Challenges in the Management of Malignant Adenomioepithelioma of the Breast: a Case Report and Review of the Literatures

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Abstract

Background: Malignant adenomyeloblastoma is a rare tumor, with no guidelines available for its treatment.

Case presentation: We discuss a case of malignant adenomyeloblastoma of the right breast in a 59-year-old woman. The patient underwent a lumpectomy, and pathological diagnosis of malignant adenomyeloblastoma was distinct from the preoperative needle-biopsy diagnosis of intraductal papilloma. The patient underwent mastectomy and chemotherapy immediately. However, local recurrence was occurred 11 months after the initial operation. We summarize the characteristics of patients with malignant adenomyeloblastoma in PubMed and Web of Science databases, and share our experience and discoveries. Statistics included the univariate and multivariable Cox proportional hazards models. Overall, 34 patients were analyzed.

Conclusions: At diagnosis, the median age was 59.3 years and the median tumor size was 30.0 mm. The most common initial surgery was breast-conserving surgery (50%), and a proportion of patients underwent axillary lymph node dissection (32%). Age, max diameter, and axillary status were associated with overall survival. Complete surgical excision with adequate margins is the most important treatment. Patients may not benefit from remedial adjuvant therapy, but may benefit from prompt postoperative adjuvant therapy. Multidisciplinary cooperation and follow-up are essential for the management of these patients. Our data would provide novel insights into a rare tumor that might avoid over- or under-treatment of the patients.

1. Introduction

Adenomyoepithelioma (AME) of the breast is a rare tumor with the biphasic proliferation of the epithelial and myoepithelial cells[1], which was first reported in 1970[2]. According to the 2019 World Health Organization (WHO) classification, AME is one of the epithelial-myoepithelial tumors, and malignant AME exhibits malignant transformation in either or both components. Malignant AME is rare in clinical practice. Yet, malignant AME has a high incidence of recurrence or even distantly metastasize to lung, bone, brain, and other sites. Hence, it is worthwhile to pay more attention to malignant AME. The previous reports about the malignant AME in the breast are limited and we know little about the tumorigenesis, progress, prognosis, and consensus of the treatment. We herein present a case of a 59-year-old woman with local recurrence, and summarize and analyze the patients in the databases, in order to provide a deeper understanding of the malignant AME and its management.

2. Case Presentation

The patient was a 59-year-old woman, whose chief complaint was lumps discovered accidentally in right breast for 2 months. There was a 20-year history of benign tumor resection in the left breast and no family history of breast cancer. According as the ultrasound (US) is imaging, a 1.0×0.9 cm lesion was found in the lower midregion of the right breast and the Breast Imaging Report and Data System (BIRADS) grade was 4b (Fig. 1). Multifocal lesions in bilateral breasts were also discovered whose BIRADS-US grade was 3. Neither enlarged ipsilateral axillary nor supraclavicular lymph nodes were palpable. The patient was admitted to Center for Thyroid and Breast Surgery, Xuanwu Hospital, Capital Medical University in January 2020. After initial clinical evaluation, a core needle biopsy was performed and the pathological report showed ductal epithelial hyperplasia. Considering the BIRADS-US grade, right lumpectomy was firstly performed. The mass was separated around it and completely removed.

Postoperative pathological examination illustrated that the resected tumor was identified as a malignant AME measured 0.7×0.5×0.5cm. Microscopy revealed lobulated or nodular tumors with a biphasic proliferation of epithelial and myoepithelial cells. Myoepithelial cells exhibited active proliferation and frequent mitosis, and central necrosis could be seen in tumors. Immunohistochemistry staining revealed that a positive expression of P63, E-cadherin, calponin, and CD56, and a partial expression of CK5/6 (Fig. 2). Additionally, the estrogen receptor (ER) was positive only in the part of glandular epithelium. The progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) were negative. Accordingly, a diagnosis of malignant AME was made. The same diagnosis was made in the pathology consultation at the Peking Union Medical College Hospital and the General Hospital of the People's Liberation Army within the next month.

Right mastectomy combined with sentinel lymph node biopsy was performed later. The intraoperative frozen section examination showed no metastasis in 5 sentinel lymph nodes. The residual lesions of malignant AME measured 3×1.5cm was found in the postoperative pathological examination, and the composition was myoepithelial carcinoma. Immunohistochemistry staining revealed that the lesion was positive for P63, calponin, α-actin, and CD10, and focally positive for CK5/6. Additionally, ER, PR and HER-2 were as same as the first immunohistochemistry result, and index of Ki-67 reached 50% (Fig. 3).

Epirubicin + Cyclophosphamide combined with sequential Taxol was employed for adjuvant chemotherapy, considering a potentiality of local recurrence and distant metastatic. No side effect was found except for alopecia.

