CASE REPORT

MULTIDISCIPLINARY MANAGEMENT OF SMALL CELL CARCINOMA OF THE BREAST: A CASE REPORT

TORU MURATA[1], MASAHIRO FUJII[1], KAZUHISA AKAHANE[1], KOJI ODA[1],
TOSHIHIRO OHAMA[2], YASUSHI YATABE[3], and KENJI KAWADA[4]

[1]*Department of Breast Oncology, Aichi Cancer Center Aichi Hospital, Okazaki, Aichi, Japan*
[2]*Ohama Clinic, Okazaki, Aichi, Japan*
[3]*Department of Pathology and Clinical Laboratories, Aichi Cancer Center Central Hospital, Nagoya, Japan*
[4]*Department of Medical Oncology, Nagoya Daiichi Red Cross Hospital, Nagoya, Japan*

ABSTRACT

We report a case of primary small cell carcinoma (SCC) of the breast in a 59-year-old female. To the best of our knowledge, there are only 44 cases of this disease reported in the English literature. The patient also had regional nodal metastases, but no distant metastases. She underwent neoadjuvant chemotherapy according to a regimen of pulmonary SCC, and combination of cisplatin and etoposide (CDDP+VP16). The tumor partially responded to neoadjuvant chemotherapy. The treatment was followed by modified radical mastectomy and adjuvant chemotherapy, i.e., EC therapy (epirubicin and cyclophosphamide). She was also administered in total 50 Gy of radiation treatment to the chest wall. At this writing, the patient has evidenced no recurrence 36 months after her diagnosis.

Key Words: Small cell carcinoma of the breast; Neoadjuvant chemotherapy

INTRODUCTION

Extrapulmonary SCC has been increasingly recognized as a clinicopathological entity distinct from SCC of the lung. These tumors have been reported to arise from a wide variety of sites, including prostate, bladder, esophagus, stomach, colorectum, gallbladder, pancreas, breast, kidney, salivary gland, larynx, endometrium, ovary, and uterine cervix.[1-9] Various prognoses have been observed for extrapulmonary SCC originating from different sites, however, the clinical behavior of these tumors is generally aggressive like their pulmonary counterpart.

SCC of the breast is an exceptionally rare type of mammary neoplasm, so its treatment is poorly understood. Due to the lack of an established therapy for this disease, we treated our patient with a multidisciplinary approach combined with chemotherapy, surgery, and radiation therapy.

CASE PRESENTATION

A 59-year-old female patient presented with a firm, non-tender 3-cm mass in her right breast. There were no associated symptoms. Further investigation with mammography revealed an indistinct mass, and ultrasonogram showed a solid, hypoechoic mass with an irregular contour measuring 2.3×2.7×2.2 cm (Fig. 1a). Ultrasound-guided vacuum-assisted biopsy (Mammotome) under ultrasound guide was performed. Microscopically, the biopsy specimen showed pattern-less sheets of undifferentiated small cells with a high nuclear-to-cytoplasmic ratio, revealing hyperchromatic nuclei and indistinct cytoplasm (Fig. 2). Results of immunohistochemistry (IHC) revealed that tumor cells in the solid and unstructured area were positive for CK, synaptophysin, chromogranin A, and TTF-1, indicating an epithelial tumor with neuroendocrine differentiation. These histological and IHC findings suggested that the tumor may have been a metastasis from SCC of the lung. In order to detect a non-mammary primary site, computed tomography of the chest and the abdomen and magnetic resonance imaging of the head were performed. These investigations showed that she had no underlying lung pathology and that the breast was the primary site.

Although there is no established regimen for SCC of the breast, we administered neoadjuvant chemotherapy to the patient as is performed for SCC of the lung. We treated the patient with a regimen of cisplatin (80 mg/m2) on day 1, and etoposide (VP-16) (100 mg/m2) on days 1, 2, and 3, respectively, every 3 weeks for four courses. After completion of neoadjuvant chemotherapy, ultrasonogram and magnetic resonance image showed that the diameter of the tumor was reduced almost in half (Fig. 1b, Fig. 3). After the neoadjuvant chemotherapy, she underwent right modified radical mastectomy including level I and II axillary lymph node dissection.

