

Case Report

Pleomorphic carcinoma of breast: a case report and review of literature

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Abstract: Pleomorphic carcinoma of the breast is a rare variant of invasive breast carcinoma. Here, we report a case in a 45-year-old woman presenting a lesion composed microscopically of predominantly pleomorphic giant cells, squamous metaplastic component and focal conventional ductal carcinoma. Immunohistochemical assay showed different immunologic manifestation in respective malignant components. Despite positive lymph node metastasis, the patient has been well without evidence of recurrence or metastasis two years after operation. The implication of this report is to provide insights into further understanding of this rare tumor with review of the literature.

Keywords: Breast carcinoma, pleomorphic carcinoma, giant cell, histological classification, immunohistochemistry

Introduction

Pleomorphic carcinoma of the breast is a rare, high grade breast carcinoma predominately composed of the distinctive pleomorphic giant tumor cells with bizarre nuclei and atypical mitosis. In 2012 World Health Organization (WHO) classification [1], pleomorphic carcinoma is an uncommon variant of high-grade invasive carcinoma of no special type (NST) of breast characterized by proliferation of pleomorphic and bizarre tumor giant cells comprising >50% of the tumor cells in a background of adenocarcinoma or adenocarcinoma with spindle or squamous differentiation. There are marked nuclear pleomorphism and characteristically contains multinucleated giant tumor cells in this variant. According to previous reports, pleomorphic carcinoma has an aggressive behavior and poorer clinical outcome. A comparison of main clinicopathological features of pleomorphic carcinoma of breast reported in English literature till date is presented in **Table 1**. Herein, we report a rare case of pleomorphic carcinoma of the breast displaying pleomorphic and bizarre tumor giant cells, squamous metaplasia component, and classi-

cal invasive ductal carcinoma intermingled together within the tumor in a 45-year-old woman. Moreover, we reviewed the available literature to gain more comprehension this rare variant of breast cancer.

Clinical data

A 45-year-old woman noted a mass in her left breast for one month and visited our hospital. She had no past history of malignancy and no family history of breast carcinoma. In physical examination, a hard, firm and painless mass about 3.5 cm in diameter was palpable in the lower outer quadrant of the left breast and one enlarged lymph node was touched in the left axilla. There were no abnormalities in the right breast. Serum tumor markers and other routine blood test were normal. Ultrasonography indicated a infiltrative, irregularly shaped and poorly circumscribed hypoechoic mass measuring 3×2.6 cm in size and 2.1 cm away from the nipple and graded it for BI-RADS IV. Molybdenum target radiography also revealed a focal high density mass and gave the same grading as BI-RADS IV. The mass was excised for frozen section and was primordially diagnosed as inva-

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Table 1. Previous studies of pleomorphic carcinoma of breast reported in the English literature

Author	Year	Cases	Age (year)	Tumor size (cm)	Lymph nodes status
Silver & Tavassoli [2]	2000	26	28-96 (median, 51)	0.5-15 (average, 3.9)	12/23 positive*
Lenicek et al [3]	2007	1	83	5.8	Negative
Nguyen et al [9]	2010	37	23-78 (median, 49)	1.2-11.6 (average, 3.5)	17/33 positive*
Zhao et al [5]	2010	10	23-78 (median, 50)	1.0-15.0 (average, 4.4)	4/10 positive*
Yamaguchi et al [4]	2010	1	17	5.5	Positive
Caruso et al [6]	2011	1	65	2.5	Positive
Tacchini et al [7]	2011	1	44	1.2 & 0.6 [#]	Negative
Cordoba et al [8]	2012	2	76 & 46	5.0 & <1.0	NM

Notes: *positive cases/total detected cases; [#]this case has two independent masses; NM, not mentioned.

sive carcinoma of breast. The patient then underwent a radical mastectomy with left axillary lymph nodes clearance. The disease in this patient was staged as T2N1M0IIB. Then four circles of chemotherapy were started. About two years after the operation, the patient was still alive and had no signs of cancer recurrence or metastasis.

