



Review Article

Epithelial-myoepithelial Neoplasms of the Breast: Diagnostic Challenges and Emerging Molecular Features



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Abstract

Background and objectives: Epithelial-myoepithelial neoplasms of the breast are biphasic tumors composed of both epithelial and myoepithelial cell populations. Their rarity, broad morphologic spectrum, and evolving molecular characterization pose substantial diagnostic challenges, underscoring the need for an integrated review of their diagnostic and molecular features. This review aims to provide a comprehensive overview of epithelial-myoepithelial neoplasms of the breast, emphasizing their morphologic spectrum, diagnostic challenges, and emerging molecular features.

Methods: This narrative review is based on a review of the pertinent English-language literature and the author's firsthand experience as a practicing breast pathologist.

Results: Benign epithelial-myoepithelial tumors include pleomorphic adenoma and classic adenomyoepithelioma. Pleomorphic adenoma of the breast closely resembles its salivary gland counterpart as well as the benign mixed tumor of the skin. In contrast, adenomyoepithelioma is unique to the breast and exhibits a broad spectrum of histomorphologic patterns. Most adenomyoepitheliomas follow a benign clinical course; however, atypical adenomyoepitheliomas may demonstrate more aggressive behavior, including local recurrence, malignant transformation, and, rarely, metastasis. Molecular studies have identified *PLAG1/HMGA2* rearrangements in a subset of pleomorphic adenomas and recurrent *HRAS Q61* and *PI3K-AKT* pathway alterations in adenomyoepitheliomas. In malignant adenomyoepithelioma, the malignant component may arise from the ductal epithelial cells, the myoepithelial cells, or both.

Conclusions: The rarity of epithelial-myoepithelial tumors, together with their marked histologic heterogeneity, makes them diagnostically challenging and underscores the potential for diagnostic pitfalls.

Introduction

Epithelial-myoepithelial tumors of the breast represent a heterogeneous group of biphasic neoplasms composed of both epithelial and myoepithelial cell populations. This category includes pleomorphic adenoma (PA), adenomyoepithelioma (AME), and its malignant counterpart, malignant adenomyoepithelioma (M-AME).¹⁻³ Although these tumors are rare, they exhibit a broad histomorphologic spectrum and variable immunophenotypic

profiles. Together with the limited understanding of their molecular pathogenesis, these features can pose diagnostic challenges. Thus, this review aims to provide a comprehensive overview of epithelial-myoepithelial neoplasms of the breast, emphasizing their morphologic spectrum, diagnostic challenges, and emerging molecular features. Adenoid cystic carcinoma (AdCC) also exhibits a dual population of epithelial and myoepithelial cells with diverse growth patterns and histologic features that are indistinguishable from those seen in salivary gland counterparts. However, AdCC is classified as a distinct salivary gland-type carcinoma of the breast. Although not a focus of this narrative review, AdCC is discussed in the differential diagnosis. A comparison table and representative photomicrographs are provided to serve as an aid to practicing pathologists.

Pleomorphic adenoma

PA of the breast is a benign neoplasm that morphologically

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resembles its counterparts in the salivary glands and skin (also known as benign mixed tumor).¹ It demonstrates variable cytologic and architectural features of both epithelial and myoepithelial components, typically embedded within a chondromyxoid stroma. PA of the breast is exceedingly rare, with only scattered case reports and small series reported in the literature⁴⁻⁸; however, it may be underreported, and its true incidence remains unknown.

PA may arise in either the male or female breast.⁵ It typically presents as a well-circumscribed nodule, although it may be associated with microcalcifications, which can raise radiologic suspicion for malignancy.⁹ Tumor size varies but is usually in the range of 1–2 cm.

Histologically, PAs of the breast are typically lobulated, noninfiltrative lesions with well-circumscribed borders, with or without a fibrous pseudocapsule (Fig. 1). The proliferating neoplastic cells comprise both epithelial and myoepithelial components arranged in variable proportions as glandular structures or strands embedded within a prominent chondromyxoid stroma. The neoplastic glands are lined by an inner epithelial layer and an outer myoepithelial cell layer. Like their salivary gland counterparts, the myoepithelial component may display diverse cytomorphology, ranging from stellate and polygonal to plasmacytoid, oval, and spindle-shaped cells. Cytologic atypia, atypical mitotic figures, and necrosis are absent in PA.¹ Rare reported features include cartilaginous or osseous metaplasia and intraductal growth.^{5,10}

The biphasic nature of PA can be confirmed by immunohistochemistry (IHC), with luminal cells expressing low-molecular-weight cytokeratins and epithelial membrane antigen, and myoepithelial cells demonstrating positivity for markers such as p63, CK5/6, CK14, S-100, SOX10, and smooth muscle myosin heavy chain (SMMHC). Of note, loss of myoepithelial cell marker expression has been reported in otherwise benign PAs; however, it may also be observed in the malignant epithelial component of carcinoma ex-PA.¹¹ Therefore, malignant transformation should be carefully excluded.

The differential diagnosis of PA includes other breast tumors characterized by mucinous or myxoid/chondromyxoid stroma, such as mucinous carcinoma, mucinous cystadenocarcinoma, matrix-producing metaplastic carcinoma, and other biphasic lesions, including AME.

Mucinous carcinoma is typically a low-nuclear-grade neoplasm composed exclusively of epithelial cells lacking a myoepithelial component and often demonstrates an infiltrative growth pattern, making it generally straightforward to distinguish from PA. Mucinous cystadenocarcinoma and matrix-producing metaplastic carcinoma should be considered when cytologic atypia, infiltrative growth, and a desmoplastic stromal response are present; however, distinction from PA may be challenging in limited samples, such as core needle biopsies.¹⁰ In contrast, PA demonstrates well-organized glands with a characteristic biphasic architecture, consisting of an inner layer of epithelial cells surrounded by a thin outer layer of myoepithelial cells. When the distinction is uncertain, IHC can be helpful in confirming the dual cell population. AME, by comparison, typically shows a more prominent and often stratified myoepithelial component (see below).