Histopathological examination of the resected specimen revealed a tumor of 14×11 mm, composed of small cells with hyperchromatic nuclei demonstrating chromatin diffusion. An in situ component found within the invasive lesion suggested that the present case is a primary extrapulmonary SCC (Fig. 4). No reactivity for estrogen or progesterone receptors was detected. HER2/neu was 1+ and Ki-67 labeling index was more than 20%. Those results suggested that
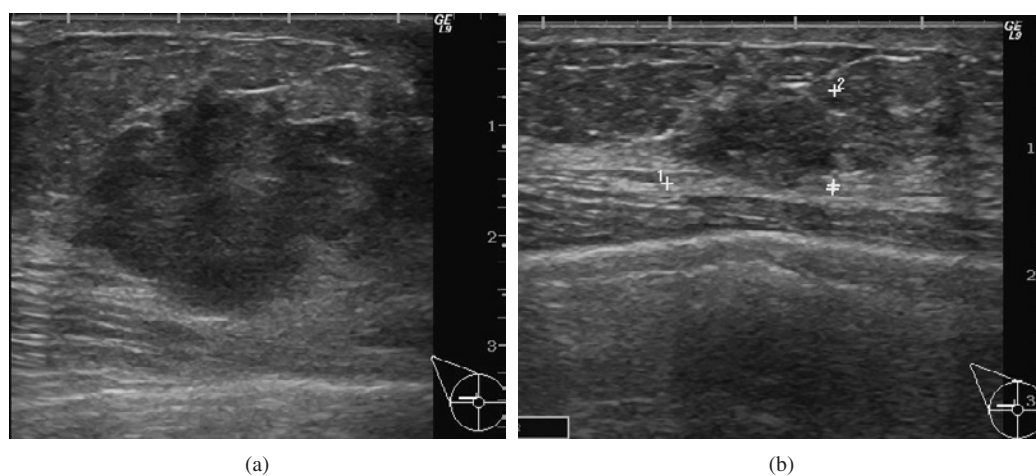

(a)   (b)

Fig. 1 (a) Ultrasonogram of tumor before neoadjuvant chemotherapy. Hypoechoic irregular mass measuring 2.3×2.2 cm is seen.
(b) After completion of neoadjuvant chemotherapy. Diameter of tumor is reduced to less than half of original size (1.3×0.8 cm).

this tumor had the potential for highly proliferative activity. Positive axillary lymph nodes were seen in 1 of 11 dissected nodes. The morphological characteristics of the lymph nodes involved were similar to those of a primary breast tumor.

She received EC therapy (epirubicin 90 mg/m2 and cyclophosphamide 600 mg/m2×4 courses) according to the standard adjuvant therapy for breast cancer. She was also administered in total 50 Gy of adjuvant radiation treatment to the ipsilateral chest wall. The patient has had no evidence of recurrence 36 months after the diagnosis.
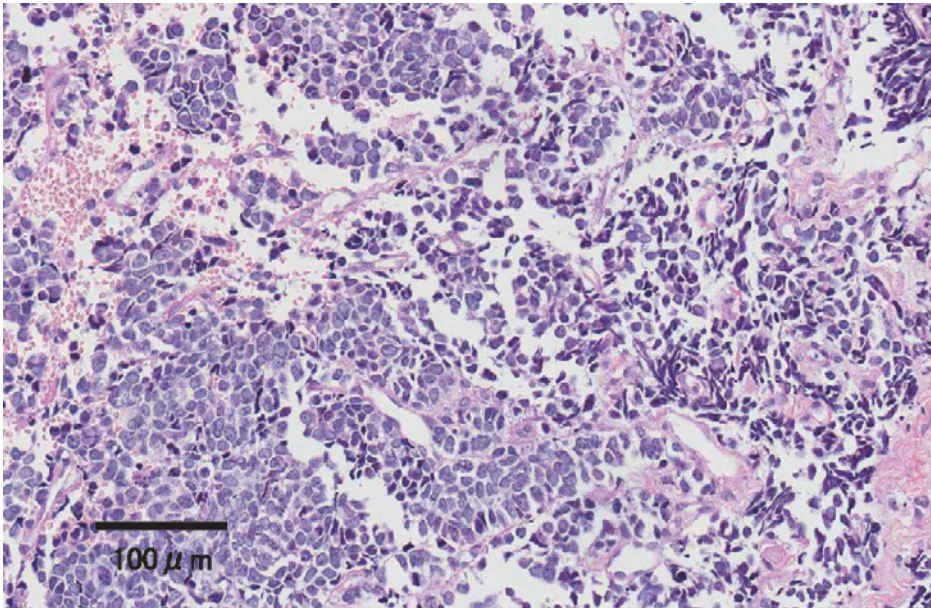

