

Case Report

Lobulated adenomyoepithelioma: a case report showing immunohistochemical profiles

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Abstract: Lobulated adenomyoepithelioma of the breast is an extremely rare lesion, with hyperplasia of myoepithelial cells and glandular epithelial cells. We present a case of a 51-year-old woman with a small painless hard lump in each breast. The lesion in the left breast was an irregular solid mass, and the right breast showed a subareolar nodule with bloodstained nipple discharge. The final diagnosis was intraductal papillary carcinoma in the right breast and lobulated adenomyoepithelioma in the left breast. In the left breast lesion, histopathologic examination revealed multiple nodules composed of proliferative glandular epithelial cells and surrounding myoepithelial cells. Solid nests of clear or eosinophilic myoepithelial cells proliferated around compressed epithelial-lined space. Smaller satellite nodules were seen. Immunohistochemistry revealed myoepithelial cells were positive for P63, smooth muscle actin, calponin, 34βE12, CK5/6 and CK14, while glandular epithelial cells were positive for AE1/AE3 and CK7. Lobulated adenomyoepithelioma has a high chance of recurrence and malignant degeneration due to inadequate excision. Therefore, understanding of the pathological morphology and accurate diagnosis is important for surgical planning. Moreover, close follow-up is recommended for patients with lobulated adenomyoepithelioma despite the lesion being reported as benign.

Keywords: Adenomyoepithelioma, breast, lobulated, myoepithelium

Introduction

Epithelial-myoepithelial cell hyperplasia of the breast is found in many benign and malignant conditions, including adenomyoepithelial adenosis, pleomorphic adenoma, adenomyoepithelioma, adenomyoepithelioma with carcinoma and adenoid cystic carcinoma. Adenomyoepithelioma is an extremely rare lesion of the breast with a high proliferation of glandular epithelial and myoepithelial cells. Fattanch further subdivided it into spindle-cell, tubular and lobulated variants [1]. In this paper, we describe a case of a 51-year-old woman with lobulated adenomyoepithelioma of the left breast and intraductal papillary carcinoma of the contralateral breast. The immunohistochemical features and differential diagnosis of lobulated adenomyoepithelioma are discussed.

Case presentation

Clinical history

A 51-year-old woman presented with bilateral breast masses. A small painless mass measur-

ing 2 × 1 cm was incidentally discovered in her left breast. Ten months later, a lump measuring 1 × 1 cm was found in her right breast, along with bloodstained nipple discharge. Physical examination revealed a soft, elastic lump (3.5 × 3 cm) in the upper inner quadrant of the left breast, with clear borders and mobility. A subareolar nodule measuring 1.5 × 1 cm was palpated in her right breast, with smelly turbid nipple discharge. There was no lymph node swelling, local tenderness, redness or orange peel-like appearance of the skin. Nipple retraction was not observed. Routine laboratory test results were all within reference range. Ultrasonography of the left breast showed a 3.5 × 3 cm mass with a heterogeneous echo pattern and ovoid or irregular hypoechoic nodules separated by funiform hyperechoic areas. Imaging of the right breast revealed a cystic and solid mass with a heterogeneous echo pattern. Bilateral excision of the breast masses was performed. There was no evidence of recurrence and lymphadenopathy 10 months after her surgery. This report received the approval of the