Material and methods

The excisional specimens were fixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E). The expression and localization of the following antigens were examined using the EnVision+ detection kit (Dako, Carpinteria, CA) with diaminobenzidine (DAB) as a substrate: pan-CK, CK8/18 (clone number 5D3), CK5/6 (D5/16B4), CK14 (LL002), HMW (34 β E12), LMW (35 β H11), EMA (E29), ER (1D5), PR (SP2), C-erbB-2 (CB11), GCDDF-15 (23A3), Vimentin (SP20), CD68 (KP1), β -HCG (ZSH17), S-100 (4C4.9), α -SMA (1A4), p53 (DO-7), p63 (4A4), Ki-67 (SP6), Desmin (D33), E-Ca (4A2C7), BCL-2 (8C8) and EGFR (EP38Y). All above primary antibodies were purchased from Maxim Company, Fuzhou, China.

Pathological findings

On gross examination, the mass was hard, circumscribed and infiltrative, measuring 3×2.5×1.5 cm in size and white-gray in color on the cut surface (**Figure 1A**). On microscopic examination of the HE sections, the lesion was composed of pleomorphic and bizarre giant cells (about 60% of the tumor), carcinoma with squamous differentiate (30%) and classical invasive ductal carcinoma component (10%).

Cytologically, the pleomorphic cells were marked giant with 5-fold variation in nuclear size at least (often > 10-fold). Numerous of these giant cells were bizarre and multinucleated (**Figure 1B-D**). The squamous metaplastic component was well differentiated. Squamous differentiation was present in 30% of the carcinoma, manifest as large polygonal cells, often in sheets, with densely eosinophilic cytoplasm (**Figure 1E, 1F**). The ordinary invasive ductal carcinoma component was present in 10% of the carcinoma (**Figure 1G**). Components of high grade ductal carcinoma in situ with necrosis and atypical ductal hyperplasia were found in the adjacent area of the lesion (**Figure 1H**). The number of mitoses was 30, 35 and 60 per 10 high-power fields (HPF) in pleomorphic giant cells, ordinary ductal carcinoma, and squamous metaplastic component, respectively. 17 lymph nodes measuring 0.2-1.5 cm were found in the homolateral axillary fat tissue and one of them (the biggest one) was affected and the tumor cells of the metastatic carcinoma were uniform spindle-shape (**Figure 1I**).

The immunohistochemical features of pleomorphic ductal carcinoma were differently presented in respective malignant components (**Figure 2A-L**). The pleomorphic giant cells were positive for LMW, CK8/18, S-100 and SMA, the carcinoma with squamous differentiation was positive for HMW, CK5/6, CK14, p63, E-Ca and GCDFP-15, while the conventional invasive ductal carcinoma was positive for HMW, LMW, CK5/6, CK8/18, CK14, GCDFP-15 and E-Ca. In the lymph node metastatic carcinoma, HMW, LMW, CK5/6, CK8/18, CK14, GCDFP-15, E-Ca and S-100 were positive detected. All above malignant components were positive for pan-CK, EMA, Vimentin and negative for ER, PR,