Local recurrence was occurred 11 months after the initial operation. An approximately 1.4×0.7 cm mass was discovered around the surgical scar (Fig. 4). Then, the lesion was further resected which sized 1.5×1.5×0.9cm. The immunohistochemistry staining was similar to the previous tumor. After a 5-month follow-up, no recurrence or other adverse complications was found. The patient understood the strong invasiveness of malignant AME and regular follow-up was continued.

3. Literature Review

A literature search was conducted in PubMed and Web of Science databases, using the search terms ‘Malignant Adenomyoepithelioma’ or ‘Malignant AME’ or ‘MAME’. The cases without the largest tumor diameter, treatment and follow-up data were excluded. 34 patients with malignant AME of the breast who had comprehensive clinical records were collected and summarized in Table 1. Time to first local recurrence and metastases, and disease duration were recorded from the first diagnosis of malignant AME. All statistical tests were two-sided, with a threshold of $P < .05$ for statistical significance. Univariate and multivariate Cox proportional hazards modeling was conducted using R software. Estimated hazard ratios were reported as relative risks with 95% confidence intervals. Overall survival (OS) referred to the interval between the date of diagnosis and the date of death, or censored at last contact. Disease-free survival (DFS) was defined as the time from the time of diagnosis until the appearance of recurrences and/or metastases.

Table 1
Summary of cases of malignant adenomyoepithelioma of the breast.

Author	No.	Age	Size(mm)/site	Axillary status	Surgery treatment	Adjuvant therapy	Time to first recurrence	Time and site to distant metastases	Disease duration (alive/died)
Kiaer	1	46	9/R	0	BCS	NS	NO	NO	3Y (alive)
Young	2	76	20/R	0	BCS	NS	NO	NO	15M (alive)
Loose	3	26	10/R	0	Excisional biopsy	NS	NO	NO	5M (alive)
Loose	4	43	35/L	0	Excisional biopsy and MRM [a]	RA [a]	15M	29M Chest wall, 54M Lung and 60M Brain	64M (died)
Chen	5	54	170/R	1	MRM	C [b]	NO	3W Bone	7M (died)
Michal	6	77	100/NS	0	Excisional biopsy	NO	5M	5M Lung	5M (died)
Pauwels	7	49	45/NS	0	BCS	NO	NO	NO	72M (alive)
Rasbridge	8	64	30/R	0	BCS	NO	NO	NO	12M (alive)
Rasbridge	9	76	17/L	0	BCS and mastectomy [a]	NO	12M	NO	60M (alive)
Rasbridge	10	72	45/R	0	MRM	NO	NO	NO	12M (alive)
Rasbridge	11	39	13/L	0	BCS and mastectomy [a]	NO	180M	NO	210M (alive)
Rasbridge	12	76	150/NS	0	BCS	NO	36M	36M Brain	36M (died)
Simpson	13	50	40/L	0	Lumpectomy and BCS [a]	E and RA [a]	12M	25M Lung	39M (died)
Takahashi	14	60	90/R	0	Radical mastectomy	C and RA [b]	NO	24M Lung, Bone, MLN	43M (died)
Bult	15	52	16/L	0	MRM	C and RA [b]	NO	12Y Thyroid	12Y (died)
Kihara	16	86	40/L	0	Mastectomy	NO	NO	3M Lung	3M (died)
Jons	17	71	30/R	0	BCS	E	NO	2Y Liver on autopsy	2Y (died)
Noel	18	67	50/L	0	Mastectomy	RA	6M	1Y Lung	18M (alive)
Han	19	69	25/R	0	Lumpectomy	NO	NO	NO	9M (alive)
Petrozza	20	60	17/R	0	Lumpectomy	RA	NO	NO	4Y (alive)
Xu	21	54	23/L	0	Lumpectomy	NO	NO	NO	5Y (alive)
Xu	22	48	20/L	0	BCS	NO	NO	NO	8Y (alive)

Abbreviations: R, right; L, left; NS, not stated; BCS, breast-conserving surgery; MRM, modified radical mastectomy; C, chemotherapy; RA, radiation E, endocrinotherapy; Y, years; M, months; W, weeks; MLN, mediastinal lymph nodes; APN, abdominal paraaortic node; [a], After recurrence; [b], After metastasis; [c], After pathology.

Author	No.	Age	Size(mm)/site	Axillary status	Surgery treatment	Adjuvant therapy	Time to first recurrence	Time and site to distant metastases	Disease duration (alive/died)
Moritz	23	71	45/L	0	Mastectomy	NO	NO	NO	15M (alive)
Korolczuk	24	51	26/L	0	Mastectomy	NS	NO	5Y Lung	9Y (alive)
Logie	25	63	24/R	1/26	Mastectomy	RA	NO	NO	3Y (alive)
Zhu	26	58	30/L	1/12	BCS and MRM [b]	C and RA [b]	11M	27M Sternum and Rib	35M (died)
Zhu	27	56	30/R	0	Mastectomy	C and E	NO	NO	21M (alive)
Lee	28	67	50/R	1	MRM	C	NO	6M Lung and 18M Brain	21M (died)
Lee	29	55	23/R	0	BCS	C and RA	NO	NO	12M (alive)
Ito	30	58	25/L	0	Mastectomy	RA	NO	NO	2Y (alive)
Gafton	31	63	60/L	0	Lumpectomy	C	NO	NO	6Y (alive)
Kakkar	32	36	29/L	0	BCS	E	NO	NO	1Y (alive)
Moro	33	64	36/L	0/26	Mastectomy	C [b]	NO	8M Lung and 17M Kidney, Adrenal, Ovarian, and APN	19M (died)
Present case	34	59	7/R	0/5	Lumpectomy and mastectomy [c]	C [c]	11M	NO	18M (alive)