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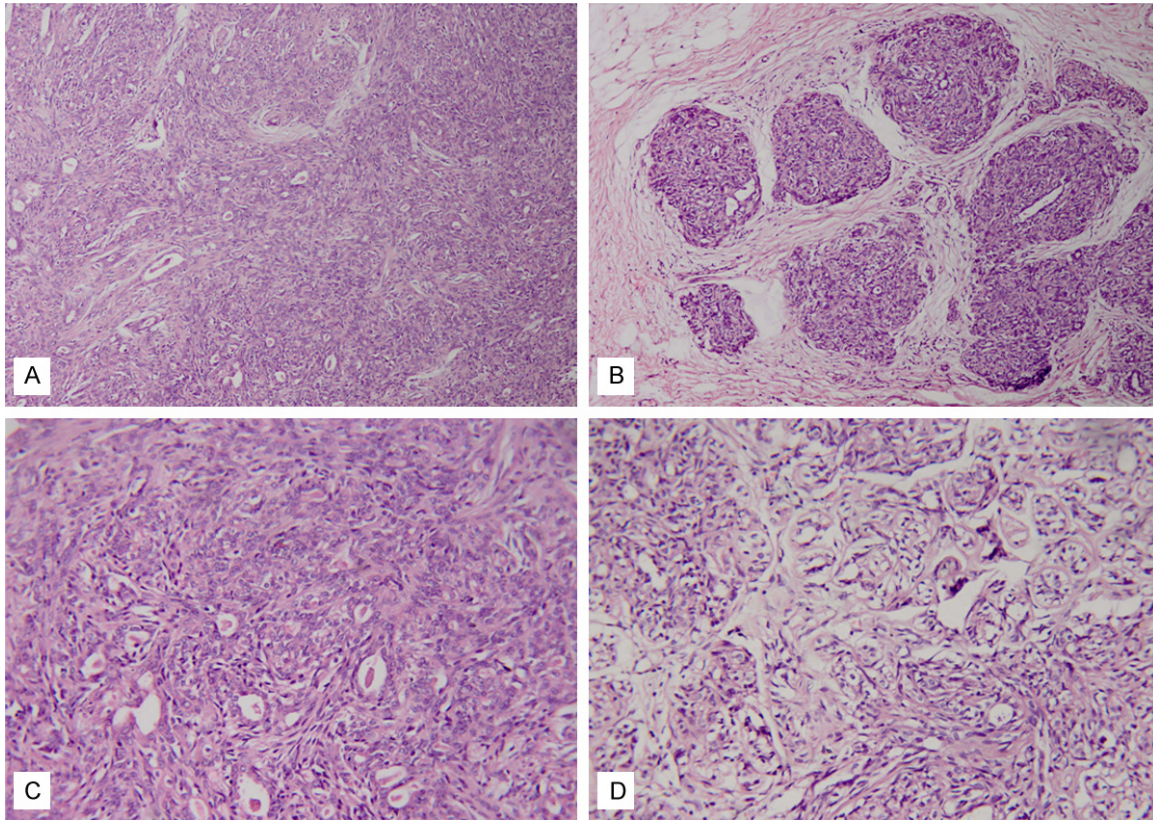


Figure 1. Morphologic findings of lobulated adenomyoepithelioma. A. The tumor was composed of biphasic proliferation of glandular epithelial cells and surrounding myoepithelial cells. B. Smaller satellite nodules revealed slight hyperplasia of both epithelial cells. C. The spindle-shaped myoepithelial cells with amphophilic cytoplasm surrounded the tubule structures and proliferated to form solid nests. D. Myoepithelial cells with clear cytoplasm proliferated to form alveolar or small nest structures.

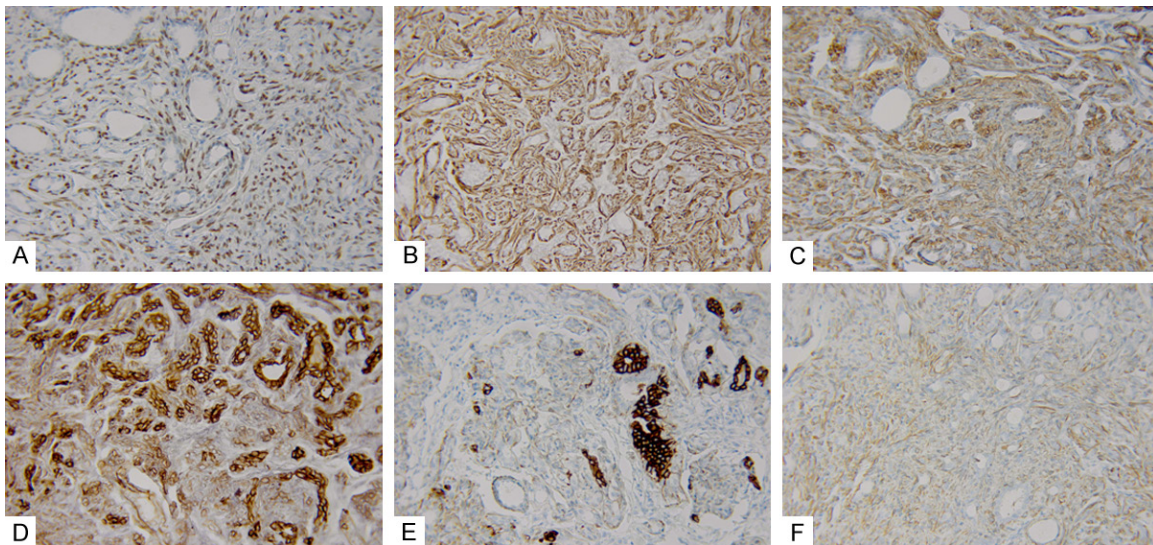


Figure 2. Immunohistochemical features of lobulated adenomyoepithelioma. Myoepithelial cells were positive for P63 (A), SMA (B) and calponin (C). Hyperplastic epithelial cells were positive for AE1/AE3 (D), but were negative for 34βE12 (E) and CK5/6 (F).

