

REVIEW

Adenomyoepithelioma of the breast: a proposal for classification

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Breast lesions with a prominent myoepithelial cell component constitute a heterogeneous group of benign and malignant neoplastic proliferations. These lesions are often dual epithelial–myoepithelial, but may be purely myoepithelial cell in nature. Benign epithelial–myoepithelial lesions typically maintain the morphology and immunophenotype of the normal bilayer epithelial myoepithelial structures. However, the distinction between the two cell components is not always clear-cut in malignant lesions in which the histogenesis of myoepithelial cells remains uncertain. Neoplastic biphasic epithelial–myoepithelial lesions of the breast include adenomyoepithelioma (AME), pleomorphic adenoma and adenoid cystic carcinoma. Four histological patterns of classical AME have been described: tubular, lobulated, spindle-cell

and adenosis variants. Overlapping patterns occur and some AMEs display an intraductal papillary pattern that may represent a fifth variant. AME can be benign or malignant. Classical AME may show atypical features, which are not sufficient for the diagnosis of malignancy (atypical AME). Atypical AME is recognised as a lesion of uncertain malignant potential with limited metastatic capability. Based on the histological features, we propose a classification of malignant AME (M-AME) into three variants: M-AME *in situ*, M-AME invasive and AME with invasive carcinoma. In this review, we provide an overview of myoepithelial lesions of the breast focusing on the classification of AME to improve not only the consistency of reporting but also help to guide further management decision-making.

Keywords: breast adenomyoepithelioma, classification, diagnosis, outcome

Introduction

The human breast incorporates a branching ductal network lined by an inner layer of polarised luminal epithelial cells and an outer layer of myoepithelial cells (MECs), separated from the stroma by a laminin-rich basement membrane. End-differentiated MECs, like epithelial cells, derive from precursor stem cells

positioned within the luminal epithelial compartment.^{1,2} MECs, localised at the epithelial stroma interface, communicate with both compartments and may function as a guardian of tissue integrity by maintaining tissue polarity.^{1–3} End-differentiated MECs are distinguished from luminal epithelial cells and myofibroblasts by location, shape and immunoprofile (Table 1). Myoepithelial and basal cell differentiation, detected by cytokeratin (CK)14, CK5/6, CK17, vimentin and epidermal growth factor receptor (EGFR) immunohistochemistry, is also seen in 20–35% of invasive breast cancers (IBCs) with a smaller proportion expressing myoepithelial myoid markers; e.g.

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Table 1. Myoepithelial cell markers commonly used in breast pathology

Marker	Comments
1 Smooth muscle actin (SMA)	SMA is a robust marker that is usually retained in poorly fixed or infarcted tissue. It is typically strongly positive in myoepithelial cells (MEC). Assuming that internal controls are appropriately positive, the absence of staining for smooth muscle actin is strong evidence that there is no myoepithelial layer. The major weakness is lack of specificity. Staining of myofibroblasts adjacent to carcinoma cells can make interpretation difficult
2 Smooth muscle myosin heavy chain (SMMHC)	SMMHC is more specific than SMA and easier to interpret but it is a less robust marker due to lower sensitivity and may not stain well in poorly fixed or infarcted tissue
3 P63	p63 is a homologue of the p53 tumour suppressor gene. p63 is more specific than SMA and SMMHC with no staining of myofibroblasts and blood vessels. Like SMMHC, p63 is a less robust marker than SMA. If the myoepithelial layer is attenuated, interpretation of p63 can be difficult, as there are large gaps between positive nuclei. It is also a squamous cell marker and can be expressed by lesional cells in some tumours
4 Basal cytokeratins (CK 14, CK5, CK5/6 and CK17)	They are expressed in MECs but are also expressed in some normal and hyperplastic epithelial cells. Basal CKs frequently stain MECs weakly, so they should not be used as myoepithelial markers on their own, but they can be very helpful if they are positive
5 CD10 (the common acute lymphoblastic leukaemia antigen)	CD10 is similar to SMMHC staining in the majority of cases but in our experience, it is less robust with expression absent in some cases for unknown reasons. Therefore, it can be useful when it is retained and positive. Focal background staining of stromal myofibroblasts can be seen with both CD10 and SMMHC, but CD10 shows a higher rate of non-specific staining of epithelial cells and it does not stain blood vessels
6 Calponin	Calponin, similar to SMMHC, is a marker of terminal smooth muscle differentiation, and it is more specific for MECs than SMA. Calponin, like caldesmon, is an actin-binding protein found in appreciable quantity in a variety of smooth muscles and some non-muscle tissues. Calponin has similar staining patterns to SMMHC
7 Other positive ME markers	P40, podoplanin (D2-40), maspin, caveolin 1 and 2, nestin, 14-3-3 sigma (stratifin), S100, P-cadherin
8 Negative markers	HER2, EMA/MUC1, BerEP4, ER, PR, AR, GCDFP-15, EpCAM with negative or weak luminal CKs and E-cadherin*

*In human mammary glands, the expression of low-molecular-weight luminal-type cyrokeratins (CK7, CK8, CK18, and CK19) and other luminal enriched markers is characteristics of the end-differentiated luminal cells. HER2, human epidermal growth factor.

smooth muscle actin (SMA) and smooth muscle myosin heavy chain (SMMHC).^{3,4} Global expression studies have confirmed the existence of a subset of IBC that features a basal/myoepithelial profile and comprises 15–20% of all breast tumours.³ It is important to differentiate IBCs that express myoepithelial or basal markers and frequently associated with a poor prognosis from breast lesions with a dual epithelial myoepithelial phenotype, which may display a benign, locally aggressive or malignant clinical course.

Breast lesions with a myoepithelial cell component

Breast lesions with prominent MEC components constitute a heterogeneous group of lesions, which are

often dual epithelial–myoepithelial but may be purely MEC in nature (Table 2). Neoplastic epithelial–myoepithelial lesions of the breast include AME [classical (benign and atypical) and malignant], pleomorphic adenoma and adenoid cystic carcinoma.^{4,5} Benign epithelial–myoepithelial lesions typically maintain the morphology and immunophenotype of the normal bilayered epithelial myoepithelial structures and are considered neoplastic proliferations of separate epithelial and myoepithelial cells. However, in malignant lesions the distinction between the two cell components is not always clear-cut, and the histogenesis of myoepithelial cells in these lesions remains uncertain.^{6–9} In practice, we consider the presence of a coexistent benign-appearing biphasic component as evidence of dual cell origin which progressed to a malignant tumour with any aberrant phenotype due

Table 2. Myoepithelial lesions in the breast

Types	Lesions
Normal myoepithelial cells (MECs)	Terminal ducts lobular units and ducts (one layer at epithelial stroma interface). Typically express almost all myoepithelial associated markers A subset of end differentiated MECs and neoplastic MECs may lack expression of myoid markers and basal CKs ¹
Basal cells	These are intermediate cells with a phenotype between end differentiated MECs and luminal epithelial cells and show expression of low and high molecular weight CKs but lack expression of myoepithelial specific markers, e.g. p63. ^{1,2} These cells are frequently seen in the proliferative pool of usual ductal hyperplasia (UDH)
MEC hyperplasia	In intraductal papilloma, in sclerosing adenosis and can be seen in fibroepithelial lesions. Myoid metaplasia and hyperplasia can be seen in elderly people as isolated changes
Benign epithelial myoepithelial lesions	Collagenous spherulosis, pleomorphic adenoma and benign AME. MEC may show mild alteration of immunophenotype
Atypical MEC neoplasms	Atypical AME
Malignant epithelial myoepithelial lesions	Malignant AME (<i>in-situ</i> , invasive and AME with carcinoma). Adenoid cystic carcinoma,* MEC typically show aberrant immunophenotype
Other lesions that show MEC differentiation	Metaplastic carcinoma and basal-like breast carcinoma may show typical basal cells immunophenotype with basal CK expression, less commonly myoid differentiation markers and rarely express p63 or p40

*Myoepithelial cells (MECs) of adenoid cystic carcinoma tend to be smaller, more hyperchromatic and basaloid appearing and have much less cytoplasm than those of adenomyoepithelioma (AME). They are mixed with the epithelioid cells, line pseudolumina rather than forming a bi-layer structure or sheets and clusters of cells.

to de-differentiation during carcinogenesis. Alternatively, these tumours may arise from a single progenitor cell (from which luminal breast carcinoma also arises) with differentiation towards cells with both luminal and basal/myoepithelial phenotypes. Molecular studies indicate that both components are neoplastic and clonally related with a common stem cell origin.⁹⁻¹¹ Regardless of histogenesis, diagnosis is based on the recognition of the dual cell population, using morphology and/or immunohistochemistry. In our experience, MECs are easily identified in benign AME; however, their identification in atypical and malignant variants is more difficult, and discordance between morphology and immunoprofile appears to be correlated with the degree of malignancy.

