

Two cases of spindle cell carcinoma of the breast – Usefulness of immunohistochemical analysis

Sumiko OKUBO¹⁾, Junichi KUREBAYASHI¹⁾, Hiroshi SONOO¹⁾
Tetsumasa YAMASHITA¹⁾, Naoki KANOMATA²⁾, Takuya MORIYA²⁾

1) Department of Breast and Thyroid Surgery, 2) Pathology 2, Kawasaki Medical School,
577 Matsushima, Kurashiki, 701-0192, Japan

ABSTRACT Spindle cell carcinoma (SpCC) of the breast is a rare variant of breast cancer that has been classified as one of the special types of metaplastic breast carcinoma (MBC). MBC consists of a mixture of cells, both epithelial and mesenchymal in origin. Immunohistochemical (IHC) analyses of SpCC show positive staining for both epithelial and mesenchymal markers. Herein, we report two patients with SpCC of the breast who were recently treated at our department. IHC analyses for cytokeratins and other mesenchymal markers were useful in making a correct diagnosis of SpCC.

(Accepted on March 9, 2012)

Key words : **Breast cancer, Spindle cell carcinoma, Immunohistochemistry**

INTRODUCTION

Spindle cell carcinoma (SpCC) has been classified into a special type of invasive ductal carcinoma in the General Rules for Clinical and Pathological Recording of Breast Cancer (16th edition)¹⁾. SpCC is a rare variant of breast cancer. Its incidence has been reported to be between 0.1 to 0.5%^{2,3)}. SpCC shows some unique pathological and clinical features. As pathological features, SpCC is a part of metaplastic breast cancer (MBC), and MBC consists of a mixture of cells, both epithelial and mesenchymal in origin. There are carcinomatous components of squamous and spindle cells, and there are sarcomatous components with a heterogeneous

pattern⁴⁾. As clinical features, rapid growth, a lack of lymph node metastasis, triple negative breast cancer (TNBC), and a poor prognosis were shown in most of the SpCC cases. Here, we report two SpCC patients who were recently treated in our department.

CASE REPORT

Case 1: A 52 -year-old female presented with an induration in her right breast. She had schizophrenia on medication, uterine myoma, and right calyceal diverticulum. On physical examination, she had hard 5cm tumor with redness in her right breast. Axillary lymph nodes were not palpable. Mammography was

Corresponding author
Junichi Kurebayashi
Department of Breast and Thyroid Surgery, Kawasaki
Medical School, 577 Matsushima, Kurashiki, 701-0192,
Japan

Phone : 81 86 462 1111
Fax : 81 86 462 1199
E-mail: kure@med.kawasaki-m.ac.jp

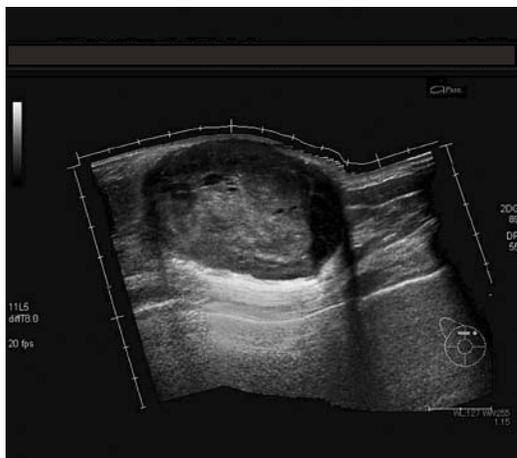


Fig. 1. Findings of the breast ultrasound examination in case 1: A low echoic mass ($90 \times 80 \times 50$ mm in size) with a heterogeneous internal echo texture was observed.

not performed due to a large size tumor. Ultrasound examination revealed a low echoic lesion in the inner-upper area of her right breast (Fig. 1). Fine-needle aspiration cytology was performed, and the result was suspicious of malignancy. In addition, core needle biopsy was performed and SpCC was suspected. Modified radical mastectomy and axillary lymph node dissection were performed. TNM classification for this case was T3N0M0, Stage II B. Adjuvant chemotherapy using tegafur-uracil was started after the operation. She had not experienced any recurrence as of one year after the operation.