Abbreviations: R, right; L, left; NS, not stated; BCS, breast-conserving surgery; MRM, modified radical mastectomy; C, chemotherapy; RA, radiation E, endocrinotherapy; Y, years; M, months; W, weeks; MLN, mediastinal lymph nodes; APN, abdominal paraaortic node; [a], After recurrence; [b], After metastasis; [c], After pathology.

The average age of 34 patients was 59.3 ± 13.1 years (26–86 years). The maximum tumor diameter ranged from 7 to 170 mm with a median size of 30.0 (20.0, 45.0) mm. The incidence of AME in the right breast was almost the same as that in the left breast.

The most common initial surgery was breast-conserving surgery (n = 17, 50.0%), while some patients underwent mastectomy (n = 14, 41.1%). There were 3 (8.8%) cases only treated with excisional biopsy, and one of them underwent a modified radical mastectomy after recurrence. A proportion of patients underwent axillary lymph node dissection (n = 11,32.4%) during initial treatment. 18 (52.9%) patients received adjuvant therapy, including chemotherapy in 10 cases, radiotherapy in 10 cases, and endocrine therapy in 4 cases. Among them, chemotherapy or radiotherapy was performed after recurrence and metastasis in 7 (20.6%) cases.

The first local recurrence occurred in 5 to 180 months after the initial excision. The median recurrence time was 1 year. 9 (26.5%) cases had a history of local recurrence. Among them, 4 cases had multiple local recurrences during follow-up. The median time of distant metastasis was 2 years. The metastatic lesion located in lung (9/14), brain (3/14), bone (3/14), thyroid (1/14), chest wall (1/14), liver (1/14), kidney (1/14), adrenal (1/14), ovarian (1/14), mediastinal lymph node (1/14) and abdominal paraaortic node (1/14). 4 cases (11.8%) had positive axillary lymph nodes. The disease duration of patients ranged from 3 to 210 months with a

median count of 24 (12, 60) months. 12 patients died as a result of the metastases accounting for 85.7% (12/14) of the patients with metastases.

The univariate and multivariate Cox proportional hazards model evaluated factors independently associated with DFS and OS (Tables 2 and 3). At univariate analyze, there was a strong trend between age and the maximum tumor diameter and DFS (P< 0.05 for all). Compared with biopsy, breast-conserving patients are less prone to recurrence or metastases (P= 0.024). Age, the maximum diameter and axillary node status may play a significant role in OS (P< 0.05 for all). Following univariate analysis, multivariate Cox proportional hazards model revealed that age, the maximum diameter and axillary node status were in line with worse OS (P< 0.05 for all). However, none of the adjuvant therapy were related to DFS or OS (P> 0.05 for all).

Table 2
Univariate and multivariate Cox proportional hazards model to analyze the correlation between characteristics of malignant Adenomyoepithelioma and disease-free survival.

Variable	Univariate analysis			Multivariate analysis		
	Hazards radio	95% CI	*P* value	Hazards radio	95% CI	*P* value
Age	1.063	1.011–1.118	0.017	1.056	0.992–1.123	0.089
Sex	0.045	0.000-1116.244	0.547			
Site	1.160	0.368–3.658	0.800			
Size	1.014	1.003–1.025	0.009	1.011	0.996–1.026	0.140
Axillary node status	0.309	0.085–1.118	0.074	2.898	0.694–12.101	0.145
Surgery						
Biopsy only	1 (reference)			1 (reference)		
Mastectomy	0.416	0.084–2.051	0.281	0.211	0.033–1.346	0.100
Breast-conserving surgery	0.138	0.025–0.769	0.024	0.068	0.010–0.473	0.007
Chemotherapy	1.055	0.235–4.745	0.944			
Radiation	3.117	0.407–23.880	0.274			
Endocrinotherapy	1.567	0.203–12.080	0.667			
Abbreviations: CI, confidence interval.						

Table 3
Univariate and multivariate Cox proportional hazards model to analyze the correlation between characteristics of malignant Adenomyoepithelioma and overall survival.

