Clinical Case Report

Medicine®

OPEN

Change of HER2 status during disease recurrence predicts good prognosis for primary squamous cell carcinoma of the breast

A case report

Yong Cao, MD, Yeli Yue, PhD, Xin Zhou, PhD, Jie luo, MD, Xiaohua Zeng, PhD, JuanHui Dong, MD, Xinrui Liang, MD*

Abstract

Rationale: Primary squamous cell carcinoma (PSCC) of the breast is one of the least common types of breast cancer. Adjuvant treatment for PSCC remains an unresolved issue.

Patient concerns: We reported a case of a 48-year-old postmenopausal female patients with a 2 × 2.5 cm lump presented with no symptoms.

Diagnoses: This patient was diagnosed as PSCC of the breast. The original tumor and first recurrence exhibited triple negative phenotype, whereas the second recurrence was HER2-positive.

Interventions: A tumorectomy with latissimus dorsi flap reconstruction for the second recurrence was performed followed by targeted therapy with trastuzumab.

Outcomes: The patient had a complete remission, which was sustained over the 25 months of follow-up after the tumorectomy.

Lessons: This is the first reported case in literature of a breast PSCC patient with switched immunohistochemical phenotypes during disease recurrence. Surgical resection with flap reconstruction and targeted therapy successfully treated the recurrence.

Abbreviations: 3D-CRT = three-dimensional conformal radiotherapy, MDT = multidisciplinary team, PSCC = primary squamous cell carcinoma, SRT = stereotactic radiation therapy.

Keywords: breast cancer, HER2, PSCC, targeted therapy

1. Introduction

Breast cancer is the most frequently diagnosed cancer in women worldwide.[1] The incidence of breast cancer in Chinese women was lower than that in European and American women in the past.[2,3] But since 1990s, incidence rate of breast cancer in China has increased significantly by 3% to 4% annually, which is much higher than the annual global increase of 0.5%.[4] With the wide adoption of modern medical techniques in China, more breast cancer patients are likely to be diagnosed and more survivors are expected.

Breast cancer is a heterogeneous entry characterized by distinct pathological features, clinical behaviors, response to treatment, and outcomes. Primary squamous cell carcinoma (PSCC) of the breast is a very rare histological subtype that is diagnosed when more than 90% of the malignant cells are squamous.[5] Due to the rarity of this subtype, adjuvant treatment for PSCC remains a controversial and unresolved issue. Hennessy et al have studied 170 cases with PSCC of the breast and concluded that this disease is extremely aggressive and better treatment is needed to improve patient outcomes.[6] In our previous study, we have searched in our pathology database from 2000 to 2015 and identified 23 SCC of the breast from a total of 2310 breast cancer cases, of which 12 were PSCC and 11 were metaplastic squamous cell carcinoma (MSCC, defined as 50% of the malignant cells showing squamous).[7] The proportion of PSCCs in our breast cancer patients (12/2310, 0.5%) was higher than the proportion of 0.1% reported previously.[5] These patients with PSCC of the breast had poor prognosis; 7 out of 12 patients (58%) died within 3 years of diagnosis.

Here we reported on patient with PSCC in whom we observed a change of immunohistochemical phenotype during therapy and a good prognosis after receiving trastuzumab in the adjuvant setting.

Editor: N/A.

YC and YY contributed equally to this work.

Patient has provided informed consent for publication of the case.

This study was supported by Key Project of Chongqing Health and Family Planning Commission.

The authors have no conflicts of interest to disclose.

Chongqing University Cancer Hospital & Chongqing Cancer Institute & Chongqing Cancer Hospital, Chongqing, China.

** Correspondence: Xinrui Liang, Chongqing University Cancer Hospital & Chongqing Cancer Institute & Chongqing Cancer Hospital, No. 181, Hanyu Road, ShaPingBa District, Chongqing 400030, China (e-mail: liangxinrui0521@126.com).*

Medicine (2019) 98:9(e14654)

Received: 11 October 2018 / Received in final form: 27 January 2019 / Accepted: 1 February 2019

http://dx.doi.org/10.1097/MD.0000000000014654

2. Case presentation

2.1. Patient has provided informed consent for publication of the case.

On September 6, 2012, a 48-year-old postmenopausal woman presented to the Breast Centre after noticing a lump in her right breast for 3 days. The symptom was not associated with any pain, nipple discharge, nipple retraction, or skin change. She was a non-smoker and had no prior history of breast disease. The patient reported no significant past medical history nor family history of cancer. She denied oral contraceptives use in the past. She had 5 pregnancies and gave birth to 1 child, who was breast-feeding for 1 year.