Neoplasms composed entirely of MECs represent one end of the spectrum of MEC proliferation. These are exceptionally rare and limited to isolated reports of benign myoepithelioma⁵ and myoepitheliosis,¹² the existence of which is not widely accepted, and malignant myoepithelioma/myoepithelial carcinoma, now regarded as a form of metaplastic carcinoma (MBC).⁴ The term 'MEC carcinoma' was used to describe rare tumours composed of malignant spindle cells with myoepithelial differentiation.^{13,14} Some of the reported cases are CK8/18-positive,¹³⁻¹⁵ associated with AME¹⁶ or *in-situ* or invasive carcinoma.¹⁷ There

is no internationally accepted definition of pure MEC carcinoma. Most cases appear to represent either MBC, malignant AME or AME with carcinoma.

Adenomyoepithelioma

HISTORICAL OVERVIEW

AME of the breast was first described by Hamperl in 1970,¹⁸ and further defined by several authors.^{12,19-21} AME is defined as a biphasic neoplasm characterised by small epithelium-lined spaces with inner luminal ductal cells and a proliferation of variably enlarged abluminal MECs.⁴ Although AME is generally regarded as a low-grade malignant tumour or a tumour with low/uncertain malignant potential,²²⁻²⁵ current evidence suggests that AME comprises a spectrum of disease ranging from purely benign lesions to frankly malignant tumours. However, given the rarity of AME and the lack of a uniform classification system to date, it has been difficult to comment upon the biological significance of the different patterns of this lesion with consequent challenges in clinical management.

Tumours showing AME morphology with malignant features have been variously described as 'malignant AME', 'AME with malignancy', 'AME with

carcinoma' and 'epithelial–myoepithelial carcinoma'.⁴ Classification of these lesions is often subjective, given the spectrum of morphology and immunoprofile, intratumoural heterogeneity and difficulty in distinguishing between the epithelial and MEC components in malignant tumours. Using a three-tiered approach, AME has been classified by some authors as benign, infiltrating and malignant.^{12,26–28} Later, the term 'atypical AME' was proposed as an alternative to infiltrating AME, with stromal infiltration not a diagnostic prerequisite.^{12,29,30} These atypical AMEs display clinical behaviour intermediate between benign and malignant AME^{30,31} and show an intermediate immunoprofile, termed 'borderline AME' by some authors.⁶ However, precise categorisation of AME remains challenging. In a central recent large collaborative study, a histological review of 43 cases unanimously considered to represent bona fide classical AME, 18 (42%) cases were reclassified as atypical/malignant AME.⁹

The 5th edition of the World Health Organisation (WHO) classification of breast tumours⁴ categorises breast AME into AME and malignant AME,⁴ acknowledging that AME encompasses benign and atypical forms. For consistency of reporting, we prefer the classification of benign, atypical and malignant AME with the term 'malignant AME' (M-AME) used to encompass malignant *in-situ* or invasive tumours, regardless of the malignant cell type.

In this review, we discuss the genetics of AME, the classification of classical AME into benign and atypical variants and the categorisation of malignant AME with emphasis on management implications.

GENETIC ALTERATIONS

Benign epithelial–myoepithelial lesions are considered to develop from separate epithelial and myoepithelial progenitor cells and often maintain the morphology and immunophenotype of the normal bilayered epithelial myoepithelial structures. The histogenesis of myoepithelial cells in malignant lesions remains uncertain, and the distinction between the two cell components is not always clear-cut. In a previous study, forced expression of Harvey rat sarcoma viral oncogene homologue (HRAS) (Q61R) in non-malignant oestrogen receptor (ER)-negative breast epithelial cells with or without a *PIK3CA* somatic knock-in resulted in the development of a lesion showing the cardinal features of AME, including the expression of MEC markers, a reduction in E-cadherin expression and an increase in AKT signalling.⁹

Regarding human tumours, AME appears to represent an example of genotypical–phenotypical correlation in the breast with variation in the genomic landscape according to ER status.⁹ While ER-positive AME frequently harbours mutations affecting *PIK3CA* or *AKT1*, up to 60% of ER-negative AMEs are underpinned by mutations affecting the *HRAS* Q61 hot-spot, which frequently coexist with *PIK3CA* or *PIK3R1* mutations.^{9,32} *HRAS* Q61 hot-spot mutations coexisting with *PIK3CA* mutations have been reported in up to 50% of epithelial–myoepithelial carcinomas of the salivary gland, suggesting an association between this constellation of genetic alterations and epithelial–myoepithelial differentiation regardless of anatomical location.³³ In a next-generation sequencing (NGS) study of 19 AMEs,³⁴ *HRAS* and *PIK3CA* hot-spot mutations were identified in six (32%) and 11 (58%), respectively, and all but one were clonal. *In-vitro* forced *HRAS* expression (Q61R) in normal epithelial cell lines resulted in a highly disorganised growth pattern, partial loss of epithelial phenotype and acquisition of aberrant myoepithelial differentiation.

It is recognised that AMEs may produce myxochondroid matrix, akin to pleomorphic adenomas.³⁵ A study investigating the presence of *HMG2* and *PLAG1* rearrangements, characteristic of pleomorphic adenoma,³⁶ revealed the presence of an *HMG2–WIF1* fusion,¹⁰ suggesting that a subset of AME might be genetically related to pleomorphic adenomas. Although some authors have not identified pathognomonic non-synonymous mutations in malignant AME compared to their benign counterparts,³² other investigators have reported changes associated with malignancy in AME, including hot-spot mutations of the *TERT* gene,⁹ homozygous deletion of *CDKN2A* (p16INK4a)⁹ and amplification of the *MYC* gene.³⁷

Classical (benign and atypical) AME

CLINICAL FEATURES

Classical AME is rare, accounting for fewer than 0.5% of breast tumours.⁴ It predominantly affects older women, with rare cases reported in men.²⁷ In our experience of 55 AMEs in Nottingham, the mean age of patients with benign and atypical AME was 54 years (range = 15–76) and 60 years (range = 40–93), respectively. AME usually presents as a solitary palpable mass, occasionally associated with serous nipple discharge. Most are located centrally in the breast. Breast cancer screening

programmes have led to the discovery of smaller AME lesions. Radiologically, AME forms a round or lobulated dense mass with margins that may be indistinct. Calcification is sometimes seen on mammography. Local recurrences have been reported in approximately 10%.^{12,19} On rare occasions AME may be associated with genetic syndromes, e.g. neurofibromatosis type 1.⁴

MACROSCOPIC FEATURES

Classical AME is usually nodular, with a generally defined margin. Focal cystic degeneration and calcification may be seen. In our experience, the mean size of benign AME was 11 mm (range = 2–40 mm) and atypical AME was 20 mm (range = 6–35 mm).

