of the epithelial cells and between 25% and 50% of the myoepithelial cells were positive for MIB-1 (Ki-67). The results confirmed the biphasic, mixed epithelial and myoepithelial, character of the tumor and ruled out a primary tumor of the thyroid.

Re-examination of the cytological slides from the fine-needle aspiration of the tumor revealed atypical cells arranged in small cohesive groups with some solitary cells and atypical naked nuclei with round to oval and partly irregular outlines, and dispersed fine granular chromatin with one or more easily recognizable nucleoli. Immunocytochemistry showed that the atypical cells were positive for alpha Sm-1 and vimentin, and negative for keratin and thyroglobulin. These results corresponded to the myoepithelial component of the tumor described above.

Because the medical history included a primary invasive carcinoma in the left breast that had been treated 12 years earlier by modified radical mastectomy, the pathology of this tumor was reexamined. The original pathology report of the biopsy specimen described a tumor measuring 1.6 cm in diameter with partly well-circumscribed and partly irregular borders. Histological examination (Fig. 2a–d) revealed that the tumor had a mostly solid and focally papillary aspect with central necrosis, focal hemorrhage, and fibrosis. A fibrous pseudo-capsule was most frequently found. In addition, focally invasive growth in adipose tissue was found. The tumor contained two different cellular components. The first component had an epithelial aspect forming glandular structures with ducts, slit-like spaces, cystic spaces, or papillary configurations. Some intraductal epithelial proliferation was seen with clinging, micropapillary, cribriform, or solid aspects. The epithelial cells were cubic or columnar with eosinophilic cytoplasm, slightly pleomorphic nuclei containing recognizable nucleoli, and up to 9 mitoses per 10 high-power fields (HPF; 400×). The cells contained intracellular glycogen and in the lumina a PAS-positive, diastase-resistant, secretion was found, with slightly positive staining of the apical portion of the cells. In addition, focal squamous metaplasia was present. Some of the cells also showed prominent eosinophilic globules in their cytoplasm, suggesting an apocrine origin. The second component had myoepithelial characteristics with cells arranged around the epithelial structures formerly described, in one or more layers, or forming solid nests or strands. These cells were large, mostly polygonal, and partly flattened, with clear or faintly eosinophilic cytoplasm. They contained round to oval or elongated, partly irregular, moderately to strongly pleomorphic, hypochromatic nuclei with one or more easily recognizable nucleoli (Fig. 2d). Most of the cells also contained glycogen (Fig. 2e, f). Mitoses were numerous (up to 28 per 10 HPF, 400×). All 13 axillary lymph nodes were negative.

The immunohistochemical analysis of the breast tumor revealed very similar results to that of the thyroid tumor (Table 1, Fig. 3a–d). Between 5% and 10% of the epithelial cells and between 10% and 20% of the myoepithelial cells were positive for MIB-1.

On the basis of both conventional light microscopical evaluation and the immunohistochemical analysis, the diagnosis of malignant adenomyoepithelioma was made, and we concluded that the tumor of the thyroid gland was a metastasis from this primary breast tumor. The patient was first treated with chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil), but because there was no response, this was followed by local radiation therapy with the addition of Adriamycin. She died 10 months after diagnosis of the thyroid metastasis, probably of complications of extensive regional disease (no autopsy was performed).

Discussion

Adenomyoepitheliomas frequently appear in the salivary glands and the skin. They are composed of an admixture