Rearrangements involving *PLAG1* and *HMG2*, which rep-

resent recurrent molecular alterations in salivary gland PAs, have also been identified in a subset of breast PAs. *PLAG1* rearrangements were detected in 2 (28.6%) of 7 cases, including a novel fusion, *TRPS1::PLAG1*.¹² In addition, *HMG2::WIF1* and *CTNNB1::PLAG1* fusion genes have been identified in breast PAs in another study, with each fusion detected in one of three PAs analyzed.¹³

PAs of the breast are benign; however, recurrence may occur following incomplete excision.¹⁴ Rare cases of malignant transformation (carcinoma ex PA) have also been reported, characterized by marked cytologic atypia, increased mitotic activity, and stromal invasion.^{12,15} In light of these uncommon but documented instances of malignant transformation, some authors have proposed that PA may be better regarded as a tumor of uncertain malignant potential.¹⁰

Adenomyoepithelioma

First described in 1970,¹⁶⁻¹⁹ AME is a biphasic neoplasm characterized by glandular structures composed of an inner layer of luminal epithelial cells and an outer layer of proliferating myoepithelial cells.² Classic AME can be further classified into benign AME and so-called “atypical AME,” the latter exhibiting histologic features intermediate between benign and malignant lesions,²⁰ as discussed in the following section.

Patients span a wide age range, from their 20s to 90s, with occasional cases reported in men.²¹ Imaging findings are nonspecific and can overlap with both benign and malignant breast lesions, such as a hypoechoic oval mass, focal asymmetry, or a complex cystic and solid mass, often with non-circumscribed margins.²² Smaller AMEs are frequently detected incidentally through breast cancer screening programs,²³ whereas larger lesions may present as palpable nodules or with nipple discharge, particularly when the lactiferous ducts are involved.²⁴ Consequently, the true incidence of AME remains unknown.

Molecular genetic characterization of AMEs has revealed a heterogeneous genomic landscape, similar to other common breast neoplasms. In this context, the mutational profile varies according to estrogen receptor (ER) status. Mutually exclusive activating mutations in *PIK3CA* and *AKT1* are frequently identified in ER-positive AMEs, whereas ER-negative tumors more commonly demonstrate recurrent *HRAS* Q61R hotspot mutations, which may co-occur with alterations in *PIK3CA* or *PIK3RI*, as well as additional *HRAS* hotspot variants such as G13R and G12S. Moreover, *HRAS* Q61R hotspot mutations are associated with atypical AMEs and those associated with carcinoma.²⁵⁻²⁷ Notably, the co-occurrence of genetic alterations that activate the MAPK and PI3K-AKT pathways has been shown to result in stronger oncogenic potential than genetic alterations affecting either pathway alone in other tumor types.²⁸

Moreover, mutations in *HRAS* are relatively common in several tumor types—including salivary gland, urinary tract, upper aerodigestive tract, and cervical carcinomas—but are exceedingly rare in breast cancers (<1%). This disparity suggests that *HRAS* mutations likely serve as a key genetic driver in ER-negative AMEs.²⁹ This notion is further supported by an *in vitro* study demonstrating that overexpression of the *HRAS* Q61R mutant in benign, ER-negative breast epithelial cells induces the acquisition of aberrant myoepithelial differentiation.²⁶ Other less frequently

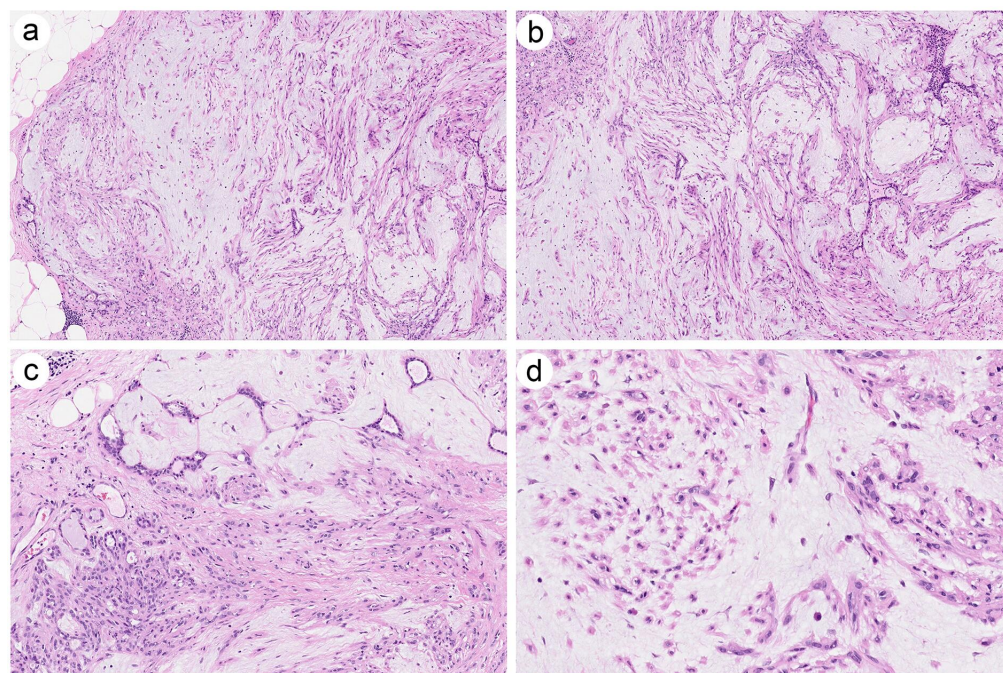


Fig. 1. Histologic features of pleomorphic adenoma. (a) A lobulated, well-circumscribed myxoid lesion with a focal fibrous pseudocapsule. (b) Abundant mucin dissecting the breast parenchyma, with a focal area of sclerosing adenosis-like architecture in the upper left. (c) Myxoid fibroadenoma-like areas accompanied by a proliferation of bland spindle cells. (d) Plasmacytoid myoepithelial cells embedded in a myxoid background, a characteristic feature of pleomorphic adenoma. Original magnifications: $\times 40$ (a, b), $\times 100$ (c), and $\times 200$ (d).

reported mutations in AMEs involve genes such as *APC*, *STK11*, *ATM*, *EGFR*, *FGFR3*, and *GNAS*, occurring either independently or in conjunction with mutations in *AKT1*.²⁵