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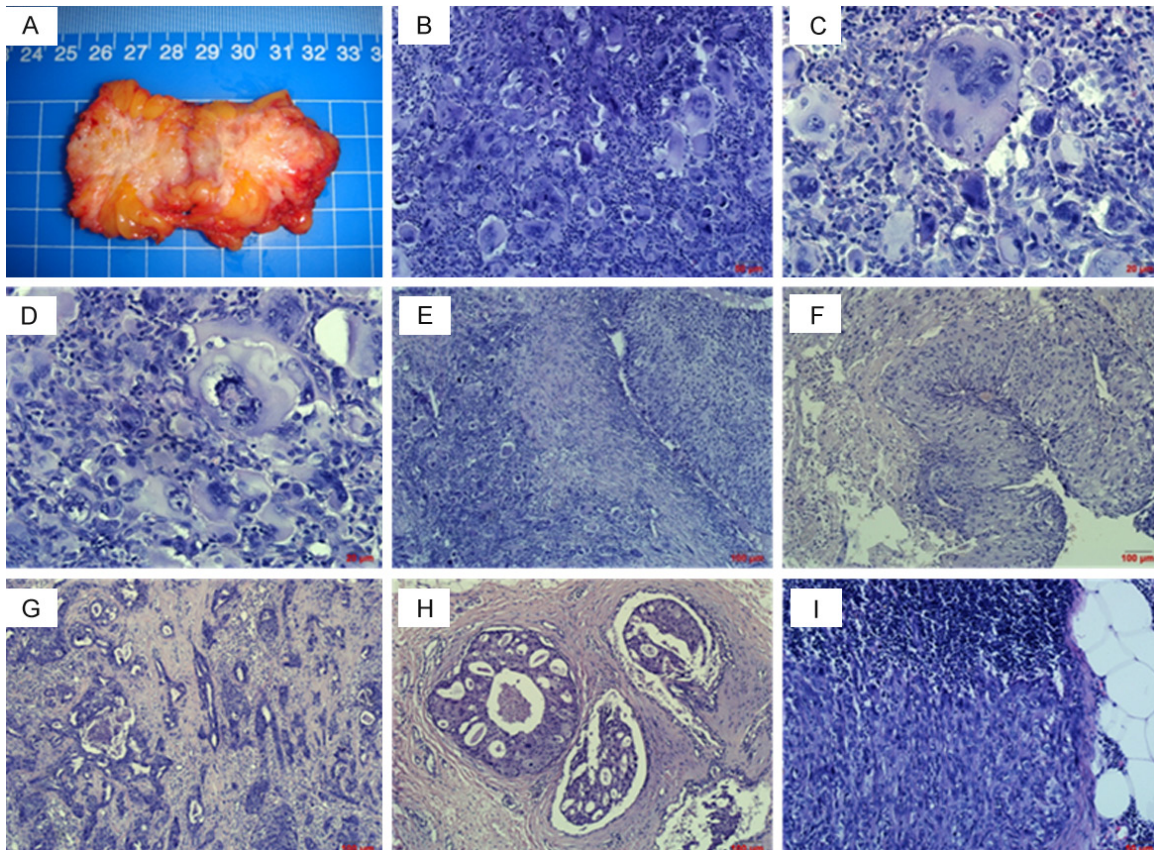


Figure 1. Macroscopic and microscopic findings. A: Gross finding showing the ill-defined margin and white-gray cut surface of the tumor; B ($\times 200$), C, D ($\times 400$): Pleomorphic giant tumor cells with bizarre and multinucleated nuclei; E, F ($\times 100$): Well-differentiated squamous metaplastic component; G ($\times 100$): Conventional invasive ductal carcinoma; H ($\times 100$): The high grade ductal carcinoma in situ component; I ($\times 100$): Metastatic carcinoma in axillary lymph node.

C-erbB-2, BCL-2, CD68, β -HCG, EGFR and Desmin. p53 positivity was found in 40% of pleomorphic giant cells, 45% of tumor cells in conventional ductal carcinoma and 75% of tumor cells in squamous differentiated carcinoma. For Ki-67 proliferation index, in pleomorphic giant cells it was 25%, in squamous differentiated carcinoma it was 60%, in conventional invasive ductal carcinoma and in axillary metastatic carcinoma it was both 40%.

Discussion

As a recently described entity of breast tumor, pleomorphic carcinoma has its unique and characteristic morphological features. It is predominantly composed of pleomorphic cells (> 50% of tumor population) and many of them are giant and multinucleated. Silver SA and Tavassoli FA firstly reported pleomorphic carcinoma and indicated it represents the extreme

end of the morphological spectrum of grade III invasive ductal carcinoma of breast [2]. In recent WHO classification, this tumor has been considered as a variant of invasive carcinoma NST. Pleomorphic carcinoma is very rare and just few studies mentioned this tumor. To the best of our knowledge, no more than 80 cases of this variant of breast cancer have been previously described in English literature [2-9].