Variable	Univariate analysis			Multivariate analysis		
	Hazards radio	95% CI	*P* value	Hazards radio	95% CI	*P* value
Age	1.082	1.021–1.147	0.008	1.076	1.004–1.154	0.039
Sex	0.044	0.000-2220.838	0.572			
Site	0.490	0.117–2.048	0.328			
Size	1.018	1.007–1.030	0.002	1.013	1.001–1.025	0.036
Axillary node status	4.443	1.051–18.775	0.043	5.656	1.163–27.514	0.032
Surgery						
Biopsy only	1 (reference)					
Mastectomy	0.597	0.115–3.092	0.539			
Breast-conserving surgery	0.223	0.040–1.247	0.088			
Chemotherapy	0.676	0.085–5.350	0.710			
Radiation	0.038	0.000-70.603	0.395			
Endocrinotherapy	1.840	0.214–15.835	0.579			
Abbreviations: CI, confidence interval.						

4. Discussion

AME of the breast is rare, especially malignant AME. Malignant AME generally occurs in 50 or 60-year-old women. Age is an important factor in prognosis, and young age at onset is a protective factor for recurrence, metastasis and death (DFS, hazards radio, 1.063; OS, hazards radio, 1.082). These lesions were mostly unilateral without significant differences between the left and right sides, and site is independent of both DFS and OS ($P > 0.05$ for both). Patients with a malignant AME of the breast could present with a palpable mass[3, 4]. The patient is usually preceded by a longstanding stable mass, followed by a period of rapid growth[5]. As expected, the maximum tumor diameter is closely associated with DFS and OS ($P < 0.05$ for both). As such, surgical intervention is called as soon as possible. Like the case in our present report, several patients are asymptomatic and merely detected by mammogram or ultrasound screening which show the relatively non-specific oval mass. It may be impossible to identify malignant AME by radiographic features alone. However, imaging techniques are non-conclusive but indispensable. Almost all of these cases presented a BI-RADS classification of 4 or higher, which means biopsies could not be omitted and reduces the occurrence of missed diagnoses simultaneously [6].

In our present case, the result of preoperative needle-biopsy showed an intraductal papilloma, while the final postoperative pathological examination demonstrated that the resected mass was a malignant AME, which extremely misleading our treatment. The study revealed that these tumors are morphological polymorphism and classified into lobulated, papillary, tubular and mixed patterns[5]. Papillary patterns are easily confused with intraductal papilloma, and some scholars have even suggested that AME is a variant of intraductal papilloma[7]. The diagnosis of intraductal papilloma is supported if myoepithelial cells are seen only in the lateral aspect of the papillary region without significant proliferation of nest-like, small nodular cells. In contrast, if the myoepithelial cells are significantly and diffusely proliferating, the lesion is more likely to be a malignant AME[8, 9]. As for intraductal papillary carcinoma, it is easy to differentiate due to the absence of myoepithelium. These lesions are quite heterogeneous with variable components on pathology, so limited tissue sampling could potentially lead to misdiagnosis[10]. Never can we ignore the false negative of biopsy, and we should emphasize radiology-pathology concordant. In cases of ultrasound abnormalities (BI-RADS 4 or higher), extended resection could reduce incidence of missed diagnoses.

The diagnosis of malignant AME generally depends on immunohistochemistry after complete resection. The conclusions of Moritani et al., combining high molecular weight cytokeratin and any one of α-SMA, calponin, and p63 would be a good panel for the diagnosis of AME[11]. In our case, the tumor was positive for α-actin, calponin, and P63, and focally positive for CK5/6, consistent with related reports. The diagnosis of malignant AME should base on the diagnosis of AME, whose malignant component often shows an infiltrative growth pattern, marked cytological atypia, a high mitotic rate, significant necrosis, and a high Ki-67[5, 8, 9].

Due to this pathology is extremely rare, no guidelines are available for its therapeutic approach. After univariate analyze, we found a significantly reduced risk of relapse among breast-conserving patients, as compared with patients with biopsy only. Complete surgical excision with adequate margins is the treatment of choice that minimize the risk of recurrence and metastasis, as reported previously [5, 12-16]. However, we summarized the literatures and found that the incidence of recurrence and metastasis is still close to 50% even after complete resection, and once recurrence and metastasis occur, the mortality rate is as high as 66%. For malignant AME, it seems that complete excision alone may not be sufficient. The metastases occur mainly via the blood system, with lungs, brain and bones as the main target organs. The proportion of involved axillary lymph nodes was 4/34 and axillary node status seems to be associated with worse OS based on statistical analysis (hazard ratio, 4.443; $P = 0.043$). Reviewing these four patients, lymphatic metastases may be associated with excessive tumor and delayed treatment. On the one hand, as mentioned previously, the maximum tumor diameter is closely related to prognosis. On another hand, the consequence of delayed treatment is rapid growth of tumor size. Therefore, axillary staging may not be necessary in small tumor, which is consistent with the relevant literature[14, 17].