Histologically, classic AME is characterized by the proliferation of both epithelial and myoepithelial cell populations within the breast lobules and/or ducts. The tumor exhibits a spectrum of architectural patterns—including tubular, lobulated, papillary, spindle cell, and adenosis-like configurations—which are often present in combination.^{2,20,21} Mitotic figures may be discernible (up to 3/10 high-power fields (HPFs)), but no atypical forms are identified. The component cells show no or minimal cytologic atypia. The stroma may be myxoid or chondroid, both of which represent common extracellular matrices produced by myoepithelial cells, in addition to the basement membrane-like material seen in sclerotic or hyalinized stroma.³⁰

The tubular pattern is typically well-circumscribed and characterized by an inner luminal epithelial cell layer surrounded by an outer layer of myoepithelial cells, thereby mimicking tubular adenoma, nodular adenosis, and occasionally, microglandular adenosis (MGA) (Fig. 2). However, the myoepithelial component in AME often demonstrates hyperplastic proliferation.^{18,19} Rarely, an infiltrative growth pattern may be observed, which has historically been referred to as adenomyoepithelial adenosis.³¹

Lobulated AME displays a multilobulated architecture with an ill-defined periphery and is composed of compressed or distorted acini surrounded by plump, proliferating myoepithelial cells embedded within a sclerotic, hyalinized stroma, likely reflecting excessive production of basement membrane materials (Fig. 2).³⁰ Myxoid or chondroid stroma may also be seen.

The spindle cell variant, characterized by a predominant proliferation of spindled myoepithelial cells, may exhibit compressed, obscured, or even inconspicuous glandular elements, and has therefore been regarded by some authorities as a myoepithelioma (Fig. 2).^{18,19} The spindled nuclei may show a fascicular or palisading arrangement, potentially mimicking myofibroblastoma or schwannoma.

AME may also exhibit prominent intraductal papillary growth merging with features of intraductal papilloma, accompanied by myoepithelial cell hyperplasia (Figs. 2 and 3).^{18,21} This pattern has been interpreted by some authorities as either a variant of intraductal papilloma or a morphologic evolution from a pre-existing intraductal papilloma.³² Others distinguish between these entities based on the extent of myoepithelial cell hyperplasia—focal in intraductal papilloma and diffuse in AME, respectively.²⁰

AMEs also display marked cytologic heterogeneity, particularly within the myoepithelial component. In addition to spindle cell morphology, the proliferating myoepithelial cells may exhibit plasmacytoid, clear cell, or myoid features. The abundant eosinophilic cytoplasm of myoid-appearing cells can closely resemble that of a leiomyoma. Variable metaplastic changes, including apocrine metaplasia as well as squamous or sebaceous differentiation, may also be present.¹⁷

IHC can be used to highlight the dual cell population and assist in the diagnosis of AME when morphology is equivocal. The ductal epithelial component is typically labeled by low-molecular-weight keratins, such as AE1 and CK7, whereas the myoepithelial cells can be identified using markers including high-molecular-weight keratins (HMWK, e.g., CK5/6 and

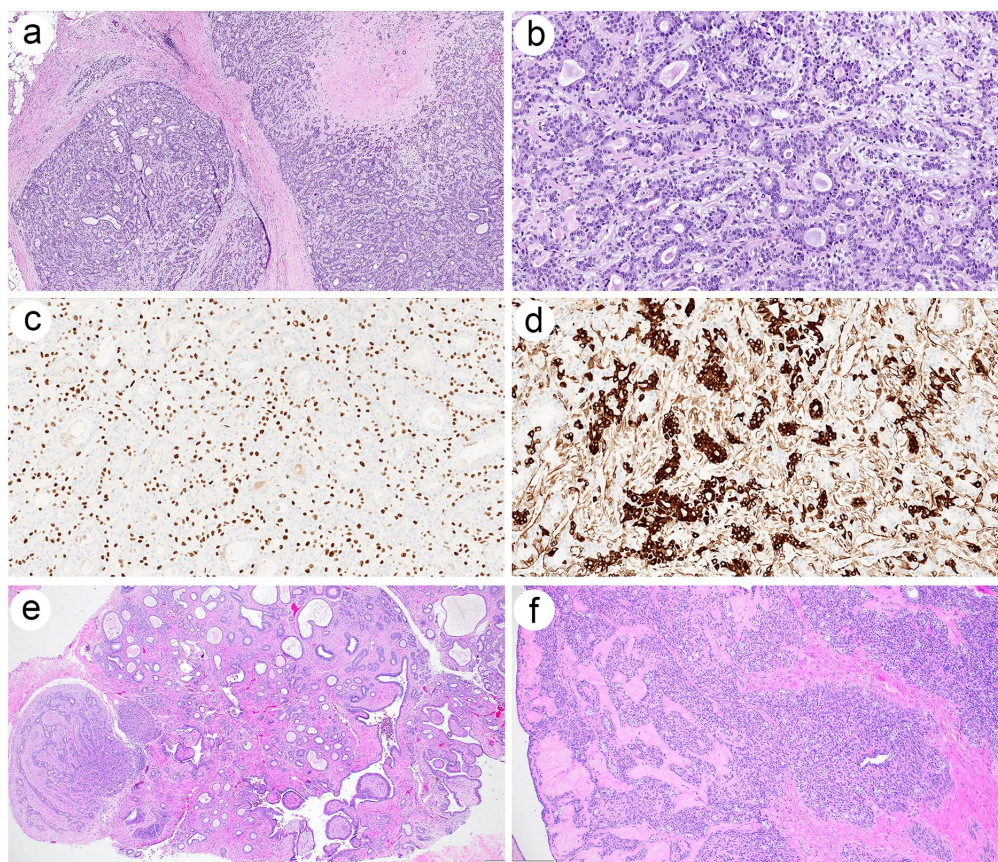


Fig. 2. Histologic and immunophenotypic features of adenomyoepithelioma. (a) A multilobulated growth pattern. The tumor is embedded within a sclerotic, hyalinized stroma. (b) Higher-power view showing areas with a tubular growth pattern and focal chondromyxoid stroma. Some glands exhibit small, round contours with intraluminal secretions, resembling microglandular adenosis. (c) A p63 stain highlights the outer myoepithelial cell layer and areas of myoepithelial hyperplasia. (d) A CK5/6 stain demonstrates the characteristic paradoxical staining pattern in the ductal epithelial cells. (e) Another adenomyoepithelioma exhibiting a focal intraductal papillary growth pattern. (f) An area of spindle cell-predominant adenomyoepithelioma with minimal glandular differentiation. Original magnifications: $\times 20$ (a), $\times 40$ (e, f), $\times 100$ (b), $\times 200$ (c, d).