Fig. 2 Microscopy of Mammotome biopsy specimen reveals patternless sheets of small cells with high nuclear-to-cytoplasmic ratio (H&E×20).
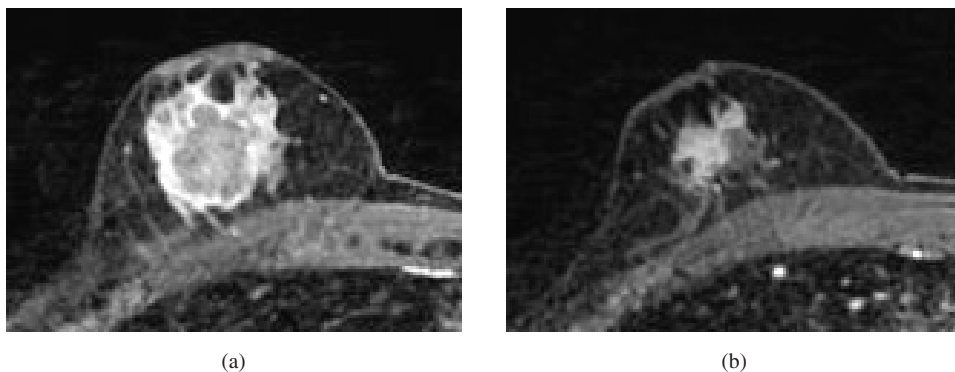

(a)　　　　　　　　　　　　　　　　(b)

Fig. 3 Horizontal sectional view of enhanced magnetic resonance image before and after completion of neoadjuvant chemotherapy.
(a) Lobulated mass of 34×28×25 mm is seen. Margin of tumor is strongly enhanced, while inside was enhanced in a mottled pattern.
(b) Post-neoadjuvant chemotherapy. Diameter of tumor is decreased to 12 mm.

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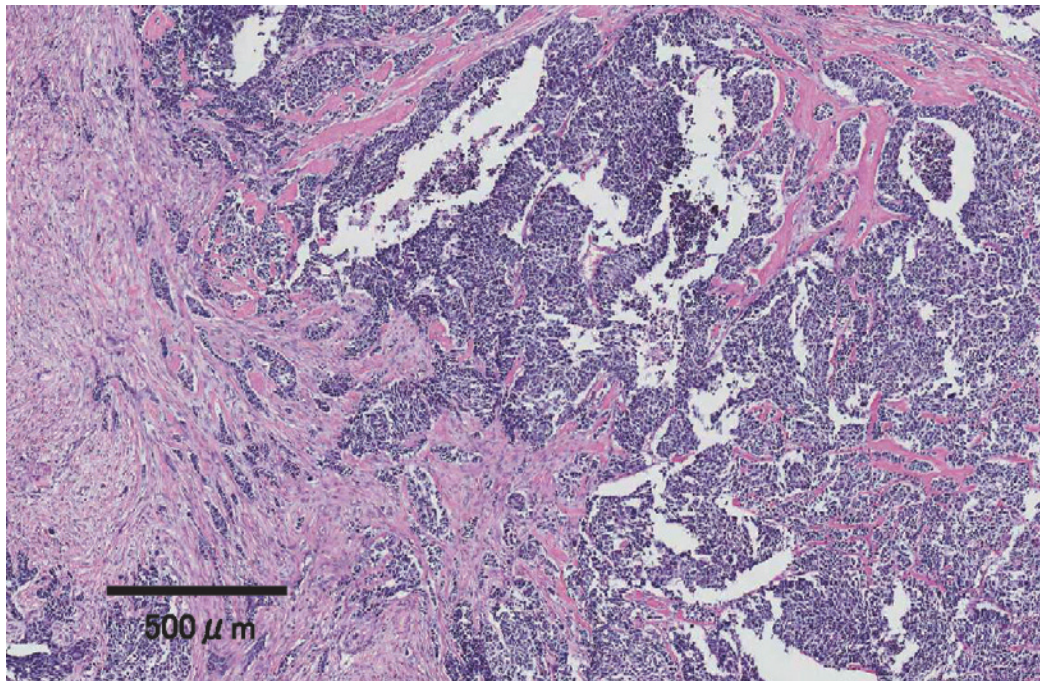
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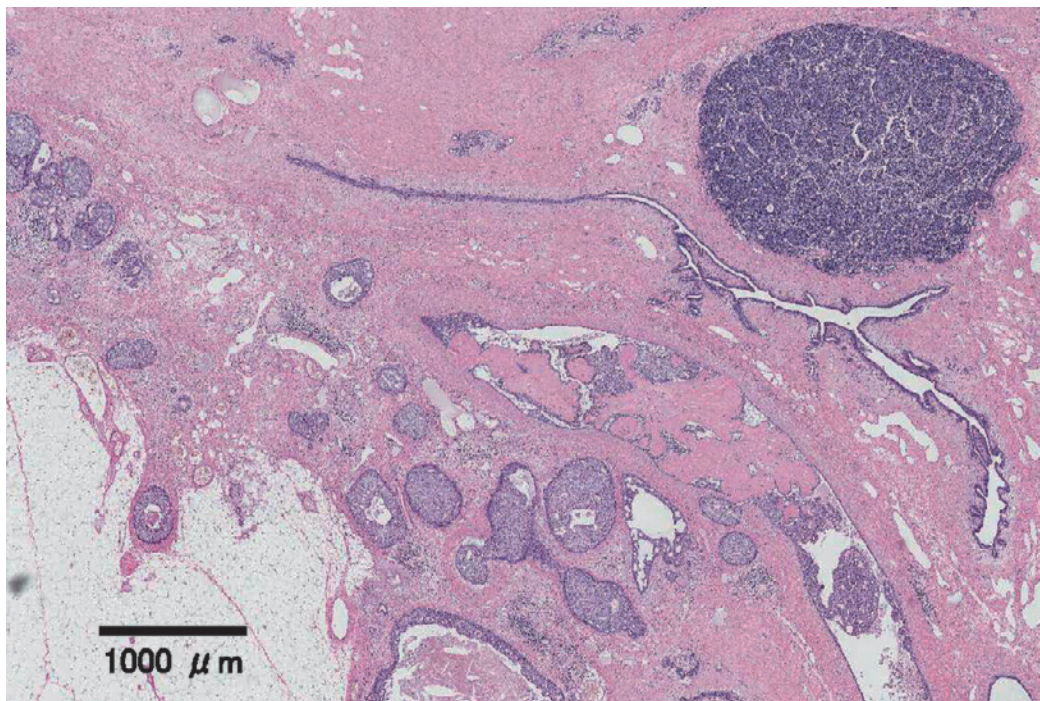
(b)