MICROSCOPIC FEATURES

Classical benign AME comprises epithelial and MECs with varying ratios within and between tumours. MECs usually dominate and are more numerous than the single basal layer component of the epithelial myoepithelial bilayer of normal breast lobules, adenosis nodules or simple papillomas (Figure 1A–D). They can be spindle-shaped or epithelioid with clear or eosinophilic cytoplasm. In classical benign AME, the MECs are often small and uniform without cytological atypia or increased mitotic activity. MECs may merge to form large sheets within which the second population of epithelial cells is present. Epithelial cells are polygonal or columnar with abundant cytoplasm and form glandular lumina at least focally. Squamous, apocrine,

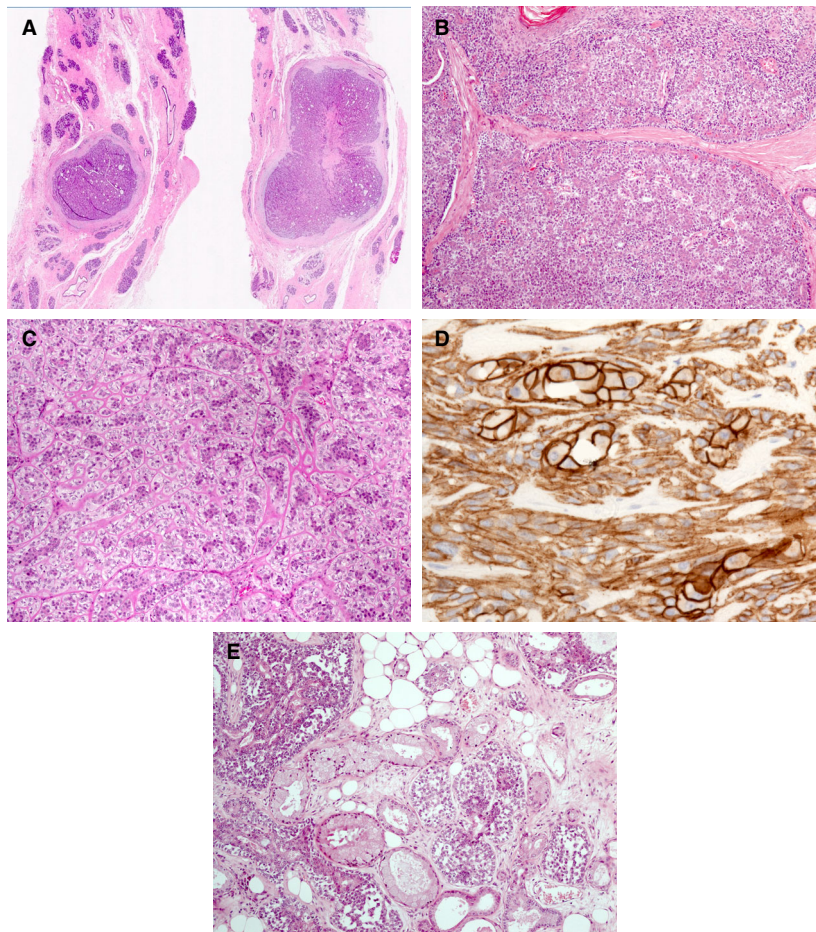


Figure 1. Low-power view of classical adenomyoepithelioma showing peripheral thick fibrous layer and appearances that overlap with pleomorphic adenoma, duct adenoma or a sclerosed papilloma with florid hyperplasia and squamous metaplasia (A). B, two cell types with epithelial cells showing eosinophilic cytoplasm and prominent myoepithelial cells showing pale cytoplasm. Focal squamous differentiation is seen in the upper part of the image. High-power view highlighting the two cell types and the lack of atypia, necrosis or high mitotic figures (C). E-cadherin staining highlighting the differential staining in the epithelial (strong staining) and myoepithelial (weak staining) cells of adenomyoepithelioma (AME) (D). E, AME with foamy cell changes.

foamy and sebaceous metaplasia may be seen (Figure 1B,E). AMEs rarely contain foci mimicking collagenous spherulosis or display a focal chondromyxoid appearance. Sclerosis and intervening fibrosis are frequently present, giving the lesion its characteristic architecture. Satellite nodules may occur around the main tumour. Peripheral fibrosis may be observed, but most AMEs do not have a capsule.

Four histological patterns of AME have been described: tubular, lobulated, spindle cell and adenosis variants.^{4,12} We and others^{25,27} have seen cases with a prominent intraductal papillary pattern,^{4,12,26} which represents a fifth (papillary) variant. Some lesions display overlapping patterns and do not always conform to a specific morphological variant.

Tubular AME comprises a proliferation of tubular structures surrounded by MECs with clear, glycogen-rich cytoplasm. This resembles tubular adenoma, but the MECs are larger with a greater degree of proliferation. The tubular structures are arranged as terminal-type ducts, sometimes with a lobular architecture, often compressed into cords. Tubular AME is usually circumscribed but unencapsulated with an expansile edge (Figure 2A), in contrast to the tubular

proliferations encountered in nodular adenosis or florid sclerosing adenosis. Focal microscopic extension into adjacent normal breast tissue may be seen.²⁷

In spindle cell AME, the MEC component predominates with florid proliferation and, as the name implies, spindle cell morphology (Figures 2B,C). Epithelial lined tubules can be difficult to identify. Nuclei may show a palisaded arrangement simulating a schwannoma. Sometimes the MECs have a plasmacytoid appearance, with eccentric nuclei and eosinophilic glassy cytoplasm resembling the 'hyaline' cells of pleomorphic adenoma. The cells may also have abundant eosinophilic cytoplasm imparting a 'myoid' appearance, simulating a leiomyoma. The distinction rests upon identification of epithelial-lined luminal spaces, assisted by immunocytochemistry. The margin tends to be pushing/circumscribed.

Lobulated AME comprises nests of cells, predominantly myoepithelial, which generally have eosinophilic cytoplasm and tend to be plumper than those seen in other AME variants. The cells are arranged in clusters, surrounded by dense 'hyaline' sclerotic collagenous matrix material that probably reflects production of excessive basement membrane-like

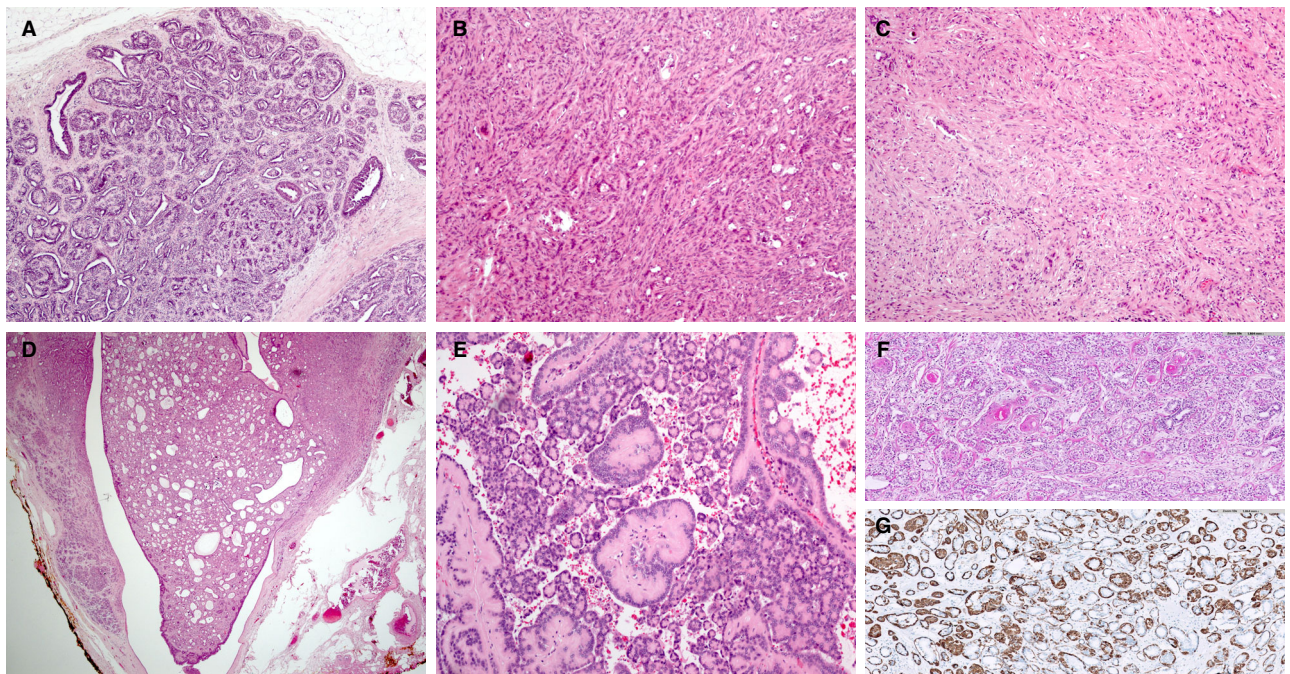


Figure 2. Classical adenomyoepithelioma with tubular growth pattern (A). B,C. The spindle-cell pattern with elongated spindle-shaped myoepithelial cells (MECs). D. Classical adenomyoepithelioma (AME) with papillary growth pattern. The diffuse prominence of the myoepithelial cell component and the pattern of myoepithelial cell proliferation together with the immunoprofile help to differentiate these lesions from intraductal papilloma with focal MEC proliferation (see Figure 3B). No atypia or increased mitotic activity are seen to qualify the lesion into atypical AME. E. Another case of papillary AME with unusual papillary growth pattern features papillary cores covered by MECs. F. AME with myoepithelial adenosis-like pattern and CK14 IHC (G).

material. The margin is usually ill-defined and irregular.