34 β E12), as well as p63, p40, SMMHC, and S-100 protein, among others. Most tumors display at least weak reactivity for CD117 (C-Kit).³³ A diagnostic caveat is that myoepithelial cells in AME may show variable and sometimes unpredictable staining patterns (Fig. 4).^{2,34,35} In addition, HMWK, p63, and p40 may also be expressed in ductal epithelial cells exhibiting squamous metaplasia (Fig. 3). Notably, HMWK can demonstrate a distinctive paradoxical staining pattern in AME, with positivity in the inner luminal epithelial cells and absence of staining in the outer myoepithelial layer (Figs. 2, 3 and 5).³⁵ Variable expression of ER and progesterone receptor is also common in AMEs, predominantly within the ductal epithelial component.²

Some AMEs exhibit a variety of atypical features but fall short of the criteria for malignant AME (see subsequent text) and are therefore classified as atypical AME.²⁰ The epithelial component, myoepithelial component, or both may show mild to moderate cytologic atypia and increased mitotic activity (up to 5/10 HPFs), with or without focal necrosis.²⁰ The presence of atypical mitotic figures, if identified, should raise concern for malignancy and prompt careful evaluation for additional features of malignant

AME. Atypical ductal hyperplasia and atypical lobular hyperplasia may also arise in AME (Fig. 5).³⁴ Rarely, the degree and extent of luminal epithelial atypia may warrant a diagnosis of ductal carcinoma *in situ* (DCIS), which should be reported and managed accordingly.^{36,37} Of note, an early study considered prominent cytologic atypia, prominent eosinophilic nucleoli, and mitotic activity of up to 5/10 HPFs to be features of atypical AME.³⁸

The differential diagnosis of AME encompasses a broad spectrum of lesions, depending on the tumor's growth pattern and the predominant cellular component. When AME presents as a solid, well-circumscribed, or lobulated mass with variable myoepithelial proliferation, the differential diagnosis includes nodular adenosis, MGA, tubular adenoma, fibroadenoma, and intraductal papilloma. AMEs with an intraductal papillary growth pattern typically exhibit more prominent myoepithelial hyperplasia than intraductal papillomas. Likewise, AMEs generally demonstrate more conspicuous myoepithelial proliferation with plumper myoepithelial cells than those observed in adenosis, tubular adenomas, or even normal breast lobules. Consequently, establishing more stringent diagnostic criteria for AME may help reduce diagnostic ambi-

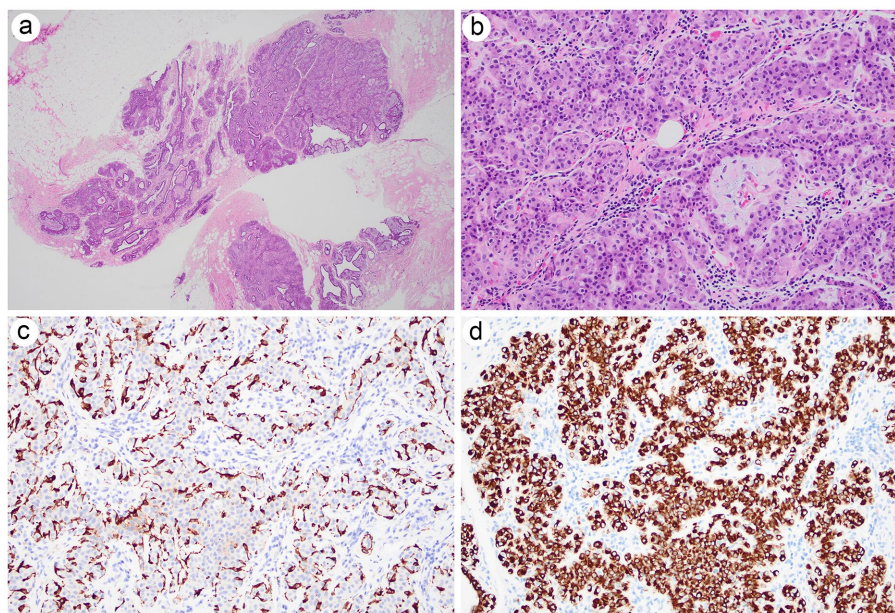


Fig. 3. Histologic and immunophenotypic features of adenomyoepithelioma. (a) Low-power microscopic view showing a multilobulated (multi-nodular) tumor. At this magnification, both tubular and intraductal papillary growth patterns are visible. (b) High-power view demonstrating closely packed, nested glandular structures composed of cells with somewhat squamoid features and focal papillary architecture. (c) Immunohistochemical staining for smooth muscle myosin heavy chain (SMMHC) highlights the outer myoepithelial cell layer, confirming the biphasic nature of the tumor. (d) Immunohistochemical staining with the high-molecular-weight keratin antibody 34βE12 demonstrates expression in the ductal epithelial cells. Original magnifications: ×20 (a), ×200 (b-d).

guity, particularly in light of the differences in clinical management among these entities. Furthermore, myoepithelial-rich AMEs may also mimic myofibroblastoma or schwannoma, further complicating the diagnostic assessment.

