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Breast Carcinosarcoma: The Report of a Unique Case Including Fibrosarcoma and Metaplasia of Squamous Carcinoma with Adenocarcinoma; a Case Report and the Literature Review

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Abstract

Introduction: Breast carcinosarcoma is an extremely rare breast tumor comprising two distinct components, a carcinomatous component and a non-epithelial component of mesenchymal origin. It is a subtype of metaplastic carcinoma with a difficult preoperative diagnosis.

Case Presentation: We present the case of a 68-year-old postmenopausal woman with squamous metaplasia coexisting with adenocarcinoma in the epithelial component of a breast carcinosarcoma. She has been admitted in Department of Breast Surgery, The First Hospital of Jilin University, Changchun, China, in 2017, with a left breast mass. Preoperative assessment and histopathological examination of biopsy samples did not confirm the diagnosis of breast carcinosarcoma. The evaluation of tissue removed during surgery showed three components: high-grade fibrosarcoma (70%), squamous cell carcinoma (25%), and adenocarcinoma (5%), which were consistent with the diagnosis of breast carcinosarcoma. Immunohistochemistry showed that the epithelial component was positive for cytokeratin (CK) 5/6, CK7, CK-pan, and P40, and the sarcomatous component was positive for vimentin and smooth muscle actin (SMA). The estrogen and progesterone receptors (ER, PR) were negative but HER-2/neu was positive (2+) in adenocarcinoma.

Conclusions: Case studies describing the clinical characteristics, diagnosis, and treatment of breast carcinosarcoma are required to raise the awareness of the heterogeneous nature of this tumor among clinicians. Large prospective studies should be conducted to identify the most beneficial therapeutic protocol.

Keywords: Adenocarcinoma, Breast, Carcinoma, Carcinosarcoma, Estrogens, Fibrosarcoma, Keratins, Metaplasia, Neoplasms, Postmenopause, Progesterone, Squamous Cell, Vimentin

1. Introduction

Breast carcinosarcoma is an extremely rare breast tumor, accounting for 0.08% to 0.2% of all malignant breast tumors (1). Breast carcinosarcoma comprises two distinct components, including a carcinomatous component and a non-epithelial component of mesenchymal origin, without evidence of a transition zone between the two components (2, 3). Breast carcinosarcoma is classified by the World Health Organization (WHO) as a subtype of metaplastic breast carcinoma (4).

Following a review of articles published in English, we summarized the morphological characteristics, pathological stages, and management of breast carcinosarcoma (Table 1). However, no reports described squamous metaplasia coexisting with adenocarcinoma in the epithelial component of breast carcinosarcoma. Here, we present a patient with squamous metaplasia coexisting with adenocarcinoma in the epithelial component of breast carcinosarcoma with a difficult preoperative diagnosis. Then, we discuss the clinical characteristics, diagnosis, and treatment of this rare condition by a literature review.

2. Case Presentation

A 68-year-old postmenopausal woman presented with a lump in her left breast in Department of Breast Surgery, The First Hospital of Jilin University, Changchun, China, in 2017. The mass was present for five years, and the skin overlying the mass was red and swollen for one month. A physical examination showed a palpable 8 cm × 8 cm mass with good mobility in the outer upper quadrant of the left breast, with redness and swelling in the overlying skin. There were no palpable axillary lymph nodes. Ultrasound of both breasts showed a mixed (cystic-solid) 58.2 mm×

Table 1. Reports Describing the Morphological Characteristics, Pathological Stages and Management of Carcinosarcoma of the Breast