Pleomorphic tumor cells can be present in other breast neoplasms. The differential diagnosis includes invasive pleomorphic lobular carcinoma, invasive carcinoma with osteoclast-like giant cells, invasive carcinoma with chorioepithelioma features, metaplastic carcinoma with giant cells and mammary sarcoma with giant cells. Careful microscopic examination and a panel of immunohistochemistry for epithelial and mesenchymal markers can lead to a correct diagnosis. Pleomorphic lobular car-

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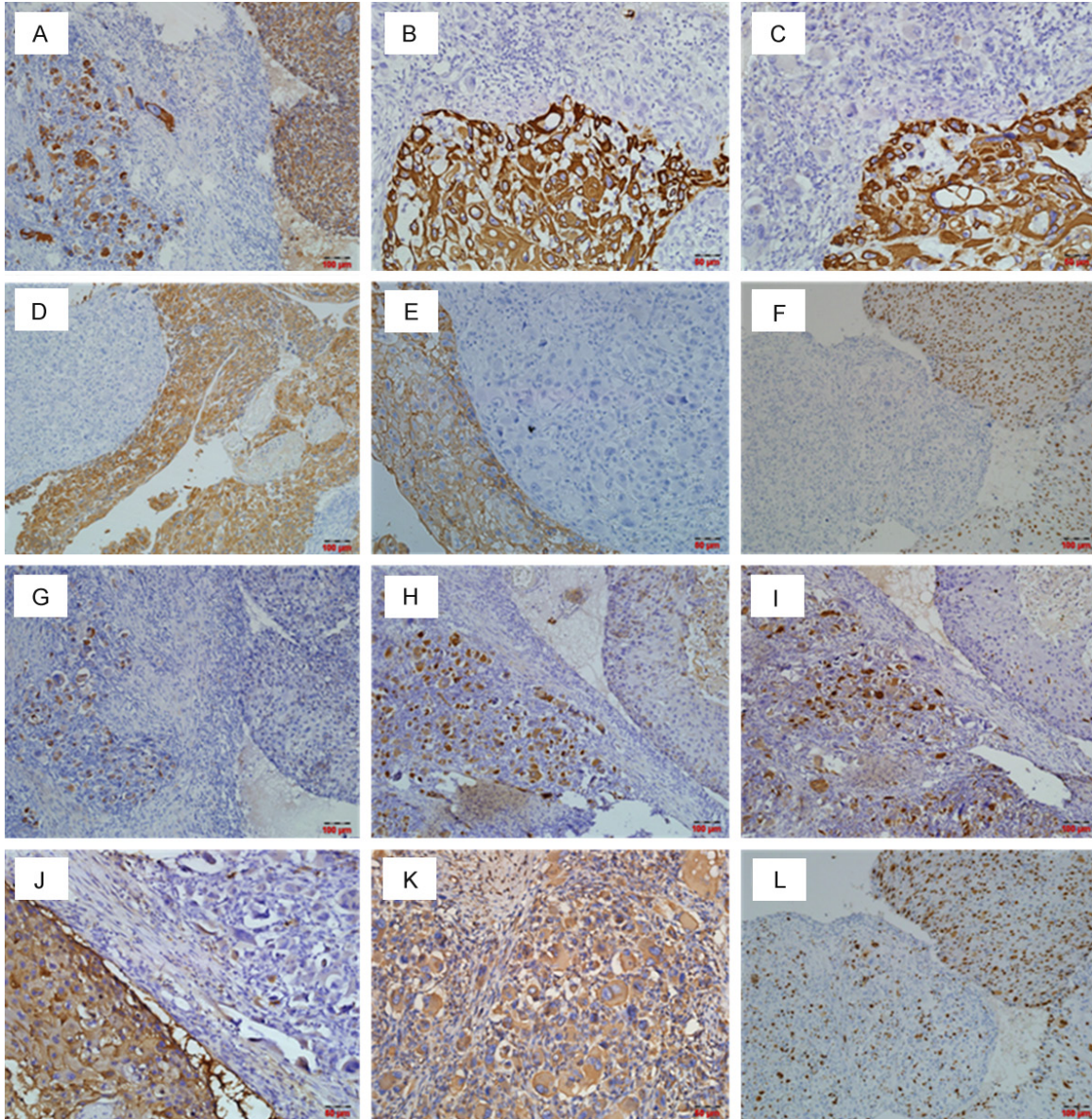