AME may have a prominent papillary component and is distinguished from intraductal papilloma by the significant increase in the MEC component throughout the lesion (Figure 2D,E). This variant may overlap morphologically with papilloma with myoepithelial cell hyperplasia (see Differential diagnosis).

An exceptionally rare variant of AME is characterised by a diffuse infiltrative pattern resembling microglandular adenosis (MGA),^{38,39} variously described as adenomyoepithelial adenosis,²⁰ adenomyoepithelioma with apocrine adenosis, AME with adenosis structure⁴⁰ and tubular AME.³⁹ We prefer the designation of 'AME with adenomyoepithelial adenosis pattern' to avoid confusion with apocrine adenosis and tubular AME. Although these lesions closely resemble MGA at low magnification, MGA is monophasic and lacks a myoepithelial component, whereas this lesion has a biphasic character.³⁹ This AME variant typically displays an infiltrative appearance with a nested rather than a single-cell pattern, and is not associated with a desmoplastic reaction (Figure 2F,G).

ATYPICAL AME

Atypical AME has been defined as AME that possesses some, but not all, the features of malignancy: overgrowth of the epithelial or myoepithelial component, mild to moderate cytological atypia, and increased mitotic activity [> 3 per 10 high-power fields (HPF)] with or without mildly infiltrative growth pattern, and/or focal necrosis.^{30,31} Using these criteria, approximately 50 and 25% of cases are classified as classical and atypical AME, respectively.^{30,31} Other authors have also considered prominent cytological atypia, prominent eosinophilic nucleoli and mitotic count up to five per 10 HPF as features of atypical AME.²⁹

It is our experience that prominent cytological atypia and occasional mitotic figures (more than three and up to five mitoses per 10 HPF) can be seen in all variants of AME and, in our view, these cases should be classified as 'atypical AME' (Table 3 and Figure 3A). We have seen two cases reported as benign AME that developed limited nodal metastases, and on review, mitotic figures and obvious cytological atypia were observed in the MEC component. Although the degree of atypia and/or the number of mitotic figures that reliably distinguish AME from atypical AME are not well-defined, we consider more

than three mitotic figures per 10 HPF and moderate cytological atypia in the MEC component sufficient for the diagnosis of atypical AME.⁵ In our experience, a Ki67 index of $> 10\%$ in the MEC component also favours atypical AME. Occasional mitotic figures (one to two per 10 HPF) in an otherwise benign AME should not trigger a diagnosis of atypical AME. At the other end of the spectrum, AMEs showing multiple atypical features (Table 3) should raise the suspicion of malignant AME (see below), similar to the approach used to classify a phyllodes tumour as malignant rather than borderline.²⁵

As cytological atypia increases, the distinction between myoepithelial and epithelial cells becomes less obvious and the immunoprofile gradually shows aberrant expression that may not be concordant with the morphology of the cell types. Infiltrative growth pattern and tumour necrosis may be seen and correlate with an increasing risk of aggressive behaviour, including local recurrences and the possibility of metastatic disease.^{5,9,27}

IMMUNOHISTOCHEMISTRY

The immunohistochemical profile of AME highlights the characteristic dual cell population. Although the MECs are usually positive for MEC markers (Table 1) the classical pattern of staining is not always observed, with intra- and intertumoural variation. Immunohistochemical findings should be evaluated in conjunction with morphology, particularly as the dominant cell type in AME may be of 'intermediate cell' with MEC-type morphology but limited or aberrant expression of classical MEC immunohistochemistry markers. It is also noteworthy that p63, p40 and basal CKs (CK14 and CK5/6) may be expressed in foci of squamous metaplasia. The glandular component is composed of columnar or cuboidal cells that are low molecular weight CK and epithelial membrane antigen-positive. E-cadherin staining frequently shows a biphasic pattern of staining with strong membranous expression in the epithelial cells and weaker, mainly cytoplasmic, expression in the MECs (Figure 1D). A similar pattern of variably strong and weak expression of low and high molecular weight CKs may be seen in both epithelial and MECs. Benign AME is typically positive for ER and PR, typically in the epithelial cell component.

DIFFERENTIAL DIAGNOSIS

AME encompasses a broad range of differential diagnoses with potential for diagnostic confusion and

Table 3. Difference between the three categories of adenomyoepithelioma (AME)

Variable	AME	Atypical AME	Malignant AME
Age	Postmenopausal women > 50 years	Postmenopausal women >50 years	Postmenopausal women >50 years
Size	Any size	Any size, can be large	May reach large size
Margins	Circumscribed ± lobulated or slightly irregular/pushing borders. May be encapsulated	Lobulated, circumscribed (or infiltrative as in the AME with tubular and adenomyoepithelial adenosis patterns)	Infiltrative (except M-AME <i>in situ</i>)
Intraductal component	Often present in the whole or part of the lesion	May be present	Often lacking
Cytological atypia	No	Mild to moderate	Marked
Necrosis	No	None or focal	May be present
Mitotic counts in the MECs	< 3/10 HPF	3–10/10 HPF	>10/10 HPF (may show atypical forms)
IHC for MEC markers	Nearly similar to normal	May show aberrant phenotype	Usually aberrant phenotype with discordance between epithelial and MEC morphology and immunoprofile
Vascular and perineural invasion	Absent	Absent	May be present
Local recurrences	Yes (more than papillomas)	More frequent	More frequent (35%) ⁴⁹
Node metastasis	No	Very low (lesion of uncertain malignant nature and limited metastatic potential)	10% ⁴⁹
Distant metastasis	No	Not reported	Approximately 20% ^{27,30}
Local excision	Complete excision to reduce local recurrence risk	Complete excision with clear margin to reduce local recurrence risk	Mastectomy or wide local excision with radiotherapy based on the clinical and imaging findings

IHC, immunohistochemistry; MEC, myoepithelial cell; HPF, high-power field.

impact upon management recommendations.³⁰ At the benign end of the spectrum, distinction from other benign breast lesions with epithelial and myoepithelial elements can be challenging, as histological criteria are not well defined and diagnosis often relies upon pathologists' experience.³⁵ In previous studies, 20% (four of 20),²⁶ 34% (12 of 35)³⁵ to 50% (12 of 24)³⁰ of cases, initially reported as AME, were reassigned on histological review to different categories. It is our practice to restrict the diagnosis of AME to cases showing a classical biphasic epithelial and myoepithelial growth pattern with MEC prominence, proliferation and expansion. The distinction of AME with a papillary configuration from papilloma with MEC hyperplasia may be difficult, and

is important due to the higher potential for local recurrence associated with AME. MEC hyperplasia in intraductal papilloma is typically focal (Figure 3B) in contrast to AME, where it is generally diffuse.²⁷ It is also noteworthy that focal intraductal papilloma-like areas may be seen in well-established AMEs, particularly in the papillary variant, and should not change the overall diagnosis of AME. IHC for MECs and detection of *HRAS* mutations in AME may assist diagnosis.^{34,41}

Pleomorphic adenoma shows prominent chondromyxoid stroma and lacks the distinct biphasic phenotype, with an intermediate phenotype more commonly (DD Figure 3C,D). The diffusely infiltrative form of AME has a growth pattern similar to MGA