After statistical analysis, all adjuvant treatments were proven not to prolong DFS or OS (hazard ratio, 0.138; $P = 0.024$). We have carefully reviewed these cases, 7 cases were given chemotherapy or radiotherapy after recurrence and metastasis, and all of these patients eventually died after metastasis. We may learn from this that remedial radiotherapy or chemotherapy does not work after the occurrence of recurrence and metastasis. At the same time, among the 9 patients treated with chemotherapy and/or radiotherapy after initial surgery, there was only one case with a bad ending. The patient delayed the treatment after biopsy, and the tumor had progressed significantly when she received treatment[17]. This may indicate that these patients may benefit from appropriate postoperative adjuvant therapy[9]. Some papers suggest that the endocrinotherapy has no clear benefit, due to the ER and PR tend to be negative[18]. For the start, not all patients received adjuvant therapy. Secondly, Patients receiving adjuvant therapy might have a higher degree of malignancy themselves. This means we need more evidence to validate the value of adjuvant therapy.

In the present study, the initial lesion was found and resected completely, which was only 0.7 cm in size. Following immediate mastectomy and chemotherapy, local recurrence still occurred. Thus, it triggered further exploration on the causes of the recurrence. First of all, the malignant component of the case is myoepithelial carcinoma. Some scholars have noticed that the increased proportion of the myoepithelial component compared to the epithelial component may lead to a worse prognosis, due to heterogeneity between proportion of epithelial and myoepithelial cells can affect treatment resistance[16].This may explain the local recurrence in our case after chemotherapy. In addition, we performed lumpectomy without attention to margins status identified from frozen section analysis, due to the benign biopsy pathology. Treatment strategies for malignant AME should be made together in a multidisciplinary way to avoid over- or under-treatment of the patients, especially radiology-pathology concordant.

5. Conclusion

The management of malignant AME still faces challenges, and the rate of recurrence, metastasis and death should not be underestimated. Age, maximum diameter and axillary status are closely associated with prognosis. The earlier the lesion is diagnosed and resected, the less risk of recurrence and metastasis in the axilla and elsewhere. Patients may not benefit from remedial adjuvant therapy, and the timing of adjuvant therapy deserves further exploration. We need to focus on multidisciplinary cooperation, in order to decide upon the best treatment regime.

Abbreviations

AME: Adenomyoepithelioma; BIRADS: the Breast Imaging Report and Data System; DFS: Disease-free survival; OS: Overall survival; US: ultrasound; WHO: World Health Organization.

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent form is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to declare.

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Authors' contributions

Hua Kang responsible for research conception and methodological design. Yuwei Ling, Kaifu Li, Yan Zhang and Ye Zhao assisted with participant recruitment and data entry. Yu Wang assisted with data analysis and interpretation. Yu Wang and Yuwei Ling wrote the original manuscript. Hua Kang prepared to review and editing. All authors have read and approved the final version of the manuscript.

