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Case Report

Malignant adenomyoepithelioma of the breast: cases report and literature review

Dandan Wang[1*], Jian Zhang[1*], Linhong Jiang[2], Xiu Chen[1], Sujin Yang[1], Junchen Hou[1], Qian Zhang[1], Jinhai Tang[1], Lei Li[1], Heda Zhang[1]

Departments of [1]General Surgery, [2]Radiation Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, P. R. China. [*]Equal contributors.

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Abstract: Background: Malignant adenomyoepithelioma (MAME) of the breast is an extremely rare breast malignancy, in which they arise from either luminal epithelial or myoepithelial components, or both. At present, there is very little clinical data of MAME. Case Report: We present two cases, one of them is a 34-year-old woman who underwent needle biopsy for a 3.2 cm-size mass in the right breast, and the pathology was MAME of breast. Another case is a 45-year-old woman who had a 3.0 cm-size mass in the right breast. We performed a breast-conserving surgery and sentinel lymph node biopsy, both of which were negative. The histopathology of these two cases was invasive carcinoma; however, these cases were eligible for MAME of the breast through combining with immunohistochemistry. Conclusions: MAME of the breast is very rare, and has a diverse cell morphology, which must be combined with immunohistochemistry to make a clear diagnosis. Besides, it should be differentiated from adenoid cystic cancer, malignant leafy tumor, spindle cell carcinoma, etc. The clinical characteristics and treatment strategies were further discussed in combination with the literature.

Keywords: Malignant adenomyoepithelioma, breast, immunohistochemistry, CK

Introduction

Despite being first described in 1970, adenomyoepithelioma (AME) remains rare and poorly understood [1]. Malignant AME (MAME) is even unusual, and its complex biological characteristics heighten diagnostic uncertainty, especially for prognosis. At present, the clinical, radiological, and histological data of AME are limited. In 2003, the WHO classified myoepithelial lesions and epithelial neoplasms as breast neoplasms and proposed that AME is a different type of myoepithelial hyperplasia, in which a few of myoepithelia or glandular epithelium cells may be cancerous. In 2012, the WHO made some adjustments to the definition of AME, that is, MAME or AME with cancerous components are uniformly classified as "adenoepithelial carcinoma", including epithelial, myogenic, and epithelial-myogenic carcinomas [2].

AME has a bicellular pattern of ductal and myoepithelial cells [3], and MAME is extremely difficult to distinguish from AME; MAME has a great risk of local recurrence or distant metastasis [3-5]. Owing to the limited options, no agreed treatment modality for breast MAME is available. This work aimed to analyze MAME through clinical characteristics, pathological characteristics, and immunohistochemistry and further learn about relevant experience by reviewing the literature related to new cases and insights into the diagnosis and treatment of breast MAME. This study followed the regulations of the National Research Ethics Committee and obtained the approval of the Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Nanjing Medical University. All participants volunteered for this study and provided informed consent.

Case 1

A 34-year-old woman had a mass on the edge of the gland in the right breast at 1-2 o'clock with tenderness. B ultrasound revealed that the