Reference	TNM	Histological Morphology	Immunohistochemical	Treatment	Follow-up Time of no Recurrence (Months)
Salemis, 2018 (4)	T4N0M0	IDC/chondrosarcoma	ER/PR (-)/HER-2 (+)	MRM/CT/RT/ Trastuzumab	60
Ghilli et al., 2017 (5)	$T_3N_0M_0$	IDC/fibrosarcoma	ER/PR/HRE-2 (-)	MRM/CT/RT	41
Accurso et al., 2016 (1)	$T_2N_0M_0$	MEAMM	ER/PR/HRE-2 (-)	Lumpectomy/SLNB/CT/RT	48
Liu et al. 2015 (6)	$T_1N_0M_0$	Mucinous carcinoma/ Malignant fibrous	ER/PR/HRE-2 (-)	BCS/CT/RT	24
Zhong et al., 2014 (7)	$T_1N_0M_{1(bone)}$	Carcinoma/Malignant phyllodes tumor	ER/PR/HRE-2 (-)	BCS/CT	Septic shock after a month
Mayir et al., 2014 (8)	$T_2N_0M_0$	IDC/sarcoma	ER/PR/HRE-2 (-)	MRM	New
Kang et al., 2014 (9)	$T_3N_0M_0$	MEAMM	ER/PR/HRE-2 (+)	MRM/CT/ET	12
Roxanis, 2013 (10)	$T_2N_0M_0$	Squamous carcinoma/ sarcoma	ER/PR/HRE-2 (-)	Lumpectomy	New
Tian and Xu, 2012 (3)	$T_3N_0M_0$	IDC/ Malignant phyllodes tumor	ER/PR/HRE-2 (-)	MRM	7
Ameen Abbasi et al., 2012 (11)	$T_2N_0M_0$	MEAMM	ER/PR/HRE-2 (-)	BCS/CT/RT	18
Ilhan et al., 2010 (12)	$T_2N_0M_0$	MEAMM	ER/PR/HRE-2 (-)	MRM/CT	54
Pai et al., 2010 (13)	$T_4N_1M_0$	IDC and Squamous carcinoma/ Chondrosarcoma	ER/PR/HRE-2 (-)	MRM/CT	New

Abbreviations: BCS, breast conservation surgery; CT, chemical therapy; ET, endocrine therapy; IDC, infiltrating ductal carcinoma; MEAMM, malignant epithelial and malignant mesenchymal; MRM, modified radical mastectomy; RT, radiation therapy.

26.1 mm mass with low-level internal echoes and fluid inside the upper quadrant of the left breast. Mammography showed a high density lobulated 5.0 cm × 5.0 cm shadow in the outer upper quadrant of the left breast and changes in tissue structure in the adjacent area (Figure 1).

The initial diagnosis was inflammation in the mammary gland. On admission, the patient had a temperature of 38°C, leukocytes of 10.71 × 10^9 /L, and neutrophils of 7.47 × 10^9 /L. She was provided with anti-inflammatory therapy. Subsequently, considering the size of the mass, its history, and the recent progression, a core needle biopsy of the breast lump and the axillary lymph nodes and the cytology of the purulent fluid were performed. The histopathological examination indicated a neoplastic lesion. Due to obtaining insufficient biopsy material, it was difficult to determine whether some heteromorphic cells were tumor cells from a metaplastic carcinoma or from a fibroepithelial neoplasm. Cytology of the purulent fluid showed typical squamous cells and a large number of segmented nuclear granulocytes. Axillary lymph nodes were negative. Mastectomy with sentinel lymph node biopsy was performed. Intraoperative biopsy of two sentinel lymph nodes showed no metastasis. Postoperatively, gross examination of the surgical specimen showed a mixed (50% cystic, 50% solid) 5 cm × 4 cm × 3 cm mass in the upper quadrant of the left breast 4 cm away from the nipple. The solid part of the mass represented a pale, tough, and papillary lesion. A cystic cavity, with a maximum diameter of 2 cm, was seen behind the nipple 0.5 cm away from the mass. Histopathology identified three components: high-grade fibrosarcoma (70%), squamous cell carcinoma (25%), and adenocarcinoma (5%). Immunohistochemistry disclosed that the epithelial component was positive for cytokeratin (CK) 5/6, CK7, CK-pan, and P40, and the sarcomatous component was positive for vimentin and smooth muscle actin (SMA) (Figure 2). The Ki-67 index was 30%. The estrogen and progesterone receptors (ER, PR) were negative but HER-2/neu was positive (2+) in adenocarcinoma. The adenocarcinoma component only accounted for 5% of the mass; therefore, fluorescence in-situ hybridization was not performed. Computed tomography scans of the chest, abdomen, and bone scans were unremarkable. The pathological stage was $T_3N_0M_0$. The patient received adjuvant chemotherapy consisting of six cycles of chemotherapy (ifosfamide and doxorubicin), but she refused adjuvant radiotherapy. The patient did not experience a recurrence in 10 months of follow-up.