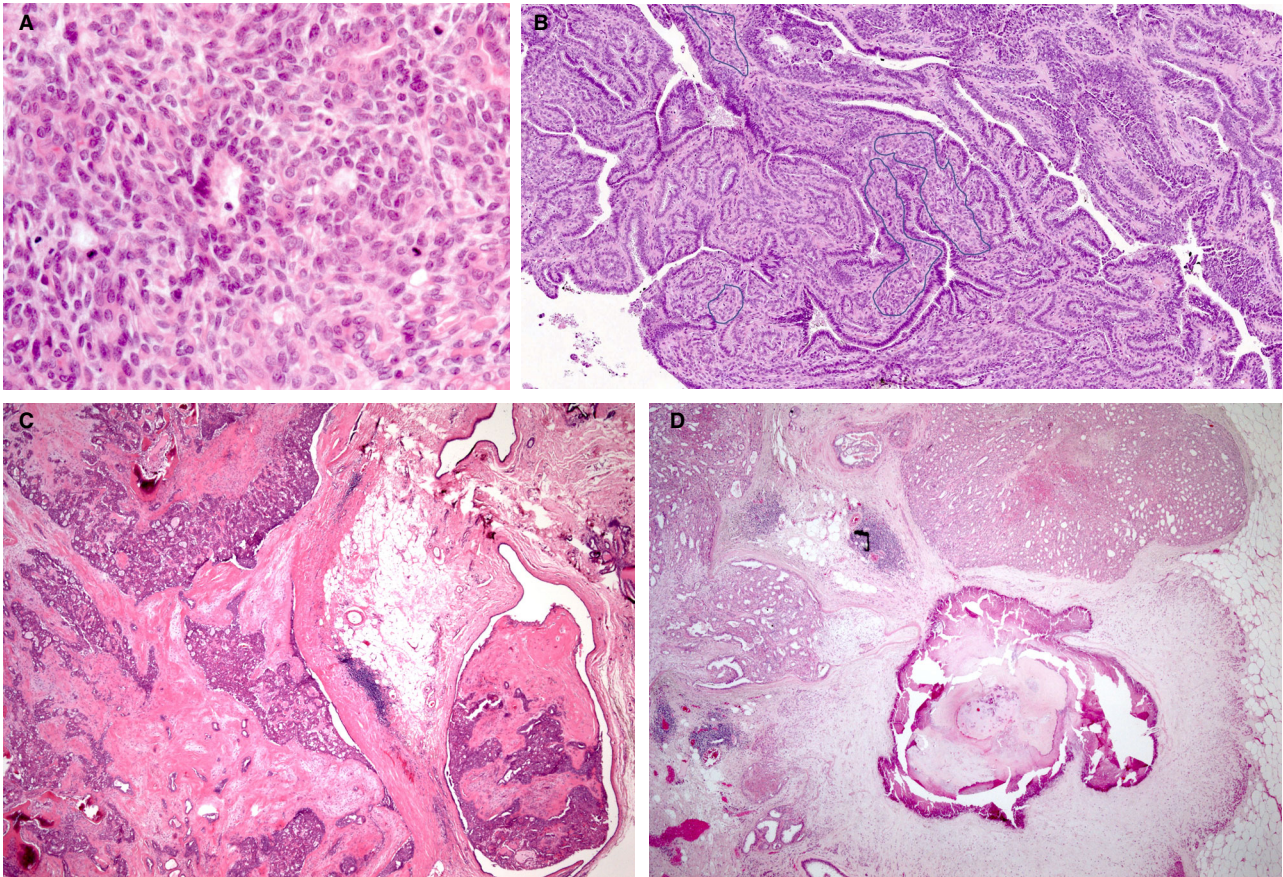


Figure 3. A, Atypical adenomyoepithelioma with increased mitotic figures (highest mitotic activity was captured in the field) but no significant atypia or other features of malignancy, therefore it is classified as atypical adenomyoepithelioma (AME). B, Focus of myoepithelial cell (MEC) proliferation in otherwise typical intraductal papilloma. Differential diagnosis figures (DD). C,D, Pleomorphic adenoma with papillary growth pattern, chondromyxoid areas and calcification. Cytology shows cells with intermediate features between epithelial and myoepithelial cells rather than the distinct biphasic appearances of AME.

and is distinguished by its biphasic cellular composition. MGA shows diffuse strong S100 positivity but lacks expression of other MEC markers, and is triple-negative. To distinguish benign, atypical AME and M-AME see Table 4.

PROGNOSIS AND TREATMENT

Despite the rarity of AME and the lack of a uniform approach to classification, current evidence suggests that the majority of classical AMEs pursue a benign clinical course and complete surgical excision is curative.⁴ Local recurrence may occur,²⁷ more commonly in the tubular variant.¹² AME with the adenomyoepithelial adenosis pattern is often extensive at diagnosis, and in our experience recurrence is more common.

Recurrent AME may show atypical or malignant features with higher potential for more aggressive

behaviour.^{38,42,43} The low recurrence rate observed in recent years most probably relates to earlier diagnosis at smaller size and thorough evaluation of resection margin status.²⁷ Although distant metastases from AMEs that apparently lacked significant cytological atypia or increased mitotic activity have been reported^{42,44} and cited in other studies,⁹ we believe that classical benign AME is an indolent tumour that may recur locally if incompletely excised, with metastatic potential restricted to atypical and malignant AMEs. Reported metastatic events in so-called benign AME may reflect undiagnosed atypia and mitotic activity in the MEC component at initial diagnosis. The use of the term 'benign metastasising AME' to describe AME lesions in the lung^{42,44} is confusing. Consideration of these cases suggests that at least some may represent additional primary lesions, as both benign^{20,37-39} and malignant⁴⁵⁻⁴⁷ AME variants have been described in the lung.

Table 4. Difference between the three categories of malignant adenomyoepithelioma (M-AME)*

Variable	M-AME <i>in situ</i>	M-AME invasive	AME with invasive carcinoma
Margins	Defined	Infiltrative	Defined in AME but infiltrative in carcinoma
Malignant cell type	Epithelial (DCIS) or MECs but with defined margins (intraductal)	Epithelial, myoepithelial or both; invasive component often merges imperceptibly with AME and typically shows less distinct epithelial/myoepithelial immunophenotype	Epithelial
Cytological atypia	Variable	Significant	Variable based on the grade of the invasive carcinoma component
Mitotic counts in the MECs	any	High	No, low
Surrounding breast tissue	± DCIS or satellite nodules	± Satellite nodules of atypical or M-AME	± DCIS
Lymph node sampling	No	Yes	Yes
staging	pTis	Based on the invasive component if distinct from the <i>in-situ</i> component otherwise based on the whole lesion.	Based on the invasive component only
Grade	Nuclear grade	Nottingham grade	Nottingham grade
Receptors	Optional (can also help in diagnosis)	Yes	Yes
Systemic therapy	No (hormone therapy can be offered if ER ₊ and large size)	Hormone therapy if ER ₋ . Discussion for chemotherapy	As for invasive carcinoma

*Cases with overlapping features exist and a pragmatic approach should be considered with interpretation of all findings. Degree of uncertainty should be highlighted in the report. MEC, myoepithelial cells; DCIS, ductal carcinoma *in situ*; ER, oestrogen.

Malignant adenomyoepithelioma

The rarity of these tumours, with their spectrum of morphological changes, makes diagnosis and classification in clinical practice challenging and subjective. Importantly, current terminology does not translate into specific management regimes and malignant tumours with AME components are treated in the same way, despite showing considerable morphological variation. We propose a pragmatic approach to the categorisation of these lesions to help guide further individualised management decisions, based on our own experience in the context of the current literature. This (i) focuses upon the distinction of tumours that are considered equivalent to DCIS (malignant *in-situ* tumours) from those that are equivalent to invasive malignancy and (ii) presents a system for the classification of malignant AME tumours equivalent to that of the papillary carcinoma,^{30,48} as each may lack a peripheral MEC layer at the

epithelial–stroma interface. We suggest that the term ‘malignant adenomyoepithelioma’ (M-AME) be used to include three variants: M-AME *in situ*, M-AME invasive (also referred to as ‘invasive adenomyoepithelial carcinoma’ or ‘IBC, adenomyoepithelial pattern’) and AME with invasive carcinoma (see below, Figures 4 and 5).