On physical examination, there was a 2×2.5 cm lump at 11 to 12 o'clock in the right breast, 3 cm away from the nipple. The lump was firm, border clear, moveable, and not fixed to the skin or chest wall. No abnormality was observed in the left breast, axillary or supraclavicular lymph nodes. Mammogram showed a mass of 2×2.2 cm with spiculated margins and microcalcifications in the up inner quadrant. Ultrasound showed an irregular hypoechoic mass of 1.1×1.6 cm with posterior enhancement, located at 11 o'clock. Within the mass, both solid and cystic components were apparent. An additional hypoechoic mass of 0.3×0.4 cm was noted on ultrasound at the up inner direction of the right breast. No positive lymph node was detected.

Core needle biopsy from the mass at 11 o'clock diagnosed PSCC confirmed by immunohistochemical staining showing a CK5/6-positive (intensity 2), E-cadherin-negative, ER-negative, PR-negative, C-erbB-2-negative, P53-positive 40%, EGFR-positive (intensity 2), and Ki-67-positive 20% phenotype, as shown in Table 1 and Figures 1–3. Biopsy reported a fibroadenoma of the mass at 1 o'clock.

To exclude other primary tumors, the patient received a series of examinations, including computed tomography (CT) scanning of the chest, bone scan, cervical and endocervical smears, and examination of the nasopharynx, esophagus, stomach, and rectum where appropriate. There were no other positive or suspicious findings.

2.2. Clinical course

The detail of the clinical course and time to progression are shown in Table 2. After lengthy discussion with the surgeon, the patient elected not to preserve her breast or axilla. We performed a modified radical mastectomy on September 12, 2012. An invasive carcinoma in the mammary gland was localized in the out-upper quadrant, measuring $2.2 \times 2 \times 1.5$ cm. None of the 22 axillaries lymph nodes removed were malignant. Microscopical examination of the mass revealed predominantly (>90%) PSCC with obvious keratin pearl and some (<10%) intraductal carcinoma, confirming the diagnosis of PSCC of the breast.

Table 1

Pathological features of the patient during disease progression.

	Original tumor	1st recurrence	2nd recurrence
Histological type	PSCC	PSCC	PSCC
ER status	–	–	–
PR status	–	–	–
H-er2 status	–	–	++
Ki-67 status	+20%	+80%	+80%
FISH test	\	\	+

FISH = fluorescence in situ hybridization, PSCC = primary squamous cell carcinoma.

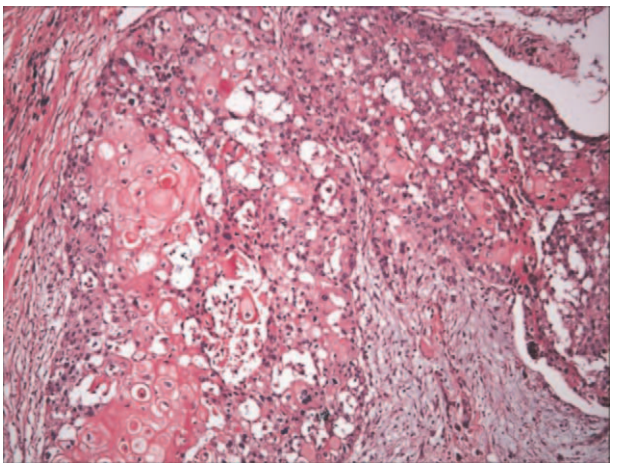

Figure 1. Hematoxylin-Eosin staining of the original tumor shows that more than 90% of the tumor cells are of squamous type, with keratin and necrotic debris (10×).