3. Discussion

Breast carcinosarcoma, a subtype of metaplastic carcinoma of the breast, is a rare and aggressive tumor (7, 11).

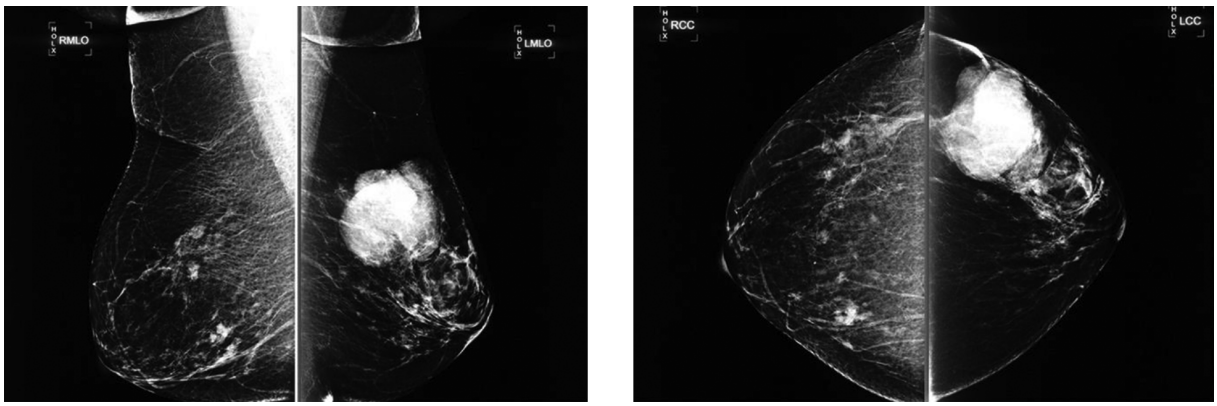

Figure 1. Mammography showing a high density lobulated 5.0 cm × 5.0 cm shadow in the outer upper quadrant of the left breast