CLINICAL FEATURES

M-AME of the breast is rare, and usually affects older women.⁴⁹ In our unpublished series of 55 AMEs the mean age at presentation was 65 years (range = 40–93). Some patients present with a longstanding mass with recent rapid size increase. The size is usually larger than benign AME.⁵⁰ In our series, the mean size of M-AME was 29 mm (range = 16–50 mm). In patients with nodal or distant metastases, size tends to be larger than those without metastases (range = 10–170 mm, median = 40 mm).⁴⁹

MACROSCOPIC APPEARANCE

M-AME shows varied macroscopic appearances from a multilobulated, well-defined mass, similar to classic AME, to a poorly defined mass with infiltrative borders. M-AME is usually firm in consistency, sometimes with cystic change. Necrosis is seen in more than half of all cases.⁴⁹

MICROSCOPIC FEATURES

M-AME in situ

M-AME in situ includes lesions with a classical AME architecture in which the epithelial component shows features of DCIS (Figure 4). The atypical cells show a cribriform or solid growth pattern with a well-defined margin or evidence of development within an intraductal-like structure. A peripheral MEC layer at the epithelial stroma interface is typically seen in the intraductal component and in small satellite foci in immediately adjacent tissue. In the main lesion, this layer is often focal or difficult to identify in view of the presence of lesional MEC marker-positive cells within the tumour (Figure 4). These tumours should be managed as *in-situ* lesions (DCIS; pTis). Akin to encapsulated and solid papillary carcinomas,^{3,51} M-AMEs with the configuration of DCIS but lacking peripheral MECs at the epithelial stroma interface should be low or intermediate-grade to be categorised as *in situ*. The presence of high-grade cytological features without evidence of an intraductal growth pattern or a peripheral MEC layer may be best regarded as M-AME invasive for management purposes.

Rarely, the AME shows expansion of the MEC component with atypical features sufficient for a diagnosis of malignancy (Table 3) but with pushing margins, an intraductal growth pattern or a peripheral MEC layer and no features of invasion. These are considered part of the spectrum of the *M-AME in situ*.

M-AME invasive (synonym: invasive adenomyoepithelial carcinoma)

This is a tumour that displays a dominant AME architecture but also has features sufficient for a diagnosis of malignancy including cytological atypia, increased mitotic activity and necrosis associated with frankly invasive foci and an accompanying stromal response (Figure 5A). The malignancy in these tumours can affect the luminal epithelial or myoepithelial components or both (Figure 5B). The transition from atypical to malignant and from *in situ* to invasive foci tends to be gradual, with merging of the various elements. These tumours encompass the so-

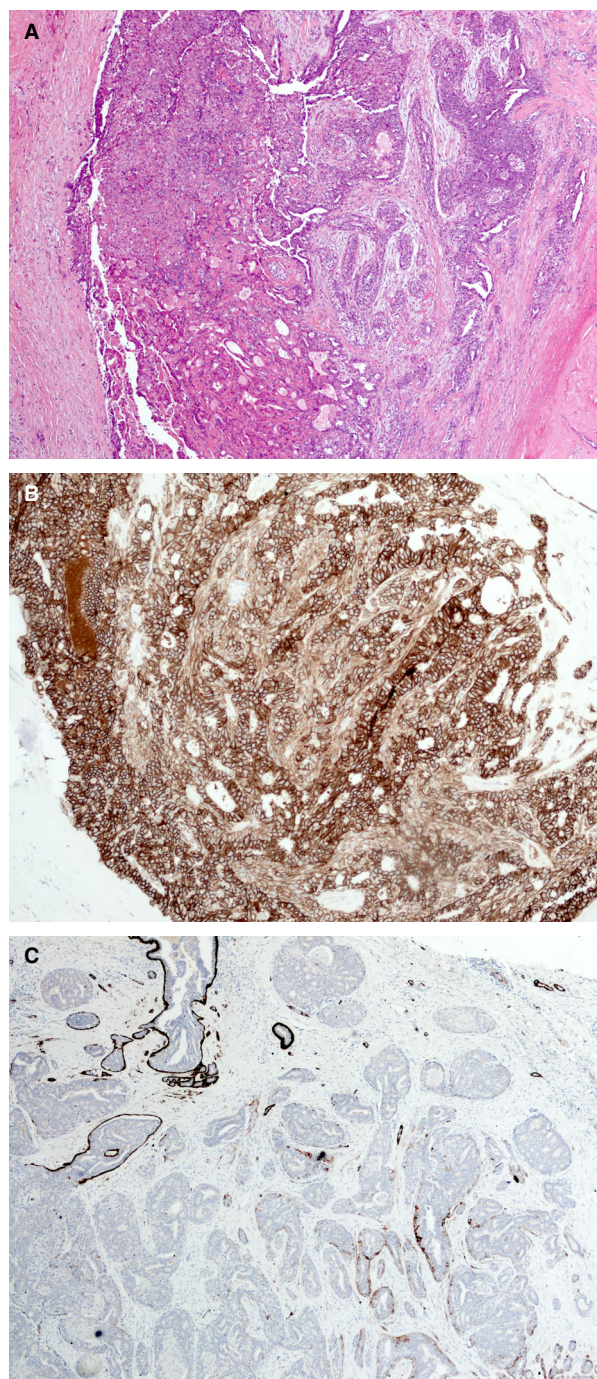


Figure 4. Malignant adenomyoepithelioma *in situ* showing appearances and immunoprofile in keeping with DCIS (A). B, E-cadherin staining, which highlights the differential staining in the epithelial (strong staining) and myoepithelial (weak staining) cells. Smooth muscle myosin heavy chain stain (C) in one area of the tumour shows focal preservation of peripheral myoepithelial cells at the epithelial stroma interface with no evidence of transition from *in-situ* to invasive lesion within the ducts that show differential preservation of myoepithelial cells providing evidence of an intraductal growth pattern in a case of malignant adenomyoepithelioma *in situ*.

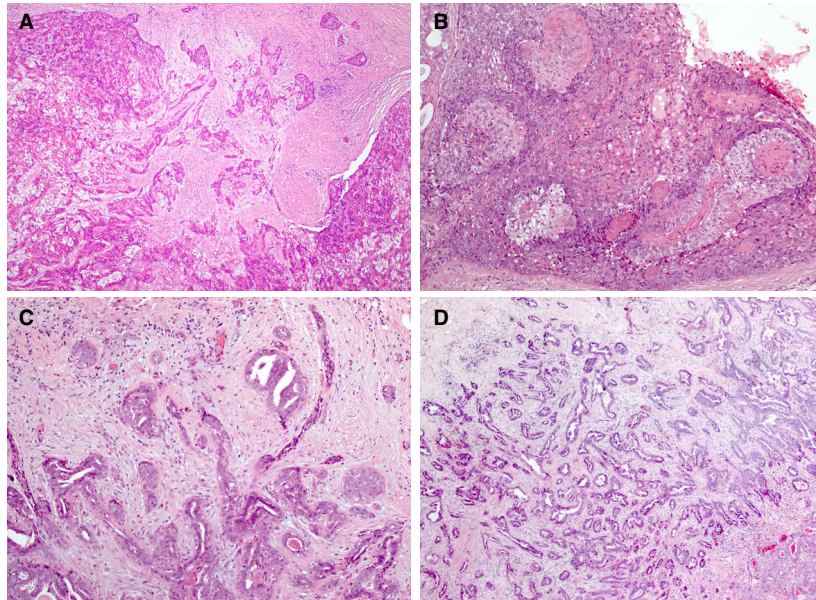


Figure 5. Malignant adenomyoepithelioma with invasion (A) showing malignant biphasic papillary growth pattern in some areas (B), with other areas showing evidence of stromal invasion which is focal in one area (C) and extensive in other area (D) but these show the same morphology and immunoprofile of the main tumour.

called ‘malignant myoepithelioma/epithelial–myoepithelial carcinoma’.²⁵ These tumours may also be referred to as ‘invasive adenomyoepithelial carcinoma’ or ‘IBC, adenomyoepithelial pattern’ to convey their designation as carcinomas for management purposes regardless of the lineage/differentiation of the malignant cell component.

The epithelial component may form solid nests, ducts, cystic trabeculae, pseudopapillary or papillary structures. Epithelial cells are recognised by the presence of abundant cytoplasm and their location lining tubules/glandular structures. Epithelial cells are usually polygonal in shape but may be spindle-shaped and form solid areas, making precise recognition difficult.⁴⁹ Importantly, the malignant epithelial component shows similar morphology and immunoprofile in the well-developed AME areas and invasive components (Figure 5C,D), in contrast to AME with invasive carcinoma (see below). The MEC component is typically arranged around the epithelial cell component in well-differentiated areas but in less differentiated areas it may disappear, be present as a small component or may form solid strands, trabeculae or large sheets of cells with malignant features. It may be the predominant component and lose its relationship with the epithelial component.