Case 2: A 66-year-old female presented with a tumor in her left breast. She had anemia, type B liver cirrhosis on medication, myoma uterus, and hemorrhoid. On computed tomography, a 10×7 cm tumor with a hematoma inside was observed (Fig. 2). Ultrasound examination revealed a low echoic lesion in the inner-upper area of her left breast. Open biopsy was performed and scirrhous or solid-tubular carcinoma was suspected. Modified radical mastectomy and axillary lymph node dissection were performed. TNM classification for this case was T4cN0M0, Stage III B. Pathological diagnosis was SpCC. The patient could not receive any adjuvant



Fig. 2. Findings of chest computed tomography in case 2: A huge breast tumor (10×7 cm in size) with a suspected intratumoral hematoma was observed.

chemotherapy due to liver cirrhosis, but radiation therapy was performed on the loco-regional area to prevent local recurrence. Unfortunately, lung and pleural metastases appeared six months after the operation. Chemotherapy including cisplatin for the treatment of metastatic diseases was administered to the patient based on the suggestions of an expert in liver diseases. Regrettably, she died nine months after the operation.

Summarized IHC results of the two cases are shown in Table 1. In addition, representative pathological findings are shown in Fig. 3 and 4.

DISCUSSION

SpCC of the breast is a rare variant of breast cancer that has been classified as under the category of metaplastic carcinoma⁵⁾. MBC is a rare poorly differentiated breast cancer characterized by the coexistence of ductal carcinoma with areas of matrix production, spindle cells, and sarcomatous or squamous differentiation⁶⁾. SpCC has characteristics of basal-like breast cancer, such as both estrogen receptor (ER) and progesterone receptor (PgR) are negative, human epidermal growth factor receptor (HER) 2 is negative, and the Ki-67 labeling index is high. About 70-90% of TNBC is classified into basal-like breast cancer.

According to a review paper with regard to 35

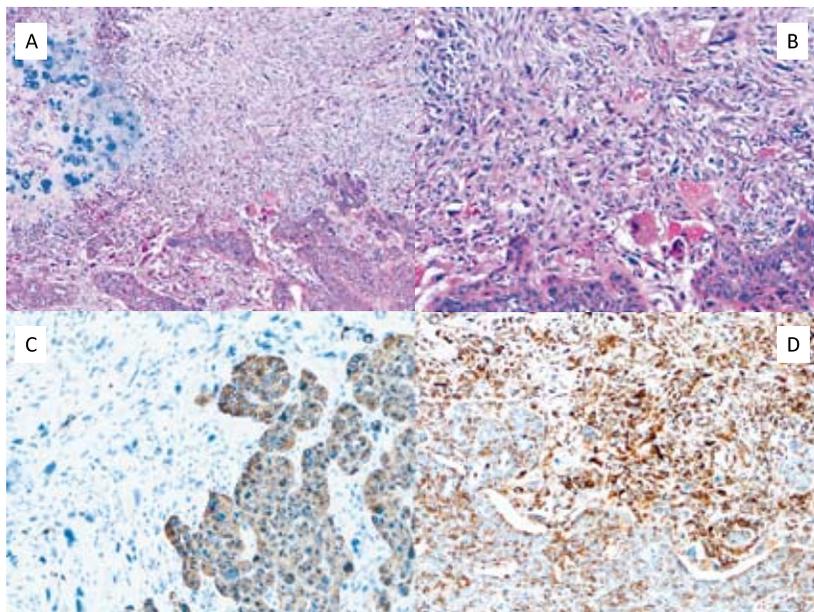


Fig. 3. Findings of HE and IHC in case 1:

- A. Epithelial component (lower), cartilaginous component (left), and spindle cells of spindle cell carcinoma.
- B. Prominent nuclear atypia is present both in epithelial and spindle cell components.
- C. Epithelial component showing diffuse cytokeratin 14 immunoreactivity. Rare spindle cells expressing cytokeratin 14.
- D. Spindle cells with strong immunoreactivity for vimentin. Epithelial component also exhibits some vimentin immunoreactivity.