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Table 1. The immunohistochemical features of adenomyoepithelial adenosis

Antibody	Ductal epithelial cells	Lobular epithelial cells	Myoepithelial cells
AE1/AE3	+	+	-
34βE12	+	-	Weak+
CK5/6	+	-	Weak+
CK7	+	Local+	-
CK14	-	-	Weak+
P63	-	-	+
Actin	-	-	+
SMA	-	-	+
S-100	-	-	+
Calponin	-	-	+
GFAP	-	-	-

ethics committee of the General Hospital of Jinan Military Command.

Gross

Gross examination of the surgical specimen from the left breast disclosed an ill-defined rubbery area measuring 3.5 × 3 cm that consisted of multiple well-circumscribed nodules. The cut surface of the lesion was uniformly solid with a gray color. A hard solid and cystic mass was observed in the right breast.

Histology and immunohistochemistry

All of the tissue was formalin fixed (10%) and processed for paraffin sections. Sections were stained with hematoxylin and eosin and for immunohistochemistry.

In the left breast sample, microscopic examination showed multiple enlarged lobules. The lobules were ill-demarcated and composed of biphasic proliferated glandular epithelial cells and surrounding myoepithelial cells (**Figure 1A**). Smaller satellite nodules were seen around the larger ones (**Figure 1B**). Fibrous and adipose connective tissue septa of varying thickness divided the lesion into rounded nests or smaller lobules. Prominent myoepithelial cells with clear or eosinophilic cytoplasm surrounding the ductal epithelial cells were noted (**Figure 1C** and **1D**). These cells occasionally proliferated to form solid nests and sheets, especially in the central region of the lobule. They were spindle shaped or cuboidal. The nuclei were generally of moderate size and round to oval.

Proliferative epithelial cells displayed tubular growth patterns with disorderly arrangement, and varying shape and size. The glandular epithelium was flattened, cuboidal or columnar. Epithelial cells tended to have hyperchromatic nuclei and dense eosinophilic to amphophilic cytoplasm, when compared with myoepithelial cells. Apocrine metaplasia was found in some enlarged ductal epithelium. Both epithelial and myoepithelial cells were blended without cytological atypia. Less than 1 mitosis per 10 high power field (HPF) was noted. Myxochondroid matrices produced by the myoepithelial cells were also noted in local regions, as seen in pleomorphic adenomas. Satellite nodules consisted of smaller distended lobules occluded by proliferating myoepithelial cells displacing and undermining the epithelial cell layer. The right breast mass revealed the typical histology of intraductal papillary carcinoma.

Immunohistochemistry can assist in the recognition of these lesions by showing the expression of myoepithelial cell markers and glandular epithelial cell markers. The myoepithelial cell population strongly expressed P63, smooth muscle actin (SMA) and calponin, was weakly positive for 34βE12, CK5/6 and CK14 (**Figure 2**), but was devoid of the expression of AE1/AE3, CK7 and glial fibrillary acidic protein (GFAP) (**Table 1**). Immunohistochemical staining of glandular epithelial cells was strongly positive for AE1/AE3 and CK7, but negative for 34βE12, CK5/6 and CK14. The remnant ductal component was positive for AE1/AE3, 34βE12, CK5/6 and CK7 (**Table 1**).

Results

The pathological diagnosis was lobulated adenomyoepithelioma of the left breast and intraductal papillary carcinoma of the right breast.

Discussion

The significant biphasic proliferation of epithelial and myoepithelial cells is rare in breast disease. Adenomyoepithelioma is a rare tumor characterized by a proliferation of layers of myoepithelial cells around epithelium-lined spaces. As a subtype of adenomyoepithelioma, lobulated adenomyoepithelioma has been called adenomyoepithelial adenosis by some scholars [2, 3], which was adopted by the World Health Organization (WHO) classification of

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breast tumors in the 2003 revision [4], but was deleted in the 2012 revision [5]. The lesions usually show multiple nodules, and immunohistochemistry confirms the hyperplasia of the myoepithelial and lobular glandular epithelial components. Moreover, it has a tendency for local recurrence and malignant transformation [1-3, 6, 7]. Therefore, we believe that lobulated adenomyoepithelioma can be described more comprehensively by the morphological characteristics and biological behaviour of the disease.