Although these tumours are classified as invasive, they are likely to behave in a more indolent fashion than AME with invasive carcinoma (see below) due

to the low volume of invasion relative to the overall size of the lesion and the gradual transition that occurs between *in situ* and invasive components. The morphological arrangement of M-AME invasive is reminiscent of invasive solid papillary carcinoma with an expected similar clinical course and consideration for a similar management plan. However, tumour size, grade and receptor status should be assessed in the invasive component which may alter prognosis and necessitate additional diagnostic work-up, e.g. clinical staging and sentinel lymph node biopsy.

AME with invasive carcinoma

This is a tumour that shows a dominant malignant component that, if arising independently, would be classified as IBC of conventional type, e.g. IBC-no special type (NST), lobular or MBC.^{52,53} The distinguishing feature is the coexistence of a classical AME. Each component is distinct and the epithelium of the AME component is morphologically different to that of the neoplastic epithelial cells. As there is insufficient evidence that the presence of a classical AME component alters the clinical behaviour of these tumours, we support the view that they should be managed as per the index IBC.

These tumours are rare, and distinction between AME with malignant transformation of the epithelial component (M-AME) from invasive carcinoma with co-existent benign AME^{54,55} is not always possible.

AME associated with a distinct malignant spindle-cell component, previously described as malignant myoepithelioma/MEC carcinoma, is currently considered as AME with MBC.⁴ It is important to distinguish this from entrapped proliferating spindle-shaped cells in areas of fibrosis, e.g. following core biopsy, that may mimic MBC. In this context, distinction of AME with these changes from MBC involves a pragmatic approach, including evaluation of the degree of cytological atypia in the spindle cell areas, location within or adjacent to the AME, comparison with the various components of the lesion, the presence of foci of carcinoma including keratin immunopositivity, stromal invasion outside the main lesion, the presence of lymphovascular invasion and lymph node metastases.

AME-like foci may also be observed in breast carcinomas that show morphological heterogeneity, e.g. MBC. Breast carcinomas showing basal/myoepithelial differentiation without a distinct AME component are classified as IBC according to morphology regardless of immunoprofile. A basal, but not myoepithelial, phenotype appears to be an independent predictor of outcome.⁵⁶

IMMUNOHISTOCHEMISTRY

M-AME may show an aberrant immunoprofile with loss of distinction of the dual cell population.⁴ The epithelial cell component may be positive for ER and EMA/MUC1 and show strong E-cadherin membrane expression. Complete absence of hormone receptor expression has been reported in 40% of AMEs, associated with nuclear atypia, necrosis and/or increased mitotic activity.⁹ HER2 is usually negative in these tumours.

PROGNOSIS AND TREATMENT

Metastases have been reported in 16–32% of tumours classified as M-AME involving lung, brain, bone, thyroid, liver and axillary lymph nodes.^{9,21,27,49} Metastases appear to be restricted to tumours larger than 2 cm,⁵⁷ with histologically defined malignancy in the myoepithelial or epithelial component.⁹ The time from presentation to distant metastases ranges from 3 weeks to 12 years.⁴⁹ The prognosis associated with M-AME with distant metastases is poor.^{58,59}

No adjuvant therapy has been proved to be effective in M-AME.⁴⁹ Complete local excision is currently recommended. M-AME with distinct carcinomatous transformation and carcinoma arising in association with classical AME should be managed in accordance with standard breast cancer protocols.

Conclusion

AME comprises a spectrum of lesions with variable morphology and clinical behaviour. Current evidence supports further refinement of the classification of AME to guide therapy. We suggest that classical AME is classified into benign and atypical and M-AME into M-AME *in situ*, M-AME invasive (invasive adenomyoepithelial carcinoma) and AME with invasive carcinoma. Despite overlapping morphology and limited data on the behaviour of the AME variants, this classification system is based on our increasing experience with these lesions, using conventional criteria and a similar approach to that utilised for stratifying papillary lesions, particularly solid papillary carcinoma (*in-situ* and invasive).

Conflicts of interest

No conflicts of interest.

References

- Gudjonsson T, Adriaance MC, Sternlicht MD *et al.* Myoepithelial cells: their origin and function in breast morphogenesis and neoplasia. *J. Mammary Gland Biol. Neoplasia* 2005; **10**: 261–272.
- Woodward WA, Chen MS, Behbod F *et al.* On mammary stem cells. *J. Cell. Sci.* 2005; **118**: 3585–3594.
- Rakha EA, Miligy IM, Gorringer KL *et al.* Invasion in breast lesions: the role of the epithelial–stroma barrier. *Histopathology* 2018; **72**: 1075–1083.
- Tan PH, Ellis IO. Epithelial myoepithelial tumours. In *The WHO Classification of Tumours* Editorial Board ed. *WHO classification of tumours*. 5th ed. Lyon: IARC Press, 2019; 39–48.
- Foschini MP, Morandi L, Asioli S *et al.* The morphological spectrum of salivary gland type tumours of the breast. *Pathology* 2017; **49**: 215–227.
- Hungermann D, Buerger H, Oehlschlegel C *et al.* Adenomyoepithelial tumours and myoepithelial carcinomas of the breast – a spectrum of monophasic and biphasic tumours dominated by immature myoepithelial cells. *BMC Cancer* 2005; **5**: 92.
- Moritani S, Ichihara S, Yatabe Y *et al.* Immunohistochemical expression of myoepithelial markers in adenomyoepithelioma of the breast: a unique paradoxical staining pattern of high-molecular weight cytokeratins. *Virchows Arch.* 2015; **466**: 191–198.
- Marian C, Boila A, Soanca D *et al.* Malignant transformation of adenomyoepithelioma of the breast by a monophasic population: a report of two cases and review of literature. *APMIS* 2013; **121**: 272–279.
- Geyer FC, Li A, Papanastasiou AD *et al.* Recurrent hotspot mutations in HRAS Q61 and PI3K-AKT pathway genes as drivers of breast adenomyoepitheliomas. *Nat. Commun.* 2018; **9**: 1816.
- Pareja F, Geyer FC, Brown DN *et al.* Assessment of HMGA2 and PLAG1 rearrangements in breast adenomyoepitheliomas. *NPJ Breast Cancer* 2019; **5**: 6.