Fig. 4 (a) Microscopic findings of resected specimen. Foci of tumor cells with high nuclear-to-cytoplasmic ratio grow in an invasive pattern (H&E×10).
(b) Intraductal components (in situ lesion) seen adjacent to invasive area (H&E×10).

DISCUSSION

Small cell carcinoma occurs very rarely in the breast. Only 44 cases have been reported in the English literature so far.[10-28] To diagnose a primary SCC of the breast, the following criteria must be met: (1) A non-mammary origin must be excluded clinically; and/or (2) an in situ component must be demonstrated histologically.[29] Although a search for an in situ component should be made, its absence is not conclusive for a metastatic lesion. Some authors claimed that the presence of an in situ carcinoma component within the breast was highly suggestive of a breast primary rather than a metastatic tumor.[12] However, this criterion was not met in most published descriptions of this rare tumor.

A review of the 44 previously reported cases revealed that SCC arising in the breast shows prominent vascular infiltration and frequent lymph node metastasis.[16] The age distribution of patients with this tumor is 28–81 years, with a mean age of 54.7 years. The size of the tumors ranges from 1.0 to 14 cm with a mean of 6.1 cm. Metastatic lesions are usually multiple. Clinical evidence of breast metastasis often appears 2 years after discovery of a known primary tumor.

Size is an important prognostic factor for breast carcinomas in general, and something which also holds for SCC of the breast.[14, 30] Shin *et al.* found that patients with a mean tumor size of 5.2 cm did appreciably worse than those with a mean tumor size of 2.6 cm. According to earlier reports, it was generally considered that prognosis of SCC of the breast was as poor as that for small cell carcinoma of the lung.[10, 11] However, recent reports show that prognosis is better if the tumors are detected in the early stages,[13, 14] and if there is no metastasis to the lymph nodes.[15]

The present case was large, more than 3 cm in size, and presented a rapid and aggressive clinical course showing a high Ki-67 labeling index without hormone sensitivity immunohisto-chemically. With those findings indicative of a poor prognosis and speculation that SCC of the breast is pathologically more similar to SCC of the lung than to common ductal carcinoma of the breast, we initially decided to treat the patient with intensive adjuvant chemotherapy based on the chemotherapy for pulmonary SCC. The commonly used chemotherapy agents are report-edly VP16 and cisplatin,[18, 27] so we administered neoadjuvant chemotherapy with a regimen of cisplatin on day 1, and etoposide (VP16) on days 1, 2, and 3 every 3 weeks for four courses, respectively. After completion of neoadjuvant chemotherapy, however, the response to treatment remained a partial remission, so a complete response was not obtained.