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Figures

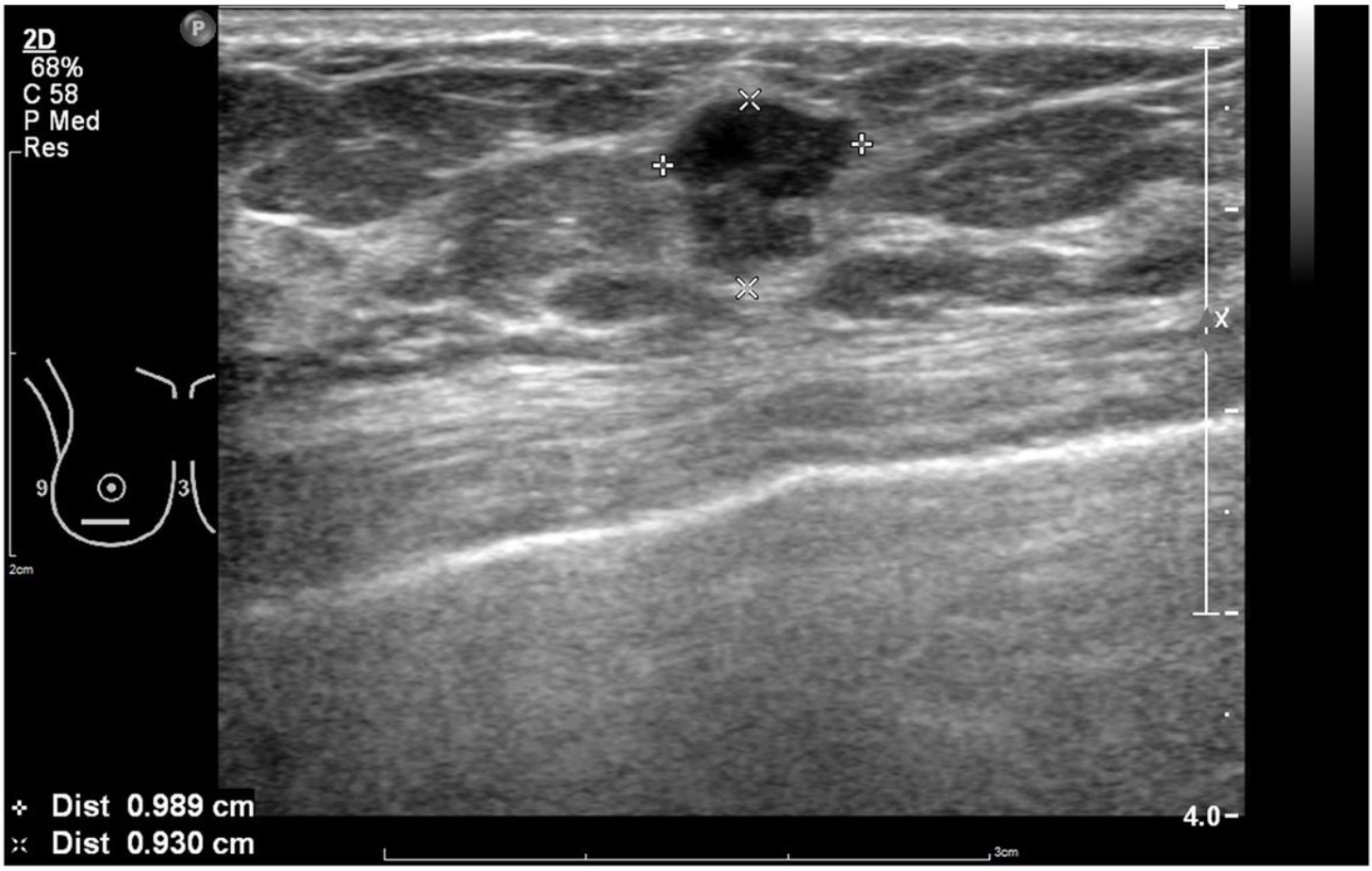

Figure 1

Ultrasound showing a solid hypo-echoic mass at 6 o'clock position.