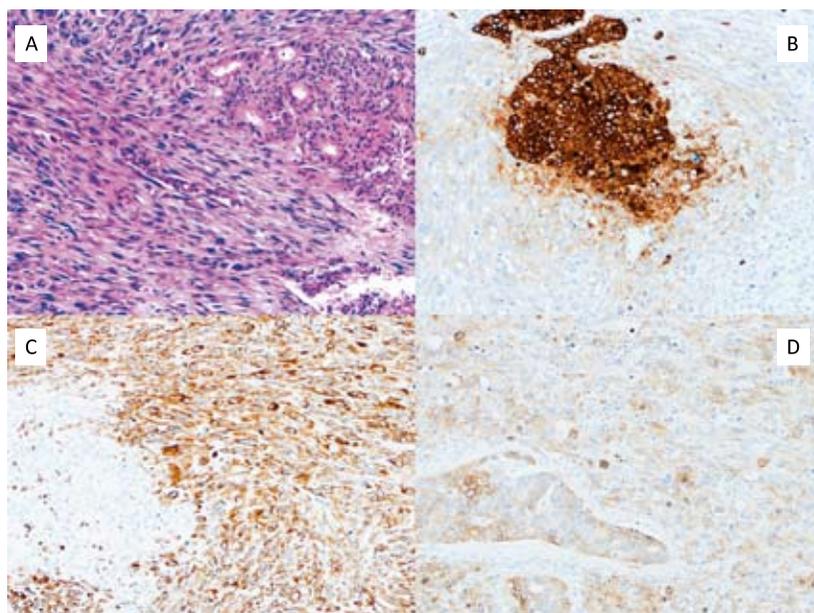


Fig. 4. Findings of HE and IHC in case 2:

- A. Spindle cell carcinoma; atypical spindle cells and epithelial component with tubular differentiation.
- B. Cytokeratin AE1/3 (broad-spectrum cytokeratin) immunohistochemistry showing intense reaction in epithelial component and weak staining in spindle cells.
- C. Vimentin immunoreactivity is present in spindle cells but not in epithelial component.
- D. EGFR was positive both in spindle and epithelial components.

Japanese cases of SpCC of the breast, the average age was 52.3 years, about 76% of cases had a tumor larger than 3 cm, and most of the SpCC tumors had a triple negative phenotype ER-negative, PgR-negative and HER2-negative²⁾. In spite of large tumor sizes, most SpCC cases did not have any metastatic lymph nodes²⁾. It has also been reported that hematogenous metastases to the lung, brain, and/or bone are frequently observed in SpCC cases⁷⁾. The two patients presented here consistently had these features. They had large tumors without any metastatic lymph node. Their tumors expressed neither hormone receptors nor HER2.

It is difficult to achieve a definitive diagnosis of SpCC before surgery in most SpCC cases. Immunohistochemical tests using tumor samples obtained by core needle biopsy sometimes facilitate a correct diagnosis of SpCC before radical surgery⁶⁾. IHC findings of SpCC showed the positivity of epithelial makers such as cytokeratin (CK) 7, pan-CK, and epithelial membrane antigen (EMA), and the positivity of mesenchymal markers such as vimentin, nestin, and smooth muscle actin (SMA). These findings are mixed in a tumor⁸⁾.

According to a comprehensive paper by Carter et al. on 29 cases of SpCC of the breast⁵⁾, the positivity

rate of CK is high; especially, the positive rate of pan-CK (MNf116) and CK14 were 90% or more.

And CK17 were more than 90%, and the positivity rates of p63 and SMA were more than 50% among the reported cases. On the other hand, the positivity rates of AE1/AE3, CAM5.2, and EMA were less than 50% among the reported cases. Carter et al. suggested that, when the diagnosis of SpCC is difficult, an IHC test of a battery of CKs including CK14 and CK17 should be performed because spindle sarcoma of the breast is very rare. Core needle biopsy was performed for case 1, and the IHC result indicated that there was a strong possibility of SpCC. Although some differences were observed in other markers, expressions of AE1/AE3 and vimentin were observed in both cases.

Even though lymph node metastasis is not observed, sufficient treatment is recommended for patients with SpCC because it tends to have distant metastases and a poor outcome. Cytotoxic chemotherapy including cisplatin is recommended as adjuvant therapy for TNBC cases including SpCC cases. Preoperative chemotherapy may be an option for the treatment of MBC. Takuwa et al. reported a case of MBC that showed a positive response to

Table 1. Immunohistochemical analyses of SpCCs of the breast in two cases

	Case 1	Case 2
ER	-	-
ER (%)	0	0
PgR	-	-
PgR(%)	0	0
HER2/neu	-	-
HER2 score	1+	1+
Ki-67	+	+
Ki-67(%)	65.8	52.2
Nuclear grade	3	3
AE1/AE3	+	+
Vimentin	+	+
S-100	+	-
Desmin	+	-
CK14	+	-
p63	-	-

ER; Estrogen receptor, PgR; Progesterone receptor, HER2; Human epidermal growth factor receptor 2, CK14; Cytokeratine 14

preoperative chemotherapy. The patient received chemotherapy containing cisplatin, docetaxel, and doxorubicin before the operation, after the chemotherapy, an almost complete response (CR) was observed with breast MRI. Partial mastectomy was performed, and a nearly pathological CR was confirmed. No recurrence has appeared for more than two years after the initial chemotherapy in the reported case⁹⁾.