In addition, the myxoid and/or chondroid stroma produced by myoepithelial cells, when present, together with the dual cell populations, may make the distinction between AME and PA challenging, as previously noted. Interestingly, the aforementioned study suggests that a subset of breast AMEs may be genetically related to PAs, or that some AMEs may arise in the setting of a PA, thereby warranting further investigation.¹³

Classic AdCC possesses a biphasic phenotype and may exhibit a tubular growth pattern that, together with its low-grade histomorphology, can simulate classic or atypical AME. The presence of a coexisting, more characteristic cribriform growth pattern (and less frequently a solid pattern) serves as a clue prompting further diagnostic workup. Identification of *MYB* or *MYBL1* gene rearrangement and, rarely, *MYB* amplification by fluorescence *in situ* hybridization or next-generation sequencing analysis helps confirm the diagnosis of AdCC.³⁹

Classic AMEs typically follow a benign clinical course and are generally cured by complete surgical excision.² However, exceedingly rare cases of so-called benign metastasizing AME have been reported.^{40,41} In addition, atypical AME presenting with nodal metastases has also been described.²⁰ Moreover, the potential for malignant transformation in AME is well recognized.⁴²⁻⁴⁴ Accordingly, it has been suggested that classic AME may be more appropriately regarded as a neoplasm of uncertain malignant potential.¹⁰ The true incidence of recurrence

in atypical AME remains undetermined due to the paucity of reported cases and the lack of large-scale studies. It is noteworthy that, as the degree of atypia increases in AME, the distinction between ductal and myoepithelial cells becomes progressively less apparent, both histologically and immunophenotypically. In such cases, other histologic features, including an infiltrative growth pattern and tumor necrosis, may correlate with an increased risk of aggressive clinical behavior.^{20,26,42,45} Comparative analysis of the molecular characteristics of paired primary and metastatic AMEs may provide further insight into the refined classification of this disease.

Malignant adenomyoepithelioma

M-AME refers to lesions in which malignancy arises from the luminal epithelial component, the myoepithelial component, or, rarely, both cell types (hence the term *epithelial-myoepithelial carcinoma* previously used by some authorities).³

Genetic analysis of matched AME and M-AME cases also supports the concept of malignant transformation arising from a pre-existing AME,^{26,43} although *de novo* tumorigenesis of M-AME remains a plausible alternative mechanism. The common molecular alterations of AME, including *HRAS* Q61R and G13R hotspot mutations and *PIK3CA* mutations, are also found in M-AME.^{25,26,46,47} *HRAS* Q61R and G13R mutations are associated with ER-negative AME with atypical histologic features and are more commonly detected in cases associated with carcinoma. In addition, homozygous *CDKN2A* deletions may be involved in the malignant transformation of ER-negative AME.²⁶ The roles of

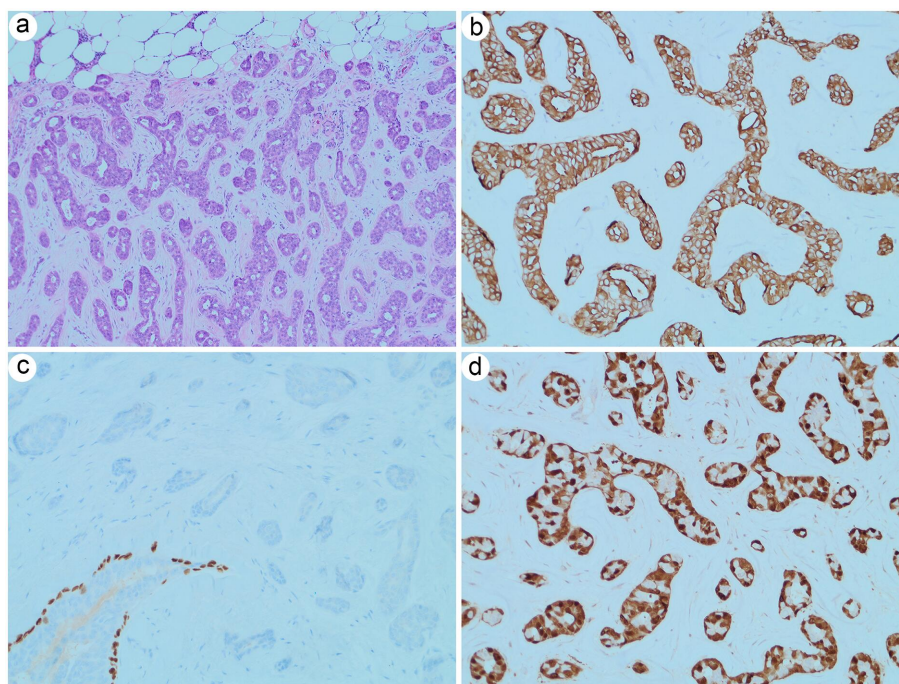


Fig. 4. Variable expression of myoepithelial markers in adenomyoepithelioma. (a) Low-power view showing a predominantly tubular growth pattern with an irregular but non-infiltrative tumor periphery. (b) Immunohistochemical staining for AE1 highlights the ductal epithelial cells. (c) Immunohistochemical staining for p63 demonstrates loss of expression in the neoplastic glands while retaining nuclear staining in an entrapped benign gland. (d) Immunohistochemical staining for S-100 protein highlights the outer myoepithelial cell layers. Original magnifications: $\times 40$ (a), $\times 200$ (b-d).

AKT1 gain-of-function alterations, amplification of the *c-MYC* gene and somatic mutations in *TERT* have also been postulated in limited studies.^{46,48} Moreover, *ERBB2* amplification has not been reported in atypical AME or M-AME.²⁶ The findings to date suggest that AME/M-AME represents a genetically heterogeneous group of neoplasms.

M-AME typically presents as larger masses than AME and demonstrates infiltrative borders in up to 50% of cases, although it may also present as a multilobulated or multinodular, well-circumscribed mass that closely resembles AME (Fig. 6).^{20,26,49} Similar to its benign counterpart, M-AME exhibits a broad spectrum of architectural patterns, including solid, tubular, spindle cell, and intraductal papillary growth.³⁴ In some cases, a transition from benign AME to M-AME can be identified, supporting the concept that malignant transformation may arise from a pre-existing AME (Fig. 6).^{3,43,50-53}

In cases in which malignancy arises from the ductal epithelial component, the tumors may exhibit morphologic features resembling invasive carcinoma of no special type or special types, such as invasive lobular carcinoma and metaplastic carcinoma. The latter may demonstrate a range of metaplastic features, including squamous differentiation, spindle cell morphology, low-grade adenosquamous differentiation, or matrix-producing characteristics.^{42,52,54,55} Rare cases of AdCC arising in this setting have also been reported, although its histogenesis remains to be elucidated.⁵⁶⁻⁵⁸ The term M-AME *in situ* has been proposed for well-circumscribed lesions with a classic AME architecture, in which the epithelial component exhibits features of DCIS without evidence of stromal invasion.²⁰ However, a caveat of this classifica-

tion is that such lesions may be difficult to distinguish from conventional DCIS, and consequently, the terminology has not been widely adopted in the literature.