Lobulated adenomyoepitheliomas have a multinodular architecture with a thick collagenous capsule that extends and lobulates the tumor cell proliferation, and microscopic satellite nodules may occur at the periphery of the tumor. The typical histological appearance consists of acinar structures composed of an inner layer of epithelial cells with eosinophilic cytoplasm surrounded by prominent myoepithelial cells. The histological findings usually show a diffuse proliferation of round or irregular tubular structures lined by a cuboidal to columnar epithelium, which may show apocrine or squamous metaplasia. Significant myoepithelial proliferation may result in nests or nodules of myoepithelial cells or compression of epithelial components. The myoepithelial cells can show a range of morphologies, including spindle, epithelioid and glycogen-rich clear cells. In our case, some regions were composed of clear myoepithelial cells with cuboidal shape, whereas others had pink to amphophilic cytoplasm and spindle shape. There was no significant nuclear atypia or mitotic activity (<2 per 10 HPF).

Identification of myoepithelial cells is very important in the diagnosis of lobulated adenomyoepithelioma [8, 9]. In immunohistochemical staining, cytoplasmic positivity for SMA and calponin and nuclear positivity for p63 reinforce the myoepithelial cells. Immunohistochemical identification of the luminal epithelial cell component can be accomplished with antibodies to low-molecular-weight cytokeratins. In this case, we confirmed that the epithelial component of tubular structures was glandular epithelium of breast lobule rather than ductal epithelium (Table 1).

Lobulated adenomyoepitheliomas may show wide variations, and they may be confused with

other myoepithelial/stromal cell-rich structures that mimic this lesion. From those reported cases, preoperative diagnosis of lobulated adenomyoepithelioma was thought to be difficult due to the lack of a specific finding on imaging, insufficient amount of tissue or histomorphologic heterogeneity on fine or core needle aspiration biopsy [7, 9-11]. The final diagnostic procedures were usually excisional biopsy and mastectomy. Lobulated adenomyoepithelioma can mimic pleomorphic adenoma, but the latter usually demonstrates chondromyxoid matrix with chondroid and/or osseous metaplasia. Histologically, lobulated adenomyoepithelioma and microglandular adenosis are similar. The latter is a rare form of adenosis characterized by uniform round glands, a non-lobular pattern with highly infiltrative borders, extension into fat and an absence of a myoepithelial component. Lobulated adenomyoepithelioma usually reveals irregularly arranged glands varying in shape and size. Tubular carcinoma with irregular tubules of varying size, shape and distribution is also a differential diagnosis. The glands in tubular carcinoma are larger than those of lobulated adenomyoepithelioma and show a characteristic angular pattern. The lining cuboidal to columnar cells show apical snouts but myoepithelial cells are absent. Desmoplastic stroma, a hallmark feature of tubular carcinoma, is absent in lobulated adenomyoepithelioma.

The behavior of lobulated adenomyoepithelioma is uncertain. Although the prognosis of patients is usually good, it appears to have low malignant potential with a tendency for local recurrence or malignant transformation. Therefore, it is important to make an accurate pathologic diagnosis and arrange appropriate management for this kind of rare breast tumor. Complete resection of the tumor with adequate margins may be recommended, owing to the tendency to develop breast cancer or malignant adenomyoepithelioma, or recurrence [12, 13]. The recurrence rate of lobulated adenomyoepithelioma is significantly higher than in spindle-cell type and tubular adenomyoepithelioma [1]. The existence of satellite nodules may be the main cause of recurrence [13]. Moreover, the recurrent nodules may appear more atypical and display more abundant mitotic activity compared with the primary tumor [1]. Therefore, re-excision is recommended in cases of suspected inadequate margins. Close follow-up is

important for patients with lobulated adenomyoepithelioma, especially for that with mitotic activity exceeding 3/HPF, focally infiltrating margins or satellite nodules.

Conclusions

Lobulated adenomyoepithelioma of the breast is an uncommon tumor characterized by biphasic hyperplasia of the glandular epithelium of the breast terminal duct lobular unit and myoepithelial cells. Preoperative diagnosis is difficult, and the final diagnostic procedures are usually excisional biopsy or mastectomy. Complete resection of the tumor is important owing to the tendency of malignant transformation and recurrence. Close follow-up is recommended, even though in this case the surgical specimen had adequate margins. Recognition of this entity, accurate diagnosis, and knowledge of the expected behavior are important in guiding the most appropriate patient management.

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Disclosure of conflict of interest

None.

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