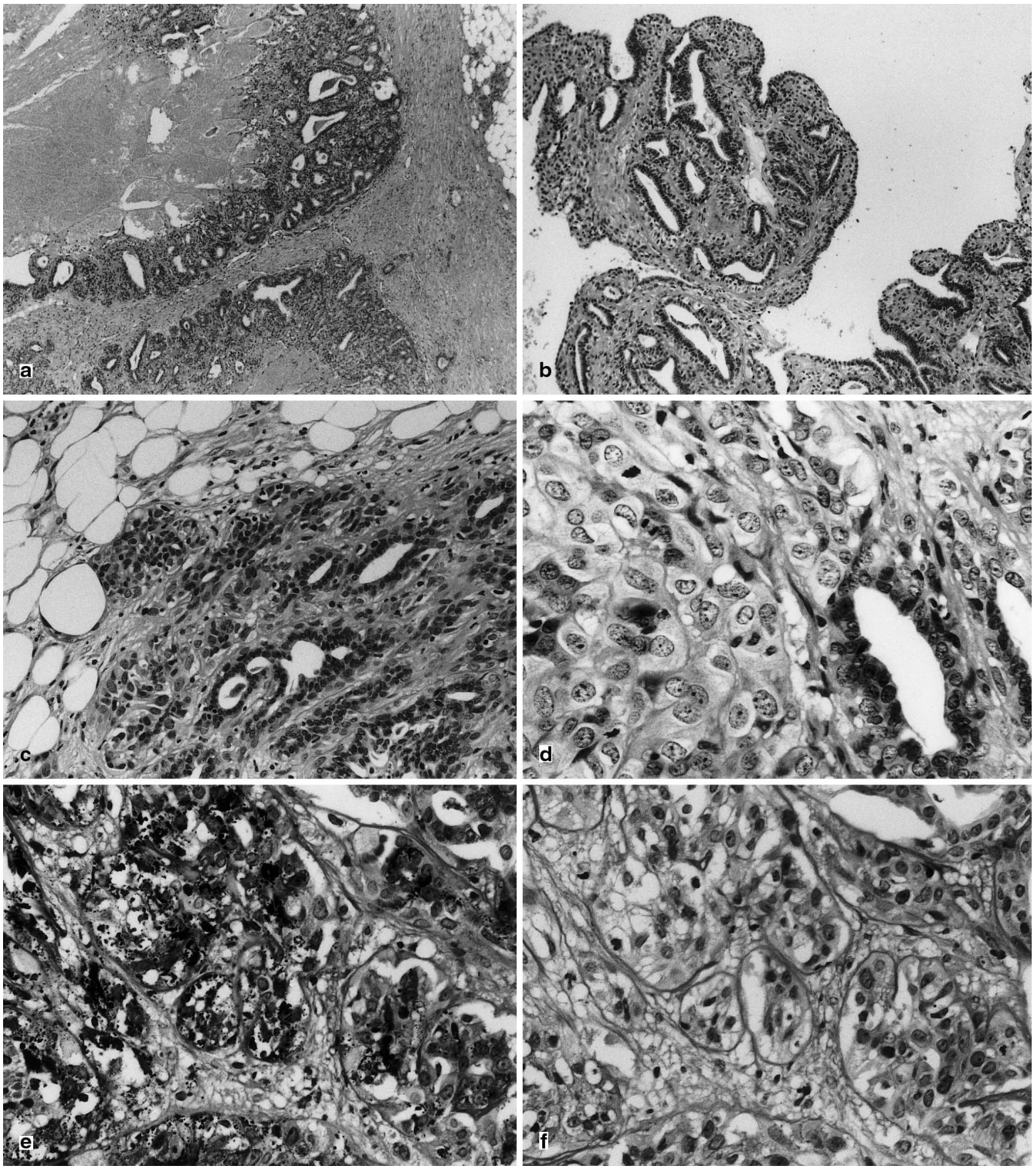

Fig. 2a–f Primary breast tumor. **a** The tumor had a lobulated aspect with a fibrous capsule (*right side*) and a large area of necrosis (*left side*). **b** Tumor area with papillary growth. **c** Irregular tubuli surrounded by pale atypical polygonal myoepithelial cells, infiltrating fat tissue. **d** Solid area of severely atypical polygonal myoepithelial cells with clear cytoplasm, hypochromatic nuclei with one or more easily recognizable nucleoli, and mitoses surrounding some tubuli. **e**, **f** The cytoplasm of the myoepithelial cells showed a strong granular staining with PAS (**e**), which disappeared with diastase digestion (**f**), representing glycogen