When the myoepithelial component predominates, the tumor may exhibit histologic features of myoepithelial carcinoma, including solid, spindle cell, epithelioid, plasmacytoid, or clear cell morphology, accompanied by nuclear atypia and increased mitotic activity. The stroma is often myxoid or chondromyxoid and, less frequently, sclerotic or hyalinized as a result of abundant basement membrane production by the neoplastic myoepithelial cells (Fig. 6).^{3,59}

Rarely, malignant transformation involves both the epithelial and myoepithelial components, resulting in a biphasic carcinoma composed of an admixture of malignant epithelial and myoepithelial cells, for which the term *epithelial-myoepithelial carcinoma* has previously been used (Fig. 7).^{43,55,59,60} In such cases, the myoepithelial component is often the predominant cell population. An underlying AME may or may not be identified.

IHC studies are useful in demonstrating the biphasic cellular composition of these tumors. However, M-AME may acquire an aberrant immunophenotype, similar to that of high-grade, triple-negative invasive ductal carcinoma or metaplastic carcinoma.³ The characteristic paradoxical staining pattern with HMWK in AME may also be retained in its malignant counterpart (Fig. 6). ER expression in M-AME may be either present or absent. However, malignant transformation has been reported more frequently in ER-negative AMEs. Furthermore, the ER status may be concordant between the benign AME and malignant M-AME components, although loss of ER expression may also occur

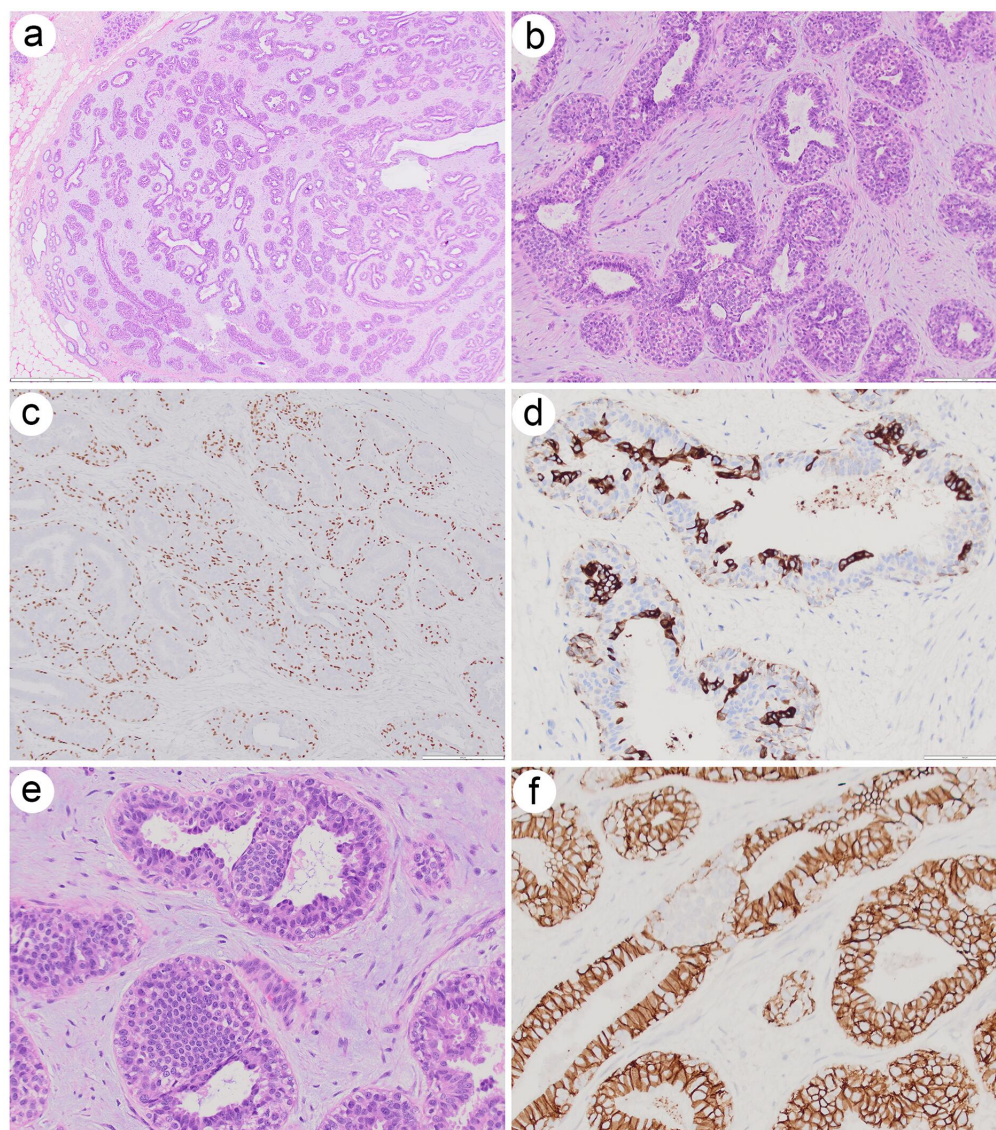


Fig. 5. Atypical ductal hyperplasia and atypical lobular hyperplasia arising in adenomyoepithelioma. (a) Low-power photomicrograph showing a lobulated tumor with fibroadenoma-like architecture. (b) Higher-power view demonstrating glands with prominent myoepithelial hyperplasia. (c) Immunohistochemical staining for p63 highlights the myoepithelial cell layer. (d) Immunohistochemical staining for CK5/6 demonstrates paradoxical expression in the ductal epithelial cells. (e) High-power view showing a focus of atypical ductal hyperplasia. (f) Immunohistochemical staining for E-cadherin demonstrates loss of membranous expression in the cells of atypical lobular hyperplasia. Original magnifications: $\times 20$ (a), $\times 100$ (b, c), $\times 200$ (d), $\times 400$ (e, f).