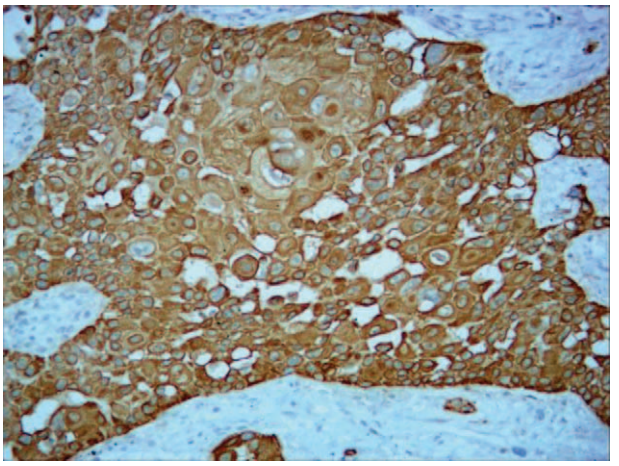

Figure 2. Immunohistochemical staining of the original tumor shows CD5/6 positive (10×).

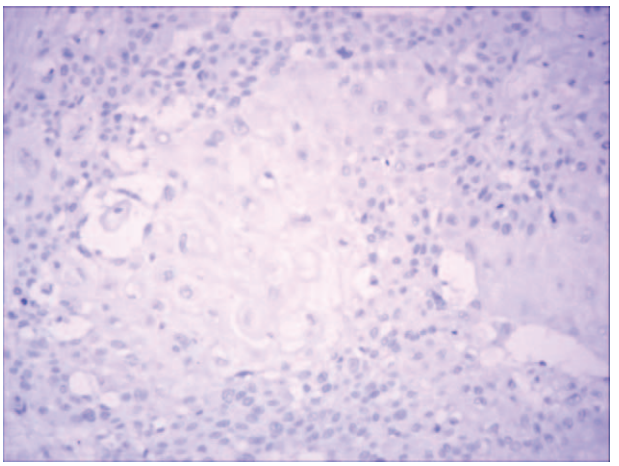

Figure 3. Immunohistochemical staining of the original tumor shows Her-2 negative (10×).

Table 2

Clinical course of the patient.

Time	Treatment	Time to progression
9-12-2012	Mastectomy	3 months
9-25-2012	TAC*5	
1-24-2013	Tumerectomy	4.5 months
2-1-2013	NP*4	
2-15-2013	Radiotherapy	
7-4-2013	S1	3.5 months
8-1-2013	Radiotherapy	
10-17-2013	G per week+ Radiotherapy	8.5 months
12-13-2013	G per month *7	
7-2-2014	TX*1	/
7-21-2014	Tumerectomy and LDMF	63 months (until now)
8-11-2014	XH*18	

G = gemcitabine, LDMF = latissimus dorsi flap, TAC = taxotere, adriamycin and cyclophamide, NP = vinorelbine and lobaplatin,; TX = paclitaxel and capecitabine, XH = capecitabine and trastuzumab.

Immunohistochemical findings were consistent with the results of preoperative biopsy except Ki-67 positivity, showing 60% of Ki-67 positive cells. Thus, the tumor was pT2N0M0, equivalent to stage IIa.

After surgery, the multidisciplinary team (MDT) conference board planned an adjuvant chemotherapy with 6 cycles of docetaxel (100 mg/m^2), pirarubicin (50 mg/m^2), and cyclophosphamide (700 mg/m^2) (so-called TAC chemotherapy) according to NCCN guidelines. After 5 cycles of TAC chemotherapy, the patient complained of a mass near her right axilla. Ultrasound showed a mass of 2.4 × 2.5 cm in the pectoralis major muscle on the front edge of the axilla, with both solid and cystic components present. Fine needle biopsy indicated SCC with necrosis. A tumorectomy was performed on January 24, 2013. Local recurrence was confirmed by pathological analysis, which revealed a PSCC of the breast with the same immunohistochemical results as the primary tumor except more Ki-67 positive cells (80%), as shown in Table 1.

The case was then discussed in an MDT conference and chemotherapy with 6 cycles of vinorelbine (35 mg/m^2, d1, 8) and lobaplatin (40 mg/m^2, d1) (NP chemotherapy) was planned. In addition, immediately after the first cycle of NP chemotherapy, stereotactic radiation therapy (SRT) was delivered to the chest wall, part axilla, infraclavicular, and supraclavicular regions with 6mev-X to a dose of 50 Gy in 25 fractions.