Extra-pulmonary SCC of the breast is reportedly a very aggressive tumor for which no current standard of treatment has been agreed upon. Neoadjuvant chemotherapy has also resulted in decreased tumor size, as in our case; however, no long-term follow-up studies are available. As there has been no current standard treatment, neoadjuvant chemotherapy may be recommended to treat patients with advanced SCC of the breast; that is, because the response to neoadjuvant chemotherapy can be evaluated with diagnostic imaging and the surgical specimens.

In the reported 45 cases, including the present one, 33 patients were treated with chemotherapy. The details on the chemotherapy regimens are given for 20 of the 45 cases. The chemotherapy based on breast cancer, anthracyclines or taxanes regimens, was administered in 11 cases, while chemotherapy based on SCC of the lung, CDDP or CBDCA + VP16, was administered in 12. Neoadjuvant chemotherapy, which is considered to be a surrogate marker of prognosis, was administered in 11 cases among which the effect of neoadjuvant chemotherapy was mentioned in 7 cases; the number of pathological complete response (pCR), partial response (PR), and progressive disease (PD) were 2, 4, and 1, respectively. pCR was observed in 1 breast cancer regimen and 1 SCC regimen. PR was observed in 3 breast cancer regimens and 3 SCC regimens. According to the reported cases, there was no remarkable difference in effectiveness between breast cancer regimens and SCC regimens (Table 1).

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Table 1 Published case reports of SCC of the breast treated with chemotherapy