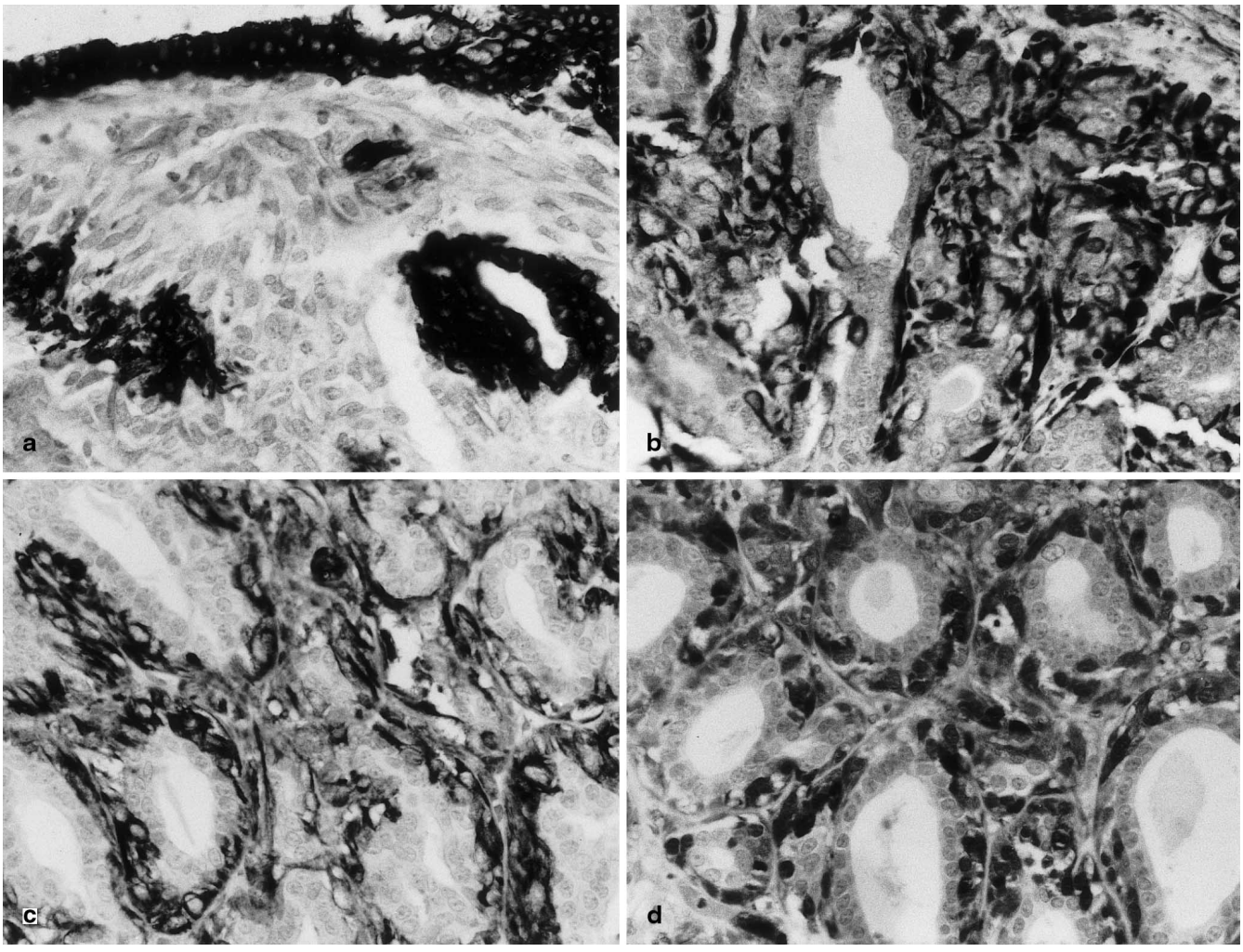

Fig. 3a–d Primary breast tumor. Immunohistochemistry. **a** Strong positive reaction of the epithelial cells for keratin CAM 5.2. **b–d** The myoepithelial cells were strongly positive for vimentin (**b**), muscle actin HHF35 (**c**), and S100 protein (**d**)