The NP chemotherapy was stopped after 3 cycles because of the enlargement of a lesion detected under the right axilla. The patient then took S-1 orally, but it had no effect to the lesion. A CT scanning revealed a 6 × 5 cm tumor compressing the axillary vein and spreading to the chest muscle. Three-dimensional conformal radiotherapy (3D-CRT) (6mev-X, 60 Gy/30f) was then delivered to the relapsed tumor. This treatment went well and the tumor regressed. However, another relapsed tumor emerged in the internal mammary region and was confirmed by fine needle biopsy. The patient then underwent 3D-CRT with a dose of 50 Gy/25f to the internal mammary region. She was treated simultaneously with weekly gemcitabine (300 mg/m^2/week) between October 18 and November 8, 2013. Afterward, gemcitabine (1200 mg/m^2, d1, d8, 21d) was given between December 13, 2013 and June 7, 2014, which was then stopped after 7 cycles because of recurrence. The relapsed tumor grew large enough to be palpable in the right axilla, along the anterior axillary line on the first rib. The MDT board decided to switch to weekly paclitaxel (120 mg/m^2) plus capecitabine (3500 mg/m^2, d1-14, 21d).

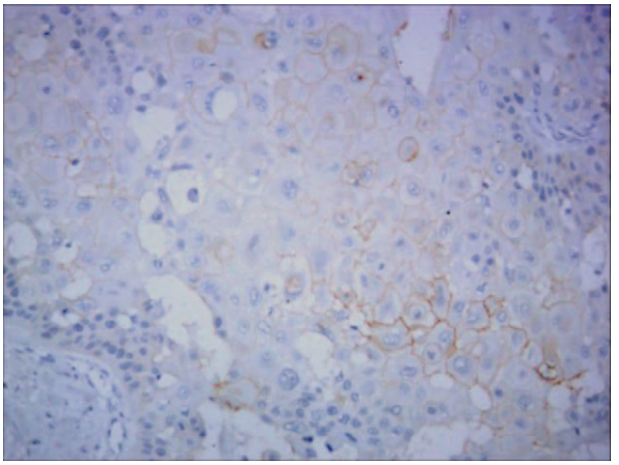

Figure 4. Immunohistochemical staining of the second recurrent tumor shows Her-2 positive (10×).

A tumorectomy with latissimus dorsi flap reconstruction was performed 1 cycle after the chemotherapy because the tumor did not reduce in size. Pathologically, the relapsed tumor was PSCC, and immunohistochemical analysis showed CK5/6-postive (intensity 2), E-cadherin-negative, ER-negative, PR-negative, C-erbB-2-positve (intensity 2), P53-positive (intensity 2)(++), and Ki-67-postive 80% (Fig. 4 and Table 2). FISH test demonstrated positive Her-2 gene amplification (Fig. 5). No vascular cancer embolus has been found. Only the margin near the axillary vein was positive.

Following surgery, the patient received 5 additional cycles of paclitaxel plus capecitabine, 1 year of trastuzumab for HER2-targeted therapy, and subsequently for one and half years, capecitabine (3000 mg/m^2, d1-14, 21d). There has no evidence of recurrence or metastasis in the 25 months follow-up since the last surgery.

3. Discussion

SCC of the breast was first reported in 1908 by Troell and the reported incidences vary between 0.1% and less than 0.04%.[5,8,9] As a metaplastic carcinoma, SCC comprises a

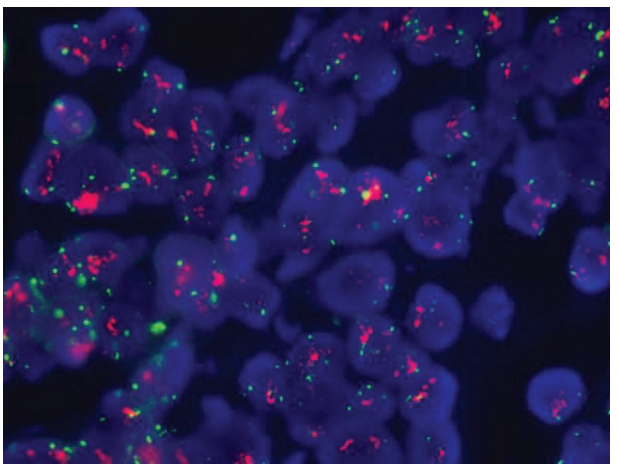

Figure 5. FISH test detects Her-2 gene amplification in the second recurrent tumor (10×). FISH = fluorescence in situ hybridization.