Figure 2. Immunohistochemical findings. Pan-CK (A, $\times 100$) protein expression is positive in both pleomorphic giant cells and squamous metaplastic component; HMW (B, $\times 200$), CK14 (C, $\times 200$), CK5/6 (D, $\times 100$), E-Ca (E, $\times 200$) and P63 (F, $\times 100$) proteins expression are negative in pleomorphic giant cells while positive in squamous metaplastic component; LMW (G, $\times 100$), CK8/18 (H, $\times 100$) and S-100 (I, $\times 100$) proteins expression are positive in pleomorphic giant cells while negative in squamous metaplastic component; EMA (J, $\times 200$) protein expression is weakly positive in pleomorphic giant cells but strongly positive in squamous metaplastic component; Vimentin (K, $\times 200$) protein is positive in pleomorphic giant cells; Ki-67 proliferation index (L, $\times 100$) in squamous metaplastic component (60%) is higher than it in pleomorphic giant cells (25%).

cinoma is a variant subtype of invasive lobular carcinomas. It also exhibits enlarged nuclei with hyperchromasia, irregularities and marked pleomorphism. However, pleomorphic lobular carcinoma often tends to grow in liner arrows and lack of E-Cadherin expression. The E-Cadherin positivity and presences of conventional ductal carcinoma component and ductal

carcinoma in situ, as in our case, can help us to distinguish these two different types of breast cancer [10, 11]. Due to the presence of giant and multinucleated tumor cells, pleomorphic carcinoma can also be misdiagnosed as invasive ductal carcinoma with osteoclast-like giant cells and invasive carcinoma with chorioepithelioma features [8, 12]. In our case, the pleomor-

phic cells were negative for CD68 and positive for CK, excluding the possibility of ductal carcinoma with osteoclastic-like cells, which, in contrast, are CD68 positive and CK negative. Similarly, because of negative expression of β -HCG in the pleomorphic cells, the diagnosis of chorioepithelioma differentiated carcinoma was also excluded. pleomorphic carcinoma can be differentiated from mammary sarcomas by the expression of series antibodies of CK, which confirms the epithelial nature of the giant cells. Metastatic carcinoma to breast is a rare event and intends to be multicentric, and the patient has a history of other primary tumor. Furthermore, in our case, the presence of ductal carcinoma in situ support that this tumor derived from breast.

Tumors composed of pleomorphic giant cells are usually designated as undifferentiated carcinomas in other organs, such as bladder, ovary, prostate and pancreas [13-16], and associated with rapid tumor dissemination and unfavorable prognosis. Pleomorphic carcinoma in breast also has been considered as a predictor of decreased overall survival. Cases of pleomorphic carcinoma of breast in most previous reports have been associated with aggressive behavior [2-8]. Moreover, in contrast to the usual situation of a positive ER/PR and overexpression of HER2 pleomorphic carcinoma was generally immunohistochemically triple-negative (ER, PR and HER2 negative), thereby adding to the challenges in the management approach of this aggressive tumor. However, in another study reported in 2010, which is the largest series (37 cases) to date, Nguyen et al indicated that not all these tumors behave badly and the presence of the spindle cell metaplastic component, higher mitotic rate and bigger tumor size are associated with the poor prognosis [9].

In our case, despite positive lymph node metastasis, the patient has been well without evidence of recurrence or metastasis two years after operation. Moreover, the mitotic rate in squamous metaplastic component is higher than it in giant cells and conventional ductal carcinoma. Immunohistochemically, the percentage of p53 positive tumor cells and Ki-67 proliferation index in squamous metaplastic component are higher than in pleomorphic giant cells and conventional ductal carcinoma. p53 is a tumor suppressor which mediates G_1 arrest and apoptosis [17]. Ki-67 is a nuclear antigen expressed in the G_1 , S and G_2 phases

[18]. Overexpression of p53 and Ki-67 suggest cell cycle control disturbances and increasing proliferation. These findings suggest that in our case, it was the squamous metaplastic component, rather than those pleomorphic giant tumor cells, determined the malignant degree of this morphological variant of breast carcinoma.

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Disclosure of conflict of interest

None.

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