of epithelial and myoepithelial cells. So far, a total of 123 cases have been described in the breasts of women [1, 5, 7, 9–14, 16, 18, 20–24, 26, 28, 29, 31–34, 36–45, 48–50, 53, 55, 59, 60, 62, 64–66, 68–70], including some cases termed as "mixed" salivary-type adenoma [35], benign mammary myoepithelioma [63], clear cell hydradenoma [19], and adenomyoepithelioma associated with low-grade adenosquamous carcinoma [25]. In addition to adenomyoepitheliomas, pleomorphic adenomas and adenoid cystic carcinomas also show an admixture of epithelial and myoepithelial cells, albeit in a rather distinct, easily distinguished, manner [2, 34, 46, 52, 67]. Tumors composed exclusively of myoepithelial cells are usually called myoepitheliomas [4, 6, 8, 15, 17, 27, 30, 47, 48, 51, 54, 56, 57, 61].

Patients with an adenomyoepithelioma of the breast usually present with a palpable mass [1, 3, 5, 7, 9–14, 16, 18, 20, 22, 26, 28, 29, 31–34, 36–41, 43–45, 48, 50, 53, 55, 58–60, 62, 64–66, 69]. Some adenomyoepitheliomas may be nonpalpable and can only be distinguished on a mammogram [32, 49, 68]. The mammogram usually displays a well-circumscribed density [3, 10, 11, 14, 22, 24, 36, 44, 49, 58, 60, 62, 66, 68]. In addition, some may include microcalcifications [10, 12, 49, 62].

Gross examination of the tumor usually reveals a well-defined, firm, hard, elastic, rubbery, or indurated mass, but sometimes it can be soft or have irregular borders. The size of the tumor can range from 0.5 to 10 cm. On the cut surface, the tumor is usually solid, but papillary growth or cystic structures may be found as well. Foci of hemorrhage or necrosis may also be seen [1, 3, 5, 7, 10, 11, 13, 14, 16, 18, 20, 24, 26, 28, 29, 31–34, 36–41, 43, 44, 48, 50, 53, 58–60, 62, 65, 66, 68–70].

Upon microscopical examination, the tumor can be found to be delineated by a true or pseudo-capsule and is composed of an epithelial and myoepithelial component. Depending on the relative abundance of each of the two different components, their respective growth patterns, and cytological appearances, the tumors can have a great variability in histological presentation. The epithelial component may form solid nests or groups, ducts, cystic, trabecular, pseudo-papillary, or papillary structures. The epithelial cells usually have a cubic or cylindrical shape. Their cytoplasm is mostly eosinophilic, but can also be clear or amphophilic. A PAS-positive, diastase-resistant,

Table 2 Pathological characteristics of reported potentially malignant adenomyoepitheliomas (+ present, – absent, *MAI* mitotic activity index = no. of mitoses/10 high-power fields (*HPF*), *LS* leiomyosarcoma, *MC* myoepithelial carcinoma, *NOTC* no other tumor component, *ACC* adenoid cystic carcinoma, *ApA* apocrine adenosis, *AcSCC* acantholytic squamous cell carcinoma, *AdSC* adenosquamous carcinoma, *AdMA* adenomyoepithelial adenosis, *UC* undifferentiated carcinoma, *IDC* invasive ductal carcinoma, *OS* osteosarcoma, *UMSCT* undifferentiated malignant spindle cell tumor, *AC* adenocarcinoma)