heterogeneous group of malignancies.[10] It is suggested that this malignancy may derive from squamous metaplasia of benign breast diseases, such as cysts, chronic inflammations, abscesses and adenofibromas, or arise directly from the epithelium of the mammary ducts.[9] A few strict criteria must be fulfilled to make the diagnosis of PSCC:

(a) The tumor must be independent from the skin and nipple; (b) More than 90% of tumor cells must be of squamous type; (c) Other primary non-mammary squamous cell carcinomas must be excluded; (d) No other invasive elements present in the tumor.[11]

In our case, the original and 2 recurrent tumors all fulfilled these criteria.

PSCC predominantly affects adult women. The median age was 50 years in a series of 30 cases reported recently.[12] Previous reports stated that it tends to be large (usually >4.5 cm) at presentation and cystic in more than 50% of cases.[13–15] But recent studies observed PSCC patients with relatively small tumor size,[13,16] and our patient presented with a relative small 2×2.5 cm lump. SCC of the breast mostly exhibits a profile of basal-like phenotype, characterized by a lack of expression of ER, PR, and HER2 while overexpression of CK5/6 and EGFR.[17–19] In our patient, this profile was observed in the original tumor and the first recurrence. But the second recurrence had a different phenotype, showing HER2 gene amplification and overexpression. Notably, this patient had favorable prognosis after the second recurrence. To our best knowledge, such switch of phenotype in this rare type of breast cancer has never been reported before.

PSCC has been associated with aggressive behavior and poor prognosis. Unfortunately, specialized and effective systematic treatment has not been established.[6,17] Currently, since most patients with PSCC exhibit the triple negative phenotype, they are usually treated in the same manner as triple negative breast cancer.[6,13,17] Cisplatin-based chemotherapy has been reported to be effective in some PSCC patients,[20,21] but did not yield favorable results in others.[6] In the study by Hennessy et al, 2 out of 33 patients with PSCC of the breast had HER2 overexpression, and both patients achieved good prognosis after receiving HER2-targeted therapy.[6] In our case, we used the standard chemotherapy regimen for triple negative breast cancer after mastectomy because the original tumor was triple negative, but the patient responded poorly to the chemotherapy and tumorectomy was carried out to remove the first relapsed tumor which was triple negative as well. The patient responded poorly to various chemotherapy and radiotherapy regimens administered after the first recurrence. The second relapsed tumor was determined to be HER2 positive and resected with latissimus dorsi flap reconstruction. HER2-targeted therapy with trastuzumab was administered and a complete remission was achieved.

The important question is which treatment played a predominant role, the resection with latissimus dorsi flap reconstruction or the HER2-targeted therapy with trastuzumab. Some previous reports found that immediate reconstruction with musculocutaneous flap was associated with better prognosis in patients with locally advanced breast cancer .[22,23] In our case, one possible explanation of the good prognosis after the second recurrence could be that latissimus dorsi flap brings new blood circulation to the chest wall, which likely increase drug concentration at the target site. On the other hand, the targeted therapy was effective in preventing the recurrence and may be more efficient after flap reconstruction.

In summary, this case report shows the importance of biopsy and immunohistochemical analysis of primary tumor and every recurrence because phenotype switch is possible. Surgery with flap reconstruction along with targeted therapy may be a possible therapeutic approach for recurrent PSCC when chemotherapy and radiotherapy fail.

Author contributions

Conceptualization: Yong Cao, Yeli Yue, Xin Zhou, Xinrui Liang.
Data curation: Yong Cao, Yeli Yue.
Investigation: Xin Zhou.
Methodology: Jie Luo.
Software: Jie Luo.
Writing – original draft: Yong Cao, Xinrui Liang.
Writing – review & editing: Yeli Yue, Xiaohua Zeng, JuanHui Dong, Xinrui Liang.