No.	Author	Published yr	Sex	Age	size (cm)	TNM	Chemotherapy	Type of regimen	NAC	Effect of NAC	Surgery	ER	HER2	Status and follow-up
1	Wade	1983	F	52	10	T4N1M1	AC+vincristine	breast	(-)	–	modified radical Mx	N.S.	N.S.	DOD, 9 m
2	Jundt	1984	M	52	NS	TxN1M0	N.S.	–	(-)	–	none	N.S.	N.S.	DOD, 14 m
3	Papotti	1992	F	50	3	T2N1M0	N.S.		(-)	–	radical Mx	(-)	N.S.	DOD, 14 m
4	Francois	1995	F	68	4.5	T2N0M0	AC+VP-16	breast, SCC	(-)	–	modified radical Mx	(-)	N.S.	DOC, 21m
5	Sebenik	1998	F	67	3.5	T2NxM0	CDDP+VP-16	lung	NAC	pCR	lumpectomy	N.S.	N.S.	NED, 33 m
6	Samli	2000	F	60	8	T4N1M0	FEC→post op.CDDP+VP-16	breast, SCC	NAC	PR	modified radical Mx	(+)	N.S.	AWM, 6 m
7	Shin	2000	F	44	2	T1N0M0	N.S.	–	(-)	–	lumpectomy	N.S.	(-)	NED, 27 m
8	Shin	2000	F	46	3.4	T2N1M0	N.S.	–	(-)	–	radical Mx	N.S.	(-)	AWM, 11 m
9	Shin	2000	F	50	2.2	T2NxM0	N.S.	–	(-)	–	lumpectomy	N.S.	(-)	NED, 35 m
10	Shin	2000	F	57	2.5	T2N0M0	N.S.	–	(-)	–	radical Mx	N.S.	(-)	NED, 10 m
11	Shin	2000	F	62	5	T2N1M0	N.S.	–	NAC	N.S.	radical Mx	N.S.	(-)	AWM, 2 m
12	Shin	2000	F	64	1.8	T1N0M0	N.S.	–	(-)	–	excision	N.S.	(-)	NED, 10 m
13	Shin	2000	F	70	4	T2NxM0	N.S.	–	(-)	–	lumpectomy	N.S.	(-)	NED, 3 m
14	Yamasaki	2000	F	41	4.5	T2N0M0	CMF	breast	(-)	–	modified radical Mx	(+)	N.S.	NED, 16 m
15	Salmo	2001	N.S.	46	4	T2N0M0	CDDP+VP16	SCC	(-)	–	lumpectomy	(-)	N.S.	NED, 9 m
16	Bigotti	2004	F	56	18	T3N1M0	N.S.	–	NAC	N.S.	radical Mx	(-)	(-)	DOD, 14 m
17	Mariscal	2004	F	53	5.5	T3N1M0	CDDP+VP16	SCC	NAC	pCR	lumpectomy	N.S.	N.S.	NED, 6 m
18	Sridhar	2004	F	58	1.6	T1N1M0	ADM+CDDP	breast, SCC	(-)	–	lumpectomy	(-)	N.S.	NED, 18 m
19	Sridhar	2004	F	75	2.5	T2N1M0	CMF	breast	(-)	–	Mx	(+)	2+	NED, 43 m
20	Adeglbola	2005	F	46	1	T1N0M0	CDDP+VP16	SCC	(-)	–	lumpectomy	(-)	(-)	NED, 48 m
21	Adeglbola	2005	F	60	1.7	T1N0M0	CDDP+VP16	SCC	(-)	–	lumpectomy	(-)	(-)	DOD,20 m
22	Adeglbola	2005	F	61	1.7	T1N1M0	CDDP+VP16	SCC	(-)	–	lumpectomy	(-)	(-)	AWM, 6 m
23	Stein	2005	F	54	2	T1N1M0	CDDP+VP16	SCC	NAC	SD	lumpectomy Mx	N.S.	N.S.	NED, 24 m
24	Salman	2006	F	50	5	T2NxM0	N.S.	–	NAC	N.S.	radical Mx	N.S.	N.S.	N.S.
25	Kitakata	2007	F	44	5	T2N1M0	EC→DTX	breast	(-)	–	modified radical Mx	(-)	(-)	NED, 22 m
26	Shaco-Levy	2007	F	28	2.5	T1N0M0	CDDP+VP16	SCC	(-)	–	lumpectomy+SLNB	(-)	(-)	NED, 10 m
27	Kinoshita	2008	F	31	4.1	T2N1M0	ADM+DTX	breast	NAC	PD	radical Mx	(-)	(-)	DOD,9 m
28	Rineer	2009	F	81	5	T4N1M0	CPT-11+CBDCA	SCC	NAC	PR	without surgery	(-)	(-)	AWM
29	Yamaguchi	2009	F	51	2.6	T2N0M0	PTX	breast	(-)	–	modified radical Mx	(-)	(-)	AWM, 12 m
30	Haji	2009	F	68	5.8	T3N1M0	DTX+EPI	breast	NAC	PR	modified radical Mx	(-)	(-)	DOD, 1 m
31	present case	2013	F	59	2.7	T2N1M0	CDDP+VP16→post op.EC	SCC, breast	NAC	PR	modified radical Mx	(-)	(-)	NED, 40 m

NAC: neoadjuvant chemotherapy, AC: doxorubicin+cyclophosphamide, FEC: 5-FU+epirubicin+cyclophosphamide, CMF: cyclophosphamide+methotrexate+5-FU, EC: epirubicin+cyclophosphamide, VP-16: etoposide, CDDP: cisplatin, CBDCA: carboplatin, DTX: docetaxel, PTX: paclitaxel, CPT-11: irinotecan, pCR: pathological complete response, PR: partial response, PD: progressive disease, Mx: mastectomy, SLNB: sentinel lymph node biopsy, DOD: dead of disease, NED: no evidence of disease, AWM: alive with metastasis, N.S.: not specified

Radiotherapy also appears to be effective in controlling the natural course of the disease either on its own or as an adjuvant therapy.[23, 26]

CONCLUSION

The best therapy for SCC of the breast is still very difficult to define since the number of reported cases and available clinical data are limited. There are no recommendations or guidelines for chemotherapy and radiotherapy for SCC of the breast. This lack of consensus is quite apparent on review of treatment schedules used in the reported cases. Although we consider neoadjuvant chemotherapy followed by radical surgery to be an acceptable treatment in advanced SCC of

the breast, the further accumulation of clinical data on this disease is an urgent task in order to establish a definitive treatment for it.

This patient was treated by radical surgery after neoadjuvant chemotherapy, followed by intensive chemotherapy. She is under follow-up and the long-term effect of the treatment regime is being monitored.

Conflict of Interest: None

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