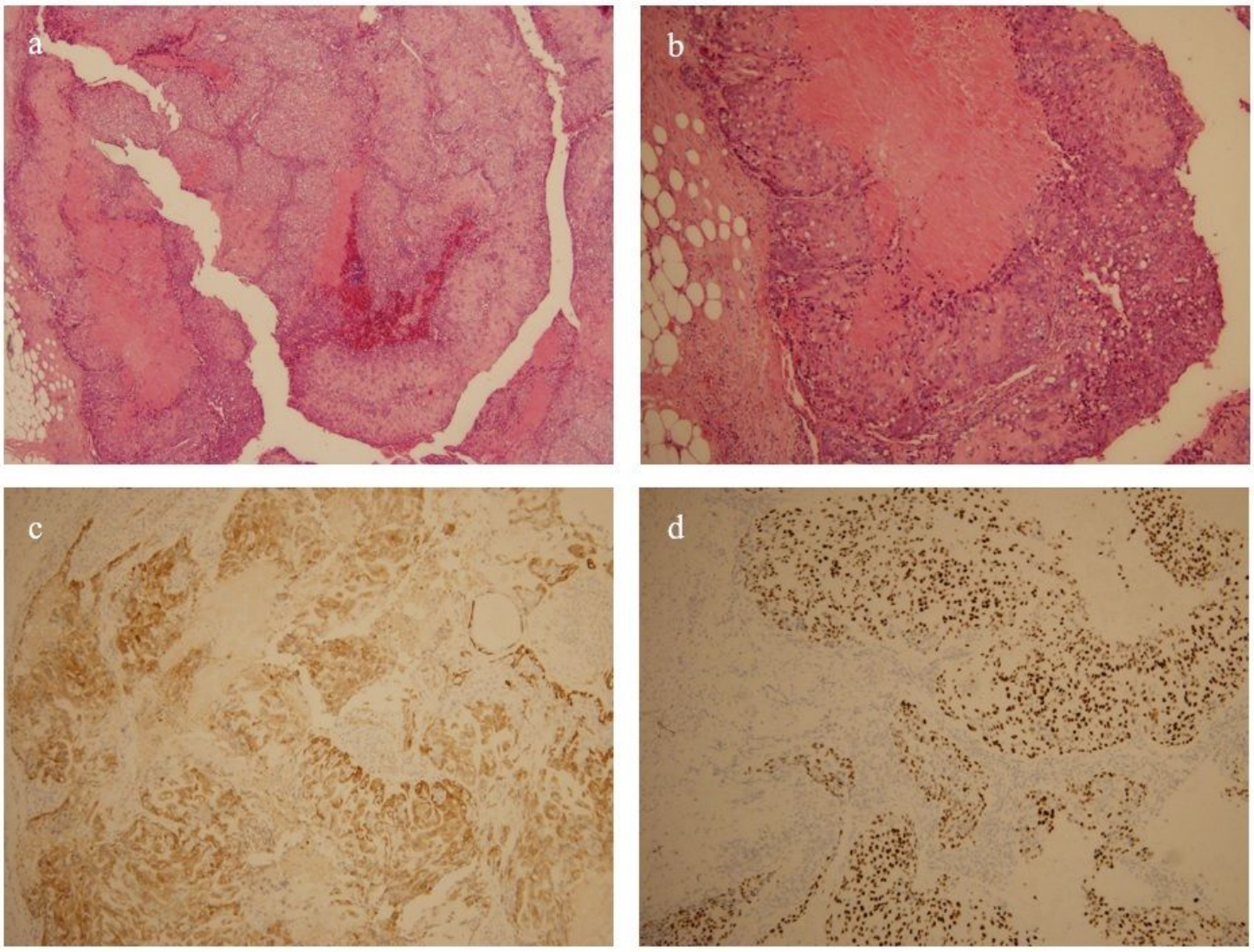

Figure 2

a Mammary adenomyoepithelioma had regular border (HE, ×40); b Adenomyoepithelioma displaying the typical bi-layered glandular architecture, comprising abluminal myoepithelial cells with clear cytoplasm and inner cuboidal epithelial cells with eosinophilic cytoplasm and apical snouts (HE, ×100); c Immunohistochemistry showing the positive expression of Calponin in myoepithelial cells (IHC, ×100); d Immunohistochemistry showing the positive expression of p63 in myoepithelial cells (IHC, ×100).