during malignant transformation.²⁶ In a single study, HRAS Q61R IHC demonstrated 100% specificity and 71% sensitivity for detecting *HRAS* Q61R mutations in AME. Therefore, it may serve as a valuable adjunct to the diagnostic workup, particularly in ER-negative AMEs.⁶¹

Similar to AME, the differential diagnosis of M-AME is broad and depends largely on its growth pattern, predominant cellular composition, and stromal characteristics. Invasive carcinomas of no special type and special types lack the coordinated biphasic proliferation that is characteristic of M-AME. Notably, the myoepithelial component may lose its spatial relationship with the epi-

thelial component or be absent in poorly differentiated areas. Consequently, the classic staining pattern may not always be discernible.³⁴ When evaluating a matrix-producing malignant neoplasm, metaplastic carcinoma should also be considered; however, unlike M-AME, it does not exhibit the distinctive dual-cell morphology and immunophenotype. While AdCC is also composed of dual epithelial and myoepithelial cell populations, it typically exhibits a distinctive architectural pattern characterized, at least in part, by a cribriform growth pattern admixed with tubular and/or solid areas. In diagnostically challenging cases, molecular testing may be helpful, as the majority of AdCC harbor *MYB* or *MYBL1*

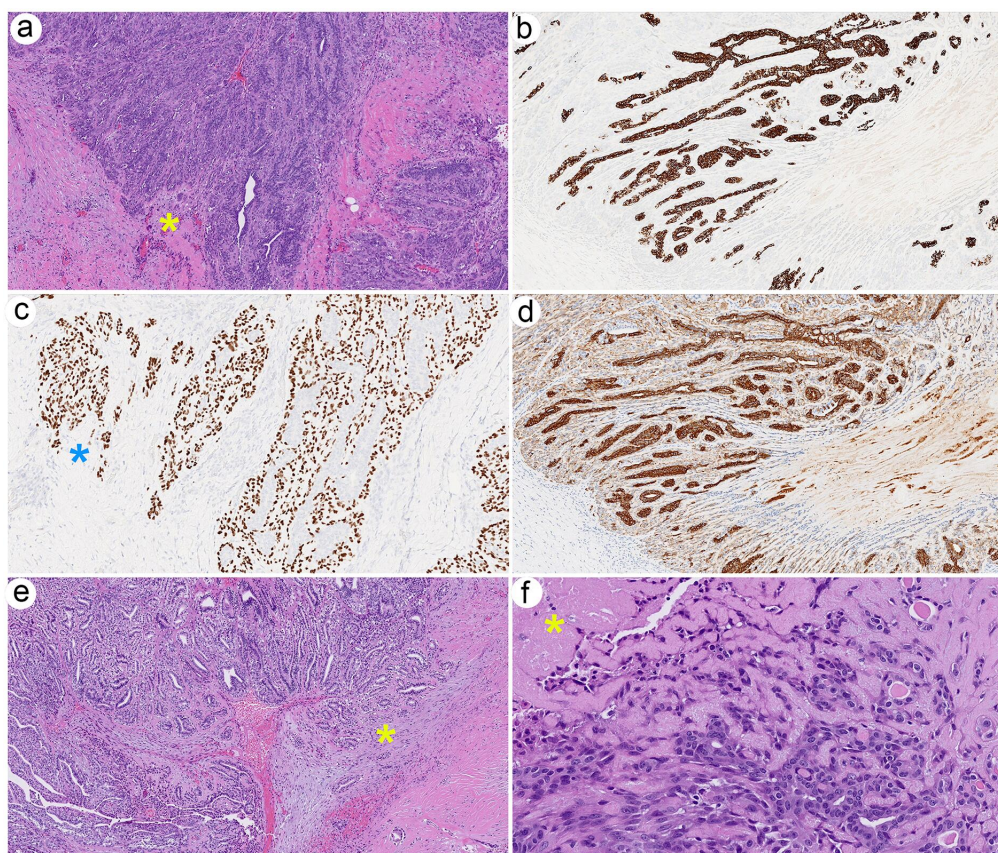


Fig. 6. Histologic and immunophenotypic features of malignant adenomyoepithelioma. (a) Low-power view showing a predominantly pushing tumor border with focal irregular cellular nests suggestive of invasion (indicated by an asterisk). (b) Immunohistochemical staining for CK7 highlights the ductal epithelial cells within the glandular structures. (c) Immunohistochemical staining for p63 highlights the proliferating myoepithelial cells and the focal infiltrative front (indicated by an asterisk). (d) Strong expression of CK5/6 in the ductal epithelial cells, in contrast to its weak expression in the myoepithelial cells. (e) Areas showing tubular and intraductal papillary growth patterns, as well as a focal infiltrative front (indicated by an asterisk). (f) High-power view demonstrates focal necrosis (indicated by an asterisk) and proliferating atypical spindled and plasmacytoid myoepithelial cells within a prominent basement membrane-like matrix. Original magnifications: $\times 20$ (a-d), $\times 40$ (e), $\times 400$ (f).

rearrangements, or *MYB* amplifications.⁶² Despite their biphasic nature, malignant phyllodes tumors rarely pose diagnostic challenges in distinguishing them from M-AME, as they are characterized by the proliferation of malignant stromal cells surrounding benign-appearing epithelial structures.

Prognostic data on M-AME remain limited because of its rarity and the lack of large cohort studies in the literature. Histologic grade and subtype may influence clinical outcomes. In particular, tumors containing a low-grade adenosquamous carcinoma component appear to be associated with a more favorable prognosis, although this observation is based on limited early evidence.⁵⁴ Regional lymph node metastases are rare and may not correlate with tumor stage. Therefore, the available data are insufficient to support routine axillary dissection.^{42,43,63-65} The lung and brain are the most common sites of distant relapse.^{54,66-68} In a National Cancer Database (NCDB)-based study of 110 patients with a median follow-up of 52 months, the 5-year overall survival for the entire cohort was 74.4%. Neither surgical technique, radiation therapy, nor chemotherapy was associated with improved overall survival. Thus, adjuvant therapy may be considered on a case-by-

case basis.⁶³ It is important to note that this study did not distinguish between benign AME and M-AME.