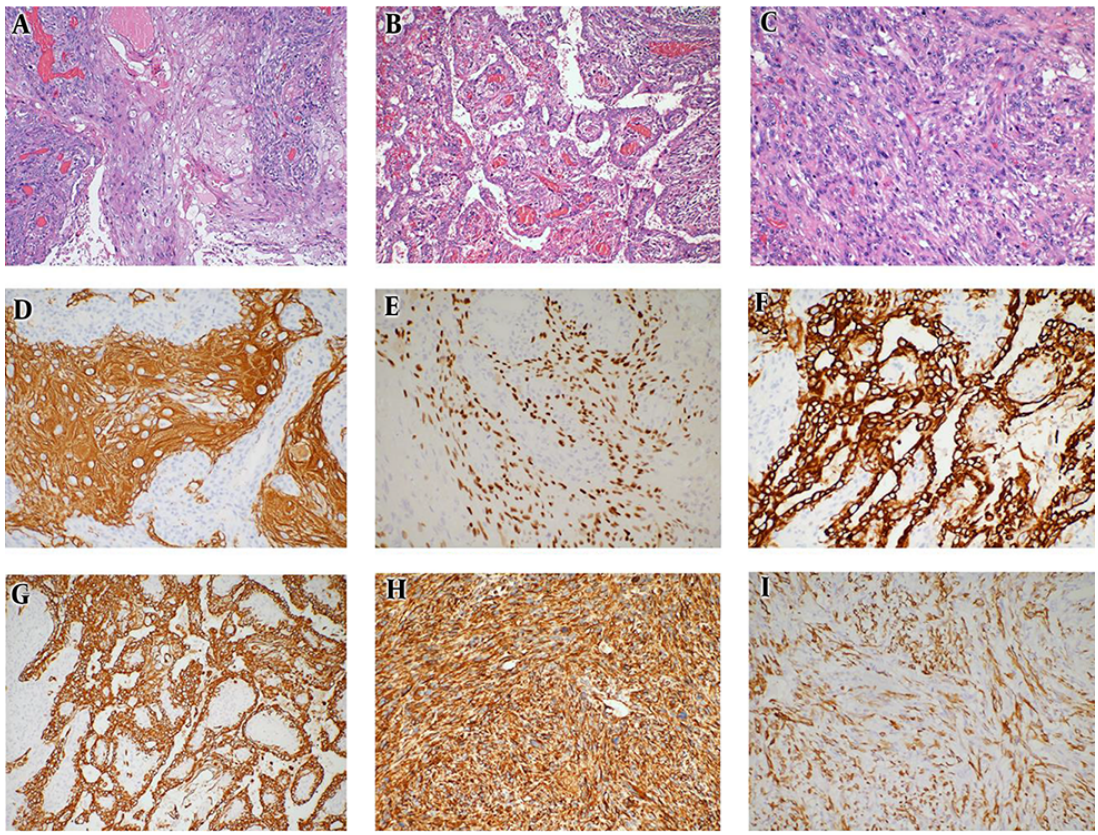

Figure 2. Microscopic findings. Squamous carcinoma cells (A, HE × 100) and adenocarcinoma cells (B, HE × 100) can be found in the epithelial components of carcinosarcoma. Sarcoma cells (C, HE × 100) can be found in the stromal components of carcinosarcoma. Immunohistochemical staining showed positivity for CK 5/6 (D × 200) and P40 (E × 200) in squamous carcinoma cells and CK7 (F× 200) in adenocarcinoma cells, but CK pan (G × 100) was positive in both carcinoma cells. Immunohistochemical staining showed positivity for vimentin (H × 200) and SAM (I × 200) in sarcoma cells.

The WHO divides the metaplastic carcinomas into squamous cell carcinomas, adenocarcinomas with spindle cell proliferation, and mixed epithelial-mesenchymal carcinomas. The mixed epithelial-mesenchymal carcinoma is further classified into carcinomas with chondroid metaplasia, carcinomas with osseous metaplasia, and carcinosar-

coma (5, 9, 10).

The histological origin of breast carcinosarcoma remains unclear, but it may be derived from stem cells with biphasic differentiation, from metaplasia of myoepithelial cells and myofibroblasts, or from preexisting fibroadenomas and phyllodes (3, 14). Most evidence suggests that tumors are of myoepithelial origin with both carcinomatous and sarcomatous characteristics on histopathology (7, 11, 13). The epithelial component of breast carcinosarcoma may contain undifferentiated adenocarcinoma, infiltrating ductal carcinoma, in-situ carcinoma, or squamous cell carcinoma. The mesenchymal component may contain undifferentiated mesenchymal cells, fibroblasts, chondrocytes, or osteoblasts (12). Squamous cell carcinoma that accounted for a small proportion of cases in previous cohorts of metaplastic breast carcinomas is very rare in breast carcinosarcoma. In the study by Wargotz and Norris, only 2 out of 40 patients with carcinosarcoma had an epithelial component of squamous metaplasia (2). However, there are no reports of a mixture of squamous cell carcinoma and adenocarcinoma in the epithelium. In the present case, breast carcinosarcoma had squamous cell carcinoma, adenocarcinoma, and sarcoma components, which were consistent with a diagnosis of carcinosarcoma.

The clinical symptoms of breast carcinosarcoma are similar to invasive ductal carcinoma, and include the presence of a large painful mass, nipple discharge, nipple depression, and skin ulceration (7, 8, 12, 14). One study reported a case of carcinosarcoma presenting as a breast abscess (15). In the present case, the affected mammary gland showed the signs of local inflammation, including redness and swelling of the skin overlying the mass. These signs and symptoms may be misdiagnosed as mastitis.

The diagnosis of breast carcinosarcoma is challenging and may involve ultrasonography, mammography, and magnetic resonance imaging (3, 14), as well as fine needle, core needle, or frozen section biopsy. Sometimes, the epithelial component forms only a small part of the carcinosarcoma, and insufficient biopsy samples might miss this component and lead to misdiagnosis (3, 4). Comprehensive macroscopic and microscopic examinations of several tissue sections from all parts of the tumor are required for an accurate diagnosis (16).

Differential diagnoses of breast carcinosarcoma include phyllodes tumors, primary breast sarcomas, and other metaplastic carcinomas. Identifying the presence of a transition zone between the carcinomatous and sarcomatous components is important for differential diagnosis (3, 16). Tumors lacking this transition zone should be considered as other types of metaplastic carcinoma.