In the latest studies, efficacies of poly adenosine diphosphate [ADP] ribose polymerase (PARP) inhibitors in patients with TNBC were reported, and oral and intravenous PARP inhibitors are under development. Their efficacies have been reported as not only monotherapy but also in the combination with various DNA-damaging agents¹⁰⁾. It is known that PARP inhibitors inhibit the repair of DNA damage and increase apoptosis in cancer cells. Major adverse events due to the agents include fatigue, nausea, vomiting, and constipation. A phase II trial comparing the efficacy between chemotherapy alone versus chemotherapy plus a PARP inhibitor, iniparib, revealed that the latter was significantly better than the former in terms of overall survival (12.2 versus 7.7 months, respectively, $P = 0.01$) in patients with metastatic TNBC¹¹⁾. On the other hand, Okushiba *et al.* reported an SpCC patient receiving multiple operations and radiation, who achieved long-term survival of more than ten years after the initial operation¹²⁾.

Toumi *et al.* investigated the outcome of patients with MBCs. Their study suggested that patients with MBC expressing CK14 tended to have a better outcome than those not expressing it⁴⁾. Interestingly, the tumor in case 2 did not express CK14. Lung and pleural metastases appeared six months after the operation in this case. In contrast, the tumor in case 1 did express CK14. No distant metastasis has been observed for a year after the initial surgery.

In conclusion, we report two cases of SpCC of the breast. SpCC is a rare carcinoma, and most of the

cases are TNBCs. An IHC test for CKs and others is very useful to diagnose SpCC. If the diagnosis of SpCC is possible before the operation, preoperative chemotherapy should be considered. In addition, if diagnosed SpCC is after an operation, aggressive postoperative chemotherapy and careful monitoring are required.

REFERENCES

- 1) Kanehara Co. LTD., The Japanese Breast Cancer Society: Tokyo, Japan, General Rules for Clinical and Pathological Recording of Breast Cancer, 16th edition, 2008, pp23
- 2) Higa J, Yamamoto H, Kanashiro T, *et al.*: A case of spindle cell carcinoma of the breast with a review of 35 cases reported in Japan between 2004 and 2006. *Jpn J Breast Cancer* 22: 340-343, 2007
- 3) Khan HN, Wyld L, Dunne B, Lec A.H.S, Pinder S.E, Evans A.J, Robertson J.F.R : Spindle cell carcinoma of the breast: a case series of a rare histological subtype. *Eur J Surg Oncol* 29: 600-603, 2003
- 4) Toumi Z, Bullen C, Tang AC, Dalal N, Ellenbogen S : Metaplastic breast carcinoma: A case report and systematic review of the literature. *Pathol Int* 61: 582-588, 2011
- 5) Carter MR, Hornick JL, Lester S, Fletcher C : Spindle Cell (Sarcomatoid) Carcinoma of the Breast: A Clinicopathologic and Immunohistochemical Analysis of 29 Cases. *Am J Surg Pathol* 30: 300-309, 2006
- 6) Beatty JD, Atwood M, Tickman R, Reiner M : Metaplastic breast cancer: clinical significance. *Am J Surg* 191: 657-664, 2006
- 7) Miyazato K, Kurashita K, Murai K, *et al.*: A case of spindle cell carcinoma of the breast with acute progression and peculiar patterns of metastasis. *Jpn J Breast Cancer* 24: 125-129, 2009
- 8) Nagata Y, Ono K, Shimokawa H, Takenaka M, Yamazaki M, Yamada S, Hanagiri T : Three Cases of Spindle Cell Carcinoma of the Breast. *J UOEH* 32: 341-348, 2010
- 9) Takuwa H, Ueno T, Ishiguro H, Mikami Y, Kanao S, Takada M, Sugie T and Toi M : A case of metaplastic breast cancer that showed a good response to platinum-based preoperative chemotherapy. *Breast Cancer* 2011 [Epub ahead of print]
- 10) Anders CK, Winer EP, Ford JM, Dent R, Silver DP,

- Sledge GW, Carey LA : Poly(ADP-Ribose) Polymerase Inhibition: "Targeted" Therapy for Triple-Negative Breast Cancer. *Clin Cancer Res* 16: 4702-4710, 2010
- 11) O'Shaughnessy J, Osborne C, Pippen JE, Yoffe M, Patt D, Rocha C, Koo IC, Sherman B.M, Bradley C : Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer. *N Engl J Med* 364: 205-214, 2011
- 12) Okushiba S, Minagawa H, Shimizu M, Ambo Y, Kaji M, Omi M, Ito K, Kondo S, Katoh H : A Case of Spindle Cell Carcinoma of the Breast Long Survival Achieved by Multiple Surgical Treatment. *Breast Cancer* 8: 238-242, 2001