Reference	No. of patients	Cellular pleomorphism	Mitoses (MAI)	Necrosis	Invasion of surrounding tissue	Associated with	Local recurrence	Metastases
[7]	1	+	+		In recurrence	LS (in recurrence)	+	–
[9]	1	+	+ (3–5)			MC	–	+ (axillary lymph node and bone)
[11]	1	+	+			NOTC	–	–
[14]	1		+ (2)			ACC	–	–
[18]	2	+	+ (16)			ApA	–	–
[20]	6	+ (1 of 6)				AcSCC (3 of 6) (1 of 3 in recurrence)	+ (1 of 3)	+ (1 of 3) (lung)
						AdSC (3 of 6)	–	–
[25]	3					AdSC	–	–
[28]	1					AdMA	+	–
[32]	2	+	+ (11–14)	+ (1 of 2)		NOTC	+ (1 of 2)	+ (1 of 2)(lung and brain)
[37]	1		+	+		UC	+	+ (lung)
[40]	1	+	+ (10)		+	NOTC	–	–
[42]	1	In recurrence	+ (3)			NOTC	+	–
[45]	7	+	+ (6–16)	+ (4 of 7)	+ (4 of 7)	IDC (2 of 7)	+ (4 of 7)	–
						NOTC (5 of 7)	–	+ (1 of 3) (brain)
[53]	1	In recurrence	+		+	OS UMSCT (in recurrence) IDC (in recurrence)	+	+ (lung)
[60]	2					MC (1 of 2)	–	+ (axillary lymph node)
						AC (1 of 2)	–	–
[64]	1	+	+ (14)			NOTC	+	+ (lung)
[69]	2	+	+ (0–3)		In recurrence (1 of 2)	NOTC	+ (1 of 2)	–
[70]	1		+	+		NOTC	–	–
Present study	1	+	+ (37[a])	+	+	NOTC	–	+ (thyroid)

[a] 9/10 HPF in epithelium+ 28/10 HPF in myoepithelium

secretion can be seen at the luminal side of the cytoplasm and/or in the lumen. The epithelial cells can also have apocrine features and may show squamous or mucinous metaplasia. Occasionally, a sebaceous cell population may be seen. Nuclear atypia has been described. Mitoses are usually scanty, but a mitotic count of up to 10 per 10 HPF has been reported. Sometimes atypical ductal hyperplasia is present, and even ductal carcinoma in situ can be seen. The myoepithelial component is arranged around the epithelial component and can form solid strands, trabeculae, or even larger sheets. The myoepithelial cells are embedded in or surrounded by a basal lamina. They are usually polygonal or spindle shaped. Their cytoplasm is usually clear, but may also be eosinophilic, pale, pink, or amphophilic. Sometimes dense hyalin-like cytoplasm is found giving the cells a plasmacytoid appearance. PAS-positive, diastase-digestible, granular staining of the cytoplasm representing glycogen is often seen, especially in the cells with clear cytoplasm. Nuclear atypia may be present as well. Mitotic counts ranging from 0 to 16 per 10 HPF have been reported. The tumor may contain foci of necrosis, and sometimes calcifications are present. Multifocal tumor spread is occasionally seen, with satellite nodules around the main tumor. It may also be associated with so-called adenomyoepithelial adenosis [1, 3, 5, 7, 9–14, 16, 18, 20, 22–24, 26, 28, 29, 31–34, 36–45, 48–50, 53, 58–60, 62, 64–66, 68–70].

Immunohistochemistry is very helpful in distinguishing the two cell types (Table 1) [1, 3, 5, 9–14, 16, 18, 20, 22, 25, 26, 28, 29, 31, 32, 34, 36–45, 48–50, 53, 58–60, 62, 64–66, 68, 69].

Tavassoli [60] has proposed a subclassification of adenomyoepitheliomas into three types; tubular, lobulated, and spindle-cell types. Our case fulfills the criteria of the lobulated type, with one or more layers of polygonal myoepithelial cells arranged around the epithelial cells, frequently with the formation of solid groups of myoepithelial cells as well (Figs. 1, 2).