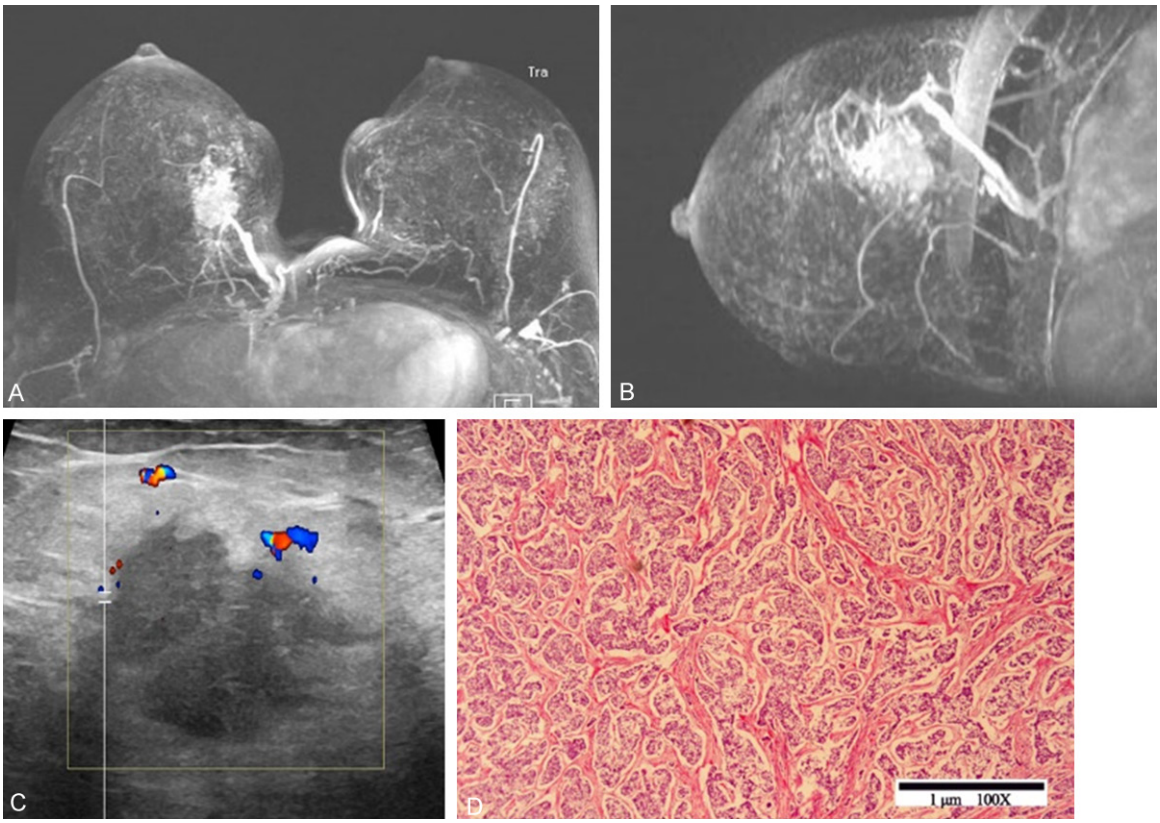

Figure 1. Imaging and pathological examinations in Case 1. A, B: Breast magnetic resonance imaging showed an upper inner mass in the right breast. C: Mammary ultrasound revealed a low echoic mass. D. Pathologic finding (H&E stain) (100 × magnification).

mass was 3.2 cm in size with hard texture, irregular morphology, angular margins, and rich blood flow. B ultrasound and MRI did not identify suspicious axillary lymph nodes. Chest CT and abdominal ultrasound did not reveal distant metastases, and routine blood, carcinoembryonic antigen (CEA), and carbohydrate antigen (CA15-3 and CA125) were within normal limits. Biochemical examination was basically normal except for slightly low albumin (38.4 g/L) and slightly high phosphorus (1.51 mmol/L). She denied having a family genetic history of breast cancer. She underwent core needle biopsy, and the pathology was malignant epithelial tumor of breast. Thus, we performed a breast-conserving surgery + sentinel lymph node biopsy. The surgical specimen presented a grey-white 2.5 × 2.2 × 2 cm^3 mass, and histopathology confirmed that it was invasive carcinoma and sentinel lymph node with no definite metastasis (0/4). All the cut margins were negative (T2N0M0, stage II_A). Immunohistochemistry (IHC) showed ER (-), PR (-), Her-2 (-), Ki67 (60% +), CK5/6 (part 2+), P53 (60% 1+), S-100 (1+), Syn (-), CD56 (-), CgA (-), P63 (a few 2+), calponin (-), GATA3 (2+), SMMHC (-), CK7 (2+), and SOX10 (2+). Combined with HE (Hematoxylin-Eosin) staining, these results suggested that the tumor was consistent with malignant myoepithelioma of the breast. The patient received postoperative adjuvant chemotherapy using the regimen of AC-T and radiotherapy after chemotherapy (**Figure 1**).