A research report by Wargotz and Norris (2) indicated that the sarcomatous component was immunoreactive for keratin in 55% of cases, immunoreactive for vimentin in 98% of cases, and immunoreactive for actin in 77% of cases. In general, breast carcinosarcoma that is positive for cytokeratin in the epithelial competent and vimentin and SMA in the mesenchymal component is ER, PR, and HER-2-negative (9, 16). However, there is often overexpression of epidermal growth factor receptor (EGFR/HER-1), which may represent a potential therapeutic target (1, 9-11).

Treatment of breast carcinosarcoma follows the NCCN guidelines for invasive ductal carcinoma. Surgery involves total mastectomy with or without axillary lymph node dissection (1). A breast-conserving approach is not usually feasible because of the large size of the tumor (14). Studies show no differences in overall or disease-free survival in patients undergoing mastectomy or breast conservation therapy (3, 5, 9, 12). Axillary lymph node metastasis is relatively rare. In a previous study, 26% of cases had metastases to axillary lymph nodes, with carcinoma as the most frequent component to metastasize; the majority of patients who developed metastases died from the tumor (2). Another study reported that the prognosis of breast carcinosarcoma was not associated with axillary lymph node metastases (14). In the present case, the patient underwent total mastectomy with sentinel lymph node biopsy.

Postoperative adjuvant therapy is often recommended for breast carcinosarcoma. However, endocrine therapy and therapies targeting HER-2 are often ineffective in breast carcinosarcoma cases that are receptor-negative with poor prognosis, similar to triple-negative invasive ductal carcinoma. Chemotherapy may include CMF (cyclophosphamide, methotrexate, and 5 fluorouracil)-based TA (anthracyclines/taxane) regimes, but side effects are undesirable (16). Radiation therapy is recommended for patients with $\geq$ 4 axillary lymph node metastases, with a tumor size of $\geq$ 5 cm and in the presence of chest wall invasion, which may prevent local recurrence (8, 12, 14, 16). Gefitinib and cetuximab, as therapeutic agents targeting EGFR/HER-1, are potent as novel treatment regimens (1, 3, 9, 13, 14). Most breast carcinosarcoma cases are not sensitive to neoadjuvant chemotherapy. In fact, caution is required when treating breast carcinosarcoma with neoadjuvant chemotherapy, as the failure of chemotherapy may lead to clinical deterioration and preoperative complications (9).

In breast carcinosarcoma, metastasis via the hematic route is more common than lymphatic metastasis (14). Distant metastases occur more frequently in the lungs and pleura than in the brain, liver, and bone (1, 4, 6). Distant metastasis at presentation is rare (16); however, one study reported that 10.3% of patients with breast carcinosarcoma had metastatic disease at the time of diagnosis, compared to only 0.9% of patients with invasive ductal carcinoma

(5). On account of its triple-negative and aggressive nature, breast carcinosarcoma has a higher risk of local recurrence within the first 5 years of diagnosis than invasive ductal carcinoma (9). Therefore, close follow-up after postoperative adjuvant therapy is essential (1).

Overall survival for breast carcinosarcoma is affected by the tumor stage. One study of 70 cases of breast carcinosarcoma reported a cumulative 5-year survival rate of 49%, which was worse than the rate for other forms of metaplastic carcinoma; 5-year survival rates for TNM clinical stages I, II, and III were 100%, 63%, and 35%, respectively (2). Another study investigating 10 patients with a diagnosis of breast carcinosarcoma reported a 3-year overall survival rate of 71.2% and 5-year overall survival and disease-free survival rates of 53.3% and 52.5%, respectively (14).

3.1. Conclusions

Breast carcinosarcoma is an extremely rare breast tumor, comprising two distinct components, including a carcinomatous component and a non-epithelial component of mesenchymal origin. It is a subtype of metaplastic carcinoma with a difficult preoperative diagnosis. Comprehensive macroscopic and microscopic examinations of several tissue sections from all parts of the tumor are required for an accurate diagnosis. Due to the very low incidence of these tumors, an optimal treatment strategy has not been defined, and the prognosis is poor. Case studies describing the clinical characteristics, diagnosis, and treatment of breast carcinosarcoma are required to raise the awareness of this rare condition among clinicians. Large prospective studies should be conducted to identify the most beneficial treatment protocol.

Footnotes

Conflicts of Interests: The authors declare no conflict of interest.

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Patient Consent: Informed consent was obtained from the patient to publish the report.

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