As intimated previously, most of the reported adenomyoepitheliomas have been considered to be benign [10, 16, 19, 22–24, 26, 31, 32, 36, 48–50, 55, 58, 60, 62, 63, 66, 68], and in other cases no judgement was given about the benign or malignant nature of the tumors [1, 3, 5, 13, 21, 29, 33–35, 38, 39, 41, 43, 44, 59, 65]. Local recurrences have been described in 20 patients [7, 20, 28, 32, 37, 42, 45, 48, 53, 60, 64, 69]. The frequency of recurrences ranged from one to six. The time within which the recurrences occurred ranged from 4 months to 23 years after initial diagnosis. The likelihood of recurrence seems to be associated with incomplete removal [48], the presence of cellular pleomorphism [7, 14, 32, 45, 64, 69], mitoses [7, 14, 37, 42, 45, 53, 60, 64, 69], necrosis [37, 45, 60], invasion of the surrounding tissue [45, 53], and association with other types of malignant tumors, such as undifferentiated carcinoma [37], invasive ductal carcinoma [45], leiomyosarcoma [7], myoepithelial carcinoma [60], acantholytic squamous cell carcinoma [20], and osteosarcoma [53].

The total of 125 cases included 35 in which the tumors were considered to be potentially malignant [7, 9, 11, 14, 18, 20, 25, 28, 32, 37, 40, 42, 45, 53, 60, 64, 69, 70] on the basis of either the features of the adenomyoepithelioma itself or the association with other types of malignant tumors (Table 2). The presence of mitoses [7, 9, 11, 14, 18, 32, 37, 40, 42, 45, 53, 64, 69, 70], with mitotic counts of up to 16 per 10 HPF [9, 14, 18, 32, 40, 42, 45, 64, 69], cellular pleomorphism [7, 9, 11, 18, 20, 32, 40, 45, 64, 69], necrosis [32, 37, 45, 70], high cellularity [37, 70], invasion of the surrounding tissue [40, 45, 53], overgrowth by myoepithelial cells [7], and the presence of satellite foci [7] were considered to be features of malignancy. Malignant tumors reported in association with adenomyoepithelioma were adenoid cystic carcinoma [14], undifferentiated carcinoma [37], invasive ductal carcinoma [45, 53], leiomyosarcoma [7], myoepithelial carcinoma [9, 60], adenosquamous carcinoma [20, 25], acantholytic squamous cell carcinoma [20], osteosarcoma [53], and undifferentiated malignant spindle cell tumor [53]. Thirteen of the 35 tumors recurred locally [7, 20, 28, 32, 37, 42, 45, 53, 64, 69] (37%), and in 5 of these cases systemic metastases developed [20, 32, 37, 53, 64]. A total of 8 cases with metastases have been reported in the literature. The sites of metastases were the axillary lymph nodes [9, 60], the lungs [20, 32, 37, 53, 64], the brain [32, 45], and the bones [9]. Features of the primary tumors that metastasized were similar to those of locally recurrent tumors, namely cellular pleomorphism [9, 32, 45, 64], high mitotic count [9, 32, 37, 45, 64], necrosis [32, 37], and association with undifferentiated carcinoma [37], myoepithelial carcinoma [9, 60], acantholytic squamous cell carcinoma [32] and osteosarcoma [53]. Recurrences were reported in 5 of the 8 cases with metastases [20, 32, 37, 53, 64]. In our case, the tumor was characterized by moderate to severe cellular pleomorphism, especially of the myoepithelial component, high mitotic count for both the epithelial (9 per 10 HPF) and the myoepithelial component (28 per 10 HPF), focal invasive growth, and necrosis. These are all potential features for malignancy.

Table 2 summarizes those histopathological features of the tumors that may predict the likelihood of recurrence and metastasis. The presence of such features of a given tumor could then result in a more extensive local treatment. In some cases systemic therapy may even be considered.

Because of this entity's potential for local recurrence and subsequent malignant progression, adenomyoepitheliomas should preferably be treated by wide local excision. We consider our case a representative example of a malignant adenomyoepithelioma, although the peculiar site of the metastasis and the 12-year time span between the primary tumor and the appearance of systemic metastasis seem somewhat atypical. Based on the reported pathological characteristics of recurrent and metastatic tumors we offer a diagnostic tool (Table 2) for classifying adenomyoepitheliomas with respect to the ability of recurrence and metastasis.

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