References

[1] Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127: 2893–917.
[2] Shin HR, Masuyer E, Ferlay J, et al. Cancer in Asia - incidence rates based on data in cancer incidence in five continents IX (1998-2002). Asia Pacific J Cancer Prevent APJCP 2010;11 Suppl 2:11.
[3] Shin HR, Joubert C, Boniol M, et al. Recent trends and patterns in breast cancer incidence among Eastern and Southeastern Asian women. Cancer Causes Control 2010;21:1777–85.
[4] Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
[5] Rosen PP. Rosen's Breast Pathology. Philadelphia, PA: Lippincott Williams and Wilkins; 2001. 455-461.
[6] Hennessy BT, Krishnamurthy S, Giordano S, et al. Squamous cell carcinoma of the breast. J Clin Oncol 2005;23:7827–35.
[7] Chen XL, Luo J, Xu FL. Squamous cell carcinoma of the breast: particularity and clinical management. Int J Clin Exp Med 2016.
[8] Gupta C, Malani AK, Weigand RT, et al. Pure primary squamous cell carcinoma of the breast: a rare presentation and clinicopathologic comparison with usual ductal carcinoma of the breast. Pathol Res Pract 2006;202:465–9.
[9] Behranwala KA, Nasiri N, Abdullah N, et al. Squamous cell carcinoma of the breast: clinico-pathologic implications and outcome. Eur J Surg Oncol 2003;29:386–9.
[10] Rosen PP. Rosen's Breast Pathology, 3rd Edition. Philadelphia, PA: Carcinoma with metaplasia: Lippincott Williams and Wilkins; 2009. 470–505.
[11] Rosen PP. Rosen's Breast Pathology, 2nd Edition. Philadelphia, PA: Lippincott Williams and Wilkins; 2001. 215–225.
[12] Zhang X, Zhang B, Zang F, et al. Clinical features and treatment of squamous cell carcinoma of the breast. Onco Targets Ther 2016;9: 3181–5.
[13] Shigekawa T, Tsuda H, Sato K, et al. Squamous cell carcinoma of the breast in the form of an intracystic tumor. Breast Cancer 2007;14:109–12.
[14] Salemis NS. Breast abscess as the initial manifestation of primary pure squamous cell carcinoma: a rare presentation and literature review. Breast Dis 2011;33:125–31.
[15] Cardoso F, Leal C, Meira A, et al. Squamous cell carcinoma of the breast. Breast 2000;9:315–9.
[16] Arafah M, Ginter PS, Taylor DC, et al. Squamous cell carcinoma in situ of the breast: report of a case. Breast J 2016; 22:573–7.
[17] Grabowski J, Saltzstein SL, Sadler G, et al. Squamous cell carcinoma of the breast: a review of 177 cases. Am Surg 2009; 75:914–7.
[18] Nayak A, Wu Y, Gilcrease MZ. Primary squamous cell carcinoma of the breast: predictors of locoregional recurrence and overall survival. Am J Surg Pathol 2013;37:867–73.

[19] Grenier J, Soria JC, Mathieu MC, et al. Differential immunohistochemical and biological profile of squamous cell carcinoma of the breast. Anticancer Res 2007;27(1B):547–55.
[20] Bhatt L, Fernando I. Primary squamous cell carcinoma of the breast: achieving long-term control with cisplatin-based chemotherapy. Clin Breast Cancer 2009;9:187.
[21] Tsung SH. Primary pure squamous cell carcinoma of the breast might be sensitive to Cisplatin-based chemotherapy. Case Rep Oncol 2012;5:561–5.
[22] Bogusevicius A, Cepuliene D, Sepetauskiene E. The integrated evaluation of the results of oncoplastic surgery for locally advanced breast cancer. Breast J 2014;20:53–60.
[23] Hsieh TY, Lin YN, Lin SD, et al. Immediate transverse rectus abdominis musculocutaneous flap reconstruction is associated with improved cancer-specific survival in locally advanced breast cancer. Ann Plast Surg 2014;73(Suppl 1):S31.