Case 2

A 45-year-old woman had a mass on the edge of the gland at 10 o'clock in the right breast, and ultrasound revealed that the cystic mass was 3.0 cm in size with hard texture, irregular morphology, marginal leaf segmentation, and rich blood flow. Breast ultrasound and MRI did not identify suspicious axillary lymph nodes. Chest CT and abdominal ultrasound did not reveal distant metastases. Routine blood, CEA, and carbohydrate antigen (CA15-3 and CA125) were within normal limits, and biochemical

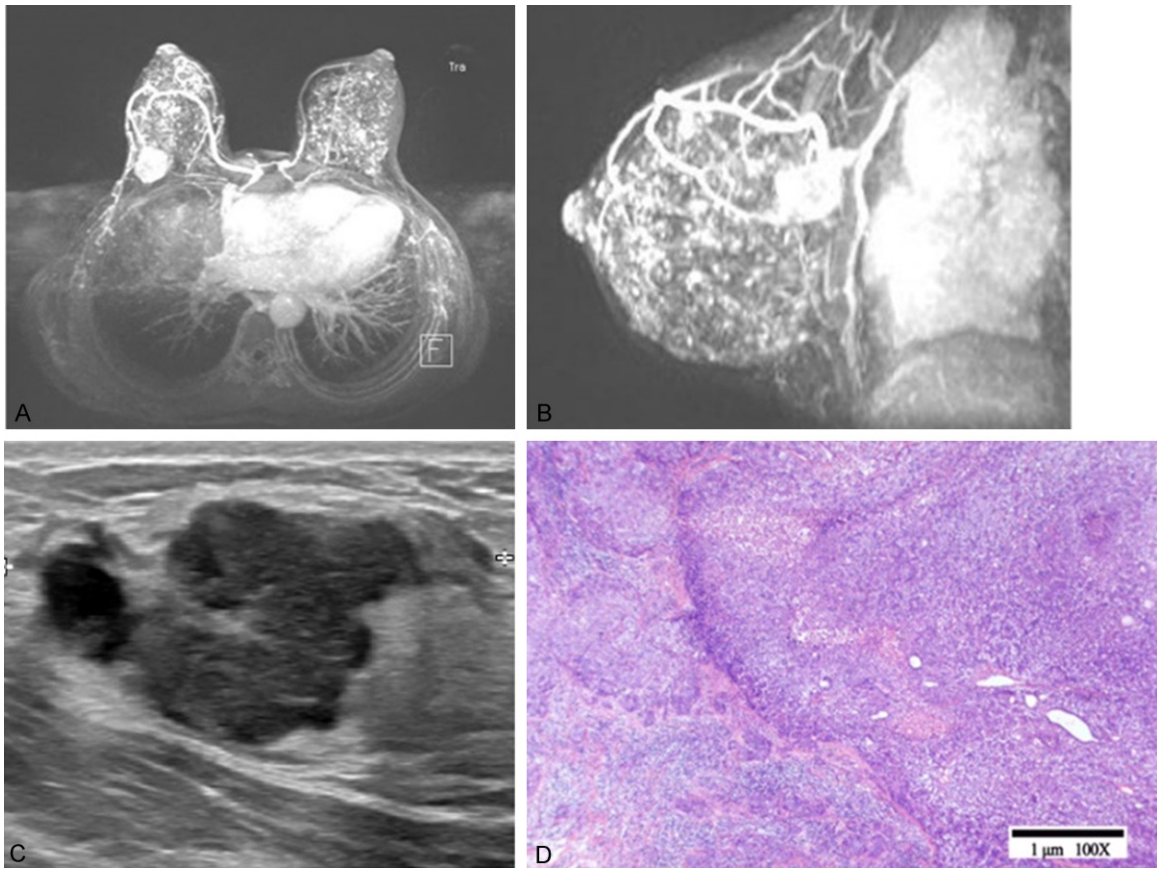

Figure 2. Imaging and pathological examinations in Case 2. A, B: Breast magnetic resonance imaging showed an upper outer mass on the edge of the gland in the right breast. C: Mammary ultrasound revealed a low echoic mass. D. Pathologic finding (H&E stain) (100× magnification).

examination was basically normal except for slightly low albumin (38.5 g/L), total cholesterol (2.93 mmol/L), and LDL cholesterol (1.63 mmol/L). She denied having a family genetic history of breast cancer. She received lumpectomy, and frozen pathology showed breast malignant tumor. In accordance with the preoperative signature, we performed breast-conserving surgery + sentinel lymph node biopsy. The surgical specimen presented a grey-white 2.2 × 2.0 × 1.5 cm^3 mass, and histopathology confirmed that it was invasive carcinoma with DCIS (ductal carcinoma in situ) and sentinel lymph node with no definite metastasis (0/5). All the cut margins were negative (T2N0M0, stage II_A). IHC showed ER (-), PR (-), Her-2 (-), Ki67 (about 75%+), CK5/6 (+), Syn (-), CgA (-), CD56 (-), P63 (+), AR (about 10% 2+), SMMHC (perimyoepithelium -), calponin (perimyoepithelium -), E-cadherin (membrane +), and p120 catenin (membrane +). Combined with HE staining, these results suggested that the tumor was consistent with malignant myoepithelioma of the breast. The patient received postoperative adjuvant chemotherapy using the regimen of AC-T and radiotherapy after chemotherapy (**Figure 2**).