The key pathologic features of benign, atypical, and malignant AME are summarized in Table 1.

Limitations

Our current understanding of these lesions remains limited, largely because of their rarity. Most available evidence is derived from individual case reports and small case series, with a paucity of larger cohort studies, a lack of unified evidence-based diagnostic criteria, and limited sample sizes in available molecular datasets. In addition, as a narrative review without a systematic literature search or formal assessment of study quality, potential selection bias in the included literature cannot be excluded.

Conclusions

Epithelial–myoepithelial tumors of the breast, although rare, encompass a broad histomorphologic spectrum and frequently

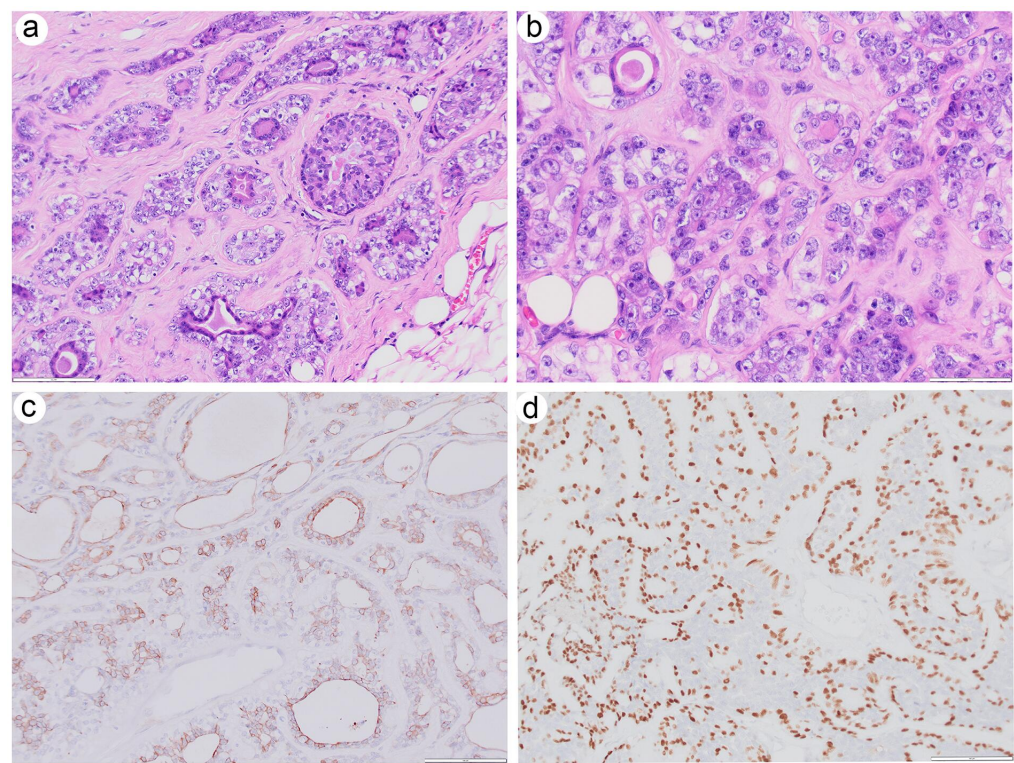


Fig. 7. Histologic and immunophenotypic features of malignant adenomyoepithelioma with biphasic malignant epithelial and myoepithelial components (epithelial-myoepithelial carcinoma). (a) Low-power view showing an infiltrative tumor with a biphasic appearance. (b) High-power view demonstrates two distinct cell populations with focal gland-forming structures and luminal secretions. (c) Immunohistochemical staining for AE1 highlights the inner ductal epithelial cells. (d) Immunohistochemical staining for p63 labels the myoepithelial component. Original magnifications: ×200 (a, c, d), ×400 (b).

Table 1. The spectrum of adenomyoepithelial neoplasms

Diagnosis	Architectural patterns	Immunophenotype	Cytologic atypia	Mitosis	Necrosis
Benign AME	Lobulated, tubular/adenosis, spindle, intraductal papillary; circumscribed or ill-defined periphery, rarely infiltrative	Similar to normal glands; may have paradoxical staining pattern with HMWK	None to minimal	None or minimal (up to 3/10 HPFs), no atypical forms	Absent
Atypical AME	Similar to classic AME; may be irregular or ill-defined/infiltrative	Often similar to classic AME	Mild to moderate	Up to 5/10 HPFs	Absent or focal
Malignant AME	Frequently infiltrative	Often discordant between the histomorphology and immunoprofile	Moderate to severe	Often brisk, may have atypical forms	May be present

AME, adenomyoepithelioma; HMWK, high-molecular-weight keratin; HPF, high-power field.

pose diagnostic challenges. Although advances in molecular genetics have substantially improved the recognition and classification of these tumors, their pathogenesis remains incompletely understood. Furthermore, the biological behavior and clinical course of lesions traditionally regarded as benign may occasionally differ from those of other benign epithelial breast neoplasms. Although PA of the breast is generally considered a benign neoplasm, some authorities have proposed classifying it as a tumor of uncertain malignant potential because of the rare possibility of

malignant transformation. Reports of so-called “benign metastasizing AME,” rare cases of lymph node metastasis, and malignant transformation underscore the need for careful evaluation and long-term clinical follow-up of biphasic epithelial–myoepithelial lesions. More stringent diagnostic criteria are warranted to distinguish classic AME, atypical AME, and M-AME, thereby facilitating accurate diagnosis and appropriate clinical management. In diagnostically challenging cases, molecular genetic analysis may serve as a valuable ancillary tool to support the diagnosis.

Moreover, continued identification of recurrent genetic alterations and actionable therapeutic targets may improve our understanding of tumor biology and enable more accurate risk stratification and individualized treatment strategies, ultimately advancing precision medicine for these rare neoplasms.

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Conflict of interest

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Author contributions

SW is the sole author of the manuscript.

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