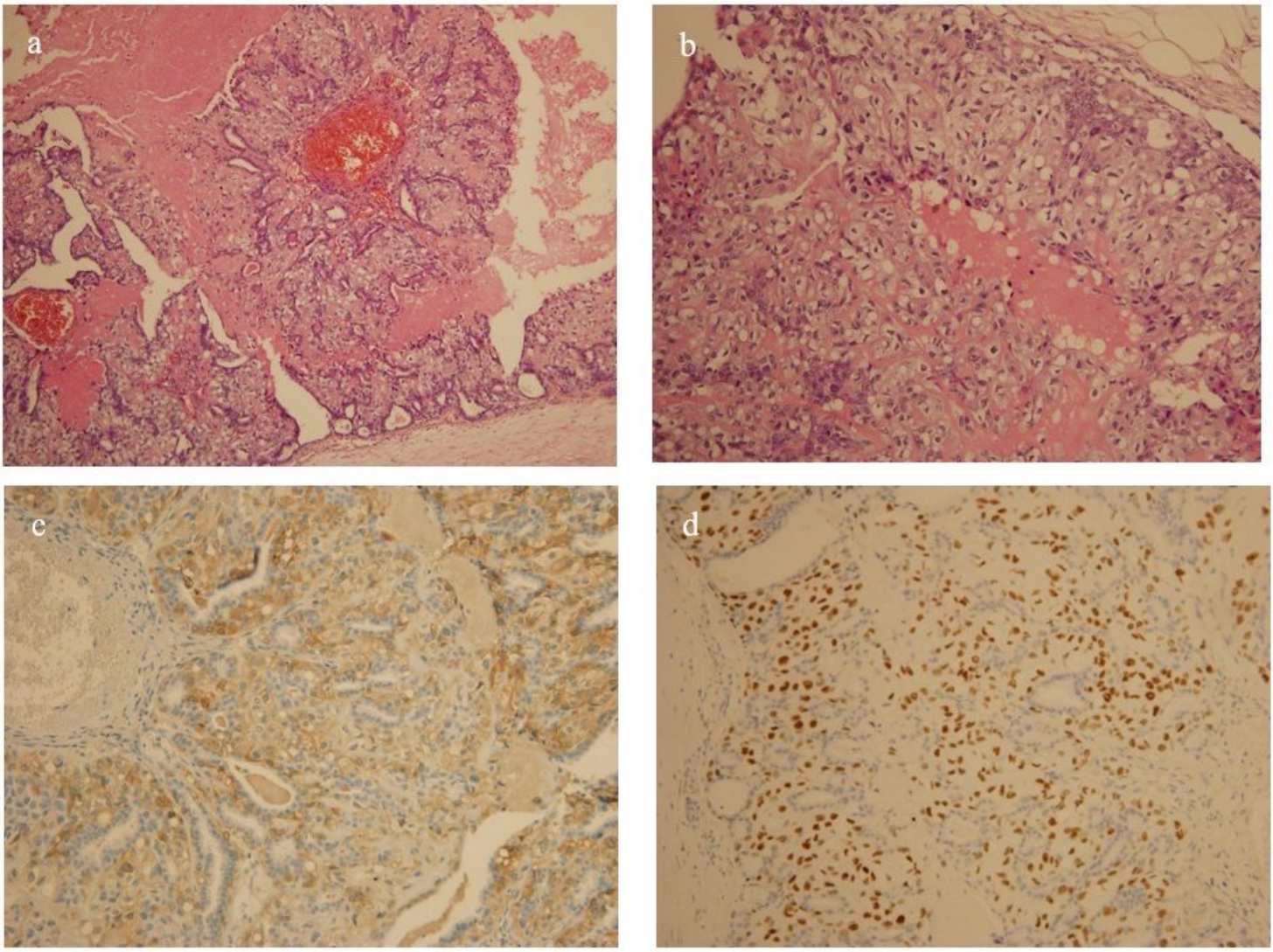

Figure 3

a Low power photomicrograph of the neoplastic mass showing a well demarcated and lobulated tumor (HE, ×100); b Features of malignancy such as increased mitotic figures, hyperchromatic enlarged vesicular nuclei containing prominent nucleoli, and marked nuclear atypia (HE, ×200); c Immunohistochemistry showing the positive expression of Calponin in myoepithelial cells (IHC, ×100); d Immunohistochemistry showing the positive expression of p63 in myoepithelial cells (IHC, ×100).

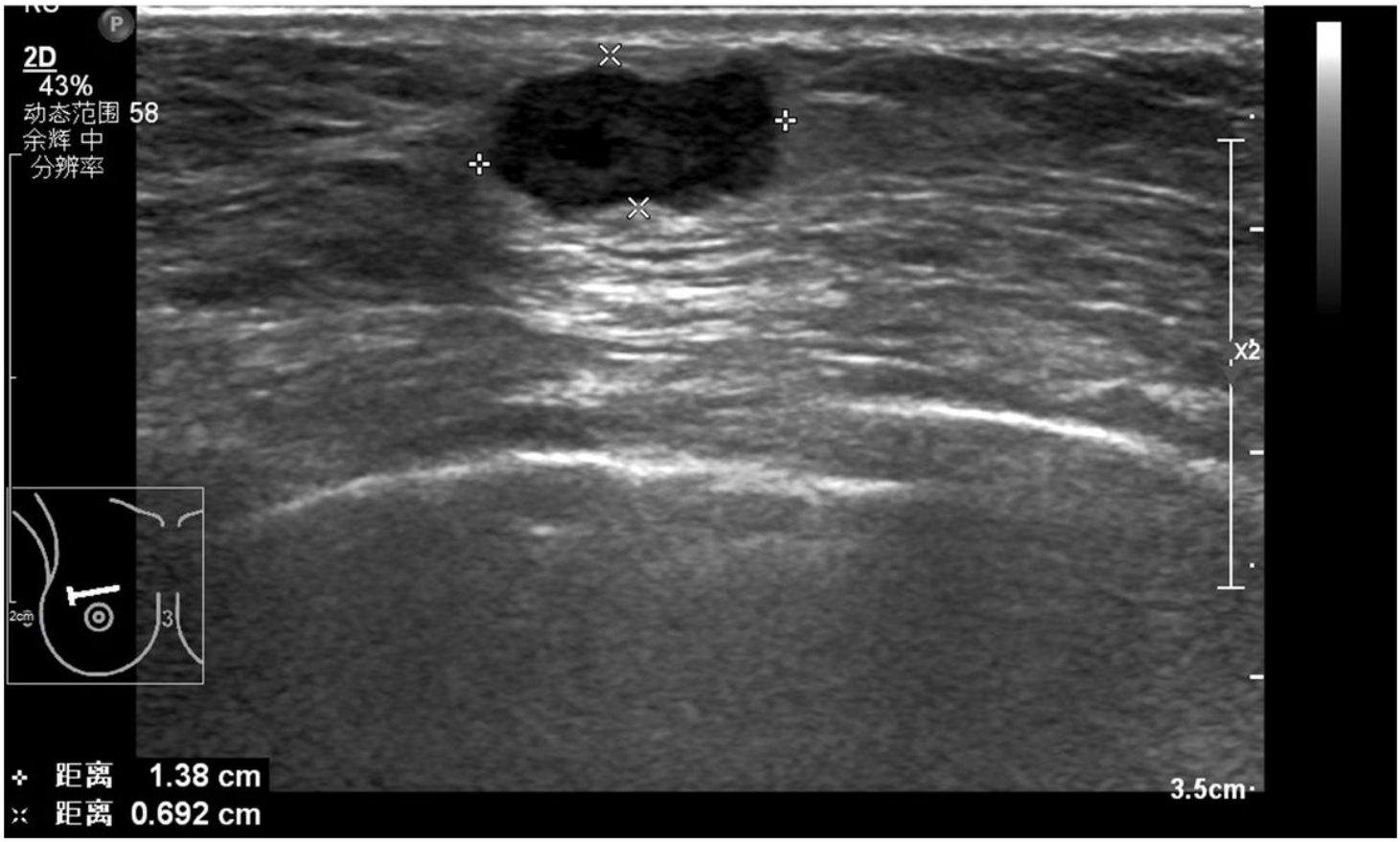

Figure 4

Ultrasound showing a 1.4-cm solid hypo-echoic mass around the surgical scar.