11. Molyneux G, Geyer FC, Magnay F-A *et al.* BRCA1 basal-like breast cancers originate from luminal epithelial progenitors and not from basal stem cells. *Cell Stem Cell* 2010; 7: 403–417.
12. Tavassoli FA. Myoepithelial lesions of the breast. Myoepitheliosis, adenomyoepithelioma, and myoepithelial carcinoma. *Am. J. Surg. Pathol.* 1991; 15: 554–568.
13. Papazian M, Kalantzis I, Galanopoulos G *et al.* Malignant myoepithelioma of the breast: a case report and review of the literature. *Mol. Clin. Oncol.* 2016; 4: 723–727.
14. Liang YF, Zeng JC, Ruan JB *et al.* Malignant myoepithelioma of the breast: a case report and review of literature. *Int. J. Clin. Exp. Pathol.* 2014; 7: 2654–2657.
15. Lingamfelter D, Chen Y, Kure K *et al.* Infiltrating myoepithelial carcinoma of the breast, a case report and cytologic–histologic correlation. *Diagn. Pathol.* 2008; 3: 7.
16. Han BO, Mori I, Nakamura M *et al.* Myoepithelial carcinoma arising in an adenomyoepithelioma of the breast: case report with immunohistochemical and mutational analysis. *Pathol. Int.* 2006; 56: 211–216.
17. Scarpellini F, Usellini L, Foschini MP. Malignant myoepithelioma associated with in situ and invasive ductal carcinoma. Description of a case and review of the literature. *Pathologica* 1997; 89: 420–424.
18. Hamperl H. The myoepithelia (myoepithelial cells). Normal state; regressive changes; hyperplasia; tumors. *Curr. Top. Pathol.* 1970; 53: 161–220.
19. Rosen PP. Adenomyoepithelioma of the breast. *Hum Pathol* 1987; 18: 1232–1237.
20. Eusebi V, Casadei GP, Bussolati G *et al.* Adenomyoepithelioma of the breast with a distinctive type of apocrine adenosis. *Histopathology* 1987; 11: 305–315.
21. Loose JH, Patchefsky AS, Hollander IJ *et al.* Adenomyoepithelioma of the breast. A spectrum of biologic behavior. *Am. J. Surg. Pathol.* 1992; 16: 868–876.
22. Petrozza V, Pasciuti G, Pacchiarotti A *et al.* Breast adenomyoepithelioma: a case report with malignant proliferation of epithelial and myoepithelial elements. *World J. Surg. Oncol.* 2013; 11: 285.
23. Kalyani R, Murthy VS. Malignant adenomyoepithelioma of breast masquerading as soft tissue lytic lesion of right iliac bone: a rare entity. *J. Clin. Diagn. Res.* 2014; 8: F03–F04.
24. Rakha EA, Badve S, Eusebi V *et al.* Breast lesions of uncertain malignant nature and limited metastatic potential: proposals to improve their recognition and clinical management. *Histopathology* 2016; 68: 45–56.
25. World Health Organisation Classification of Tumours Editorial Board. *Breast tumours*. 5th ed. Lyon: IARC Press, 2019.
26. Moritz AW, Wiedenhofer JF, Profit AP *et al.* Breast adenomyoepithelioma and adenomyoepithelioma with carcinoma (malignant adenomyoepithelioma) with associated breast malignancies: a case series emphasizing histologic, radiologic, and clinical correlation. *Breast* 2016; 29: 132–139.
27. Hayes MM. Adenomyoepithelioma of the breast: a review stressing its propensity for malignant transformation. *J. Clin. Pathol.* 2011; 64: 477–484.
28. Awamleh AA, Gudi M, Shousha S. Malignant adenomyoepithelioma of the breast with lymph node metastasis: a detailed immunohistochemical study. *Case Rep. Pathol.* 2012; 2012: 305858
29. Zhang C, Quddus MR, Sung CJ. Atypical adenomyoepithelioma of the breast: diagnostic problems and practical approaches in core needle biopsy. *Breast J.* 2004; 10: 154–155.
30. Wiens N, Hoffman DI, Huang CY *et al.* Clinical characteristics and outcomes of benign, atypical, and malignant breast adenomyoepithelioma: a single institution's experience. *Am. J. Surg.* 2020; 219: 651–654.
31. Baraban E, Zhang PJ, Jaffer S *et al.* MYB rearrangement and immunohistochemical expression in adenomyoepithelioma of the breast: a comparison with adenoid cystic carcinoma. *Histopathology* 2018; 73: 897–903.
32. Lubin D, Toorens E, Zhang PJ *et al.* Adenomyoepitheliomas of the breast frequently harbor recurrent hotspot mutations in PIK3-AKT pathway-related genes and a subset show genetic similarity to salivary gland epithelial–myoepithelial carcinoma. *Am. J. Surg. Pathol.* 2019; 43: 1005–1013.
33. Grünwald I, Vollbrecht C, Meinrath J *et al.* Targeted next generation sequencing of parotid gland cancer uncovers genetic heterogeneity. *Oncotarget* 2015; 6: 18224–18237.
34. Geyer FC, Burke K, Ng C *et al.* Massively parallel sequencing analysis of breast adenomyoepitheliomas reveals the heterogeneity of the disease and identifies a subset driven by HRAS hotspot mutations. *Cancer Res.* 2017; 77: 3379–3379.
35. McLaren BK, Smith J, Schuyler PA *et al.* Adenomyoepithelioma: clinical, histologic, and immunohistologic evaluation of a series of related lesions. *Am. J. Surg. Pathol.* 2005; 29: 1294–1299.
36. Stenman G. Fusion oncogenes in salivary gland tumors: molecular and clinical consequences. *Head Neck Pathol.* 2013; 7 (Suppl. 1): S12–S19.
37. Febres-Aldana CA, Mejia-Mejia O, Krishnamurthy K *et al.* Malignant transformation in a breast adenomyoepithelioma caused by amplification of c-MYC: a common pathway to cancer in a rare entity. *J. Breast Cancer* 2020; 23: 93–99.
38. Kiaer H, Nielsen B, Paulsen S *et al.* Adenomyoepithelial adenosis and low-grade malignant adenomyoepithelioma of the breast. *Virchows Arch. A Pathol. Anat. Histopathol.* 1984; 405: 55–67.
39. Foschini MP, Eusebi V. Microglandular adenosis of the breast: a deceptive and still mysterious benign lesion. *Hum. Pathol.* 2018; 82: 1–9.
40. Rosen PP. Myoepithelial neoplasms. In Rosen PP, ed. *Rosen's breast pathology*, 3rd edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2009; pp. 137–160.
41. Pareja F, Toss MS, Geyer FC *et al.* Immunohistochemical assessment of HRAS Q61R mutations in breast adenomyoepitheliomas. *Histopathology* 2020; 76: 865–874.
42. Nadelman CM, Leslie KO, Fishbein MC. 'Benign', metastasizing adenomyoepithelioma of the breast: a report of 2 cases. *Arch. Pathol. Lab. Med.* 2006; 130: 1349–1353.
43. Tsuda H, Mukai K, Fukutomi T *et al.* Malignant progression of adenomyoepithelial adenosis of the breast. *Pathol. Int.* 1994; 44: 475–479.
44. Korolczuk A, Amarowicz M, Bak K *et al.* Adenomyoepithelioma of the breast with late pulmonary metastases – case report and review of the literature. *J. Cardiothorac. Surg.* 2016; 11: 121.
45. Tajima S, Aki M, Yajima K *et al.* Primary epithelial–myoepithelial carcinoma of the lung: a case report demonstrating high-grade transformation-like changes. *Oncol. Lett.* 2015; 10: 175–181.
46. Cho SH, Park SD, Ko TY *et al.* Primary epithelial myoepithelial lung carcinoma. *Korean J. Thorac. Cardiovasc. Surg.* 2014; 47: 59–62.
47. Westacott LS, Tsikleas G, Duhig E *et al.* Primary epithelial–myoepithelial carcinoma of lung: a case report of a rare salivary gland type tumour. *Pathology* 2013; 45: 420–422.

48. Warriar S, Hwang S, Ghaly M *et al.* Adenomyoepithelioma with ductal carcinoma in situ: a case report and review of the literature. *Case Rep. Surg.* 2013; **2013**:521417
49. Xu J, Tang X, Iida Y *et al.* Adenomyoepithelioma with carcinoma of the breast: a report of two cases and a review of the literature. *Pathol. Res. Pract.* 2016; **212**: 130–134.
50. Damiani S, Riccioni L, Pasquinelli G *et al.* Poorly differentiated myoepithelial cell rich carcinoma of the breast. *Histopathology* 1997; **30**: 542–548.
51. Rakha EA, Varga Z, Elsheik S *et al.* High-grade encapsulated papillary carcinoma of the breast: an under-recognized entity. *Histopathology* 2015; **66**: 740–746.
52. Honda Y, Iyama K. Malignant adenomyoepithelioma of the breast combined with invasive lobular carcinoma. *Pathol. Int.* 2009; **59**: 179–184.
53. Zhu J, Li K, Dong X *et al.* Metaplastic breast carcinoma composed of epithelial–myoepithelial carcinoma and squamous cell carcinoma: a case report. *Medicine* 2018; **97**: e0364
54. Simpson RHW, Cope N, Skálová, A *et al.* Malignant adenomyoepithelioma of the breast with mixed osteogenic, spindle cell, and carcinomatous differentiation. *Am. J. Surg. Pathol.* 1998; **22**: 631–636.
55. Rasbridge SA, Millis RR. Adenomyoepithelioma of the breast with malignant features. *Virchows Arch.* 1998; **432**: 123–130.
56. Rakha EA, Putti TC, Abd El-Rehim DM *et al.* Morphological and immunophenotypic analysis of breast carcinomas with basal and myoepithelial differentiation. *J. Pathol.* 2006; **208**: 495–506.
57. Howlett DC, Mason CH, Biswas S *et al.* Adenomyoepithelioma of the breast: spectrum of disease with associated imaging and pathology. *Am. J. Roentgenol.* 2003; **180**: 799–803.
58. Moro K, Sakata E, Nakahara A *et al.* Malignant adenomyoepithelioma of the breast. *Surg. Case Rep.* 2020; **6**: 118.
59. Takahashi I, Tashiro H, Wakasugi K *et al.* Malignant adenomyoepithelioma of the breast: a case with distant metastases. *Breast Cancer* 1999; **6**: 73–77.