Discussion

Breast MAME is an extremely rare malignant tumor, and less than 100 cases of MAME have been reported [3, 6-9]. In historical examination, AME diagnosis is difficult and requires an experienced pathologist specializing in breast cancer. The pathological features of MAME have several main characteristics, such as hyperplasia of glandular epithelial or myoepithelial cells, cellular atypia, pathological nuclear divisions or high mitotic index, large and irregular nucleus, and bleeding and necrosis occurred within the tumor [10, 11]. IHC is needed for further confirmation. In general, the staining for estrogen and progesterone recep-

tors is mainly negative or rarely/weakly positive, HER-2 is negative, and typical myoepithelial markers including CK5/6, P63, SMA, and S100 are positive [12]. Small-molecule cytokeratins, including CK7, CAM 5.2, and EMA, are also positive [3]. Therefore, the diagnosis of this disease requires accurate detection and well-informed pathologists.

For patients with MAME, the stage of axillary node is vital. Although the tumor is infiltrative, rare axillary lymph node metastases occur and most patients have no clear sentinel lymph node metastasis during surgery [13, 14]. In our reported cases, the patients received sentinel lymph node biopsy and no lymph nodes were positive, which finding is consistent with most reports. Owing to the rarity of MAME, no standard treatment guidelines, including adjuvant chemotherapy and/or radiotherapy, have been established. However, some have recommended that adjunctive therapy for conventional breast cancer can be adopted for MAME [15], although no evaluation of efficacy has been conducted. In our cases, although no definite metastasis was observed in the sentinel lymph nodes, the mass was about 3 cm. Therefore, the patients received postoperative adjuvant chemotherapy with the regimen of AC-T. Xu et al. [16] reviewed 47 MAME cases and disclosed 15 patients with metastasis accompanied by poor prognosis [16]. A retrospective study of the prognosis of 110 patients with MAME showed that the expected 5-year overall survival of MAME patients is approximately 74.4% [7, 17]. Therefore, MAME requires a systemic and comprehensive treatment, including surgery, chemotherapy, radiotherapy, endocrinotherapy, target drugs, and even immunotherapy. For follow up on long-term prognosis, additional cases are needed to obtain clinical evidence.

Ginter et al. [18] confirmed that MAME has AKT1, PIK3CA, and HRAS mutation which has an important effect on PI3K/AKT/mTOR pathway. The PI3K/AKT/mTOR signaling pathway has a profound influence on breast cancer and is associated with cell proliferation, apoptosis, invasion, metastasis and DNA repair, and now some inhibitors are used in clinics, such as everolimus, temsirolimus, and sirolimus [19]. Additional cases are needed to confirm whether these drugs are also effective against MAME. An EGFR gene amplification has also been reported in MAME. Most current studies on EGFR gene amplification mainly focused on lung cancer, suggesting that these target drugs may also be effective against MAME. However, in our cases, hormone receptors were all negative and these drugs may have no effect. Thus, other target drugs for MAME must be developed.

Conclusion

We reported two cases of MAME that received breast-conserving surgery and SLNB, followed by adjuvant chemotherapy and radiotherapy. Owing to the rarity of MAME, no systemic treatments have been established. Therefore, the management of MAME will benefit from a multidisciplinary and shared decision-making approach to provide prevention and cure methods and the most appropriate treatment strategy for these patients.

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Disclosure of conflict of interest

None.

Address correspondence to: Heda Zhang and Lei Li, Department of General Surgery, The First Affiliated Hospital of Nanjing Medical University, No. 300 Guangzhou Road, Nanjing 210029, Jiangsu, P. R. China. E-mail: zhanghedazhd@163.com (HDZ); ttleileitt@njmu.edu.cn (LL)

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