Clinicopathological Examination of Metaplastic Spindle Cell Carcinoma of the Breast: Case Series

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ABSTRACT

BACKGROUND: Spindle cell carcinoma (SpCC) of the breast is a rare histological type, a subtype of metaplastic carcinoma characterized by atypical spindle cell and epithelial carcinoma. The proportions of the spindle cell and epithelial components vary among tumours. Due to its rarity, biological characteristics of this disease have been poorly studied.

METHODS: In total, 10 patients with SpCC were surgically treated at our institution from January 2007 to December 2018. We retrospectively investigated these SpCC cases, focusing on the differences between spindle cell and epithelial components. Microsatellite status was also examined.

RESULTS: Nine cases were triple-negative breast cancer (TNBC). The rates of high tumour grade were 70% in spindle cell components and 56% in epithelial components ($P = .65$), while the mean Ki67 labelling index were 63% and 58%, respectively ($P = .71$). Mean programmed death ligand 1 (PD-L1) expression in these components was 11% and 1%, respectively ($P = .20$). All 10 tumours were microsatellite stable. Patient outcomes of triple-negative SpCC did not differ from those of propensity-matched patients with conventional TNBC.

CONCLUSIONS: Spindle cell components showed higher values in factors examined, although there was no statistically significant difference. Our data reveal that these 2 components of SpCC may be of different biological nature.

KEYWORDS: Breast cancer, spindle cell carcinoma of the breast, metaplastic carcinoma, PD-L1

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Introduction

Spindle cell carcinoma (SpCC) of the breast is a rare histological type, categorized as a subtype in metaplastic carcinoma by the World Health Organization (WHO) classification of the tumour, 5th edition.[1] According to previous reports, it comprises 0.02% to 0.3% of all invasive breast carcinomas.[2,3] Spindle cell carcinoma is characterized by atypical spindle cells arranged in a multitude of architectural patterns and can be monophasic (pure) or biphasic (spindle cell and epithelial carcinomas). Spindle cell carcinoma is usually biphasic, but proportions of spindle cell and epithelial components vary among tumours. Hormone receptors and human epidermal growth factor receptor 2 (HER2) are often negative, thus leading to the denomination of triple-negative breast cancer (TNBC).[2,4,5] Patient outcomes with SpCC vary across previous reports.[2,4,6]

Due to the rarity of SpCC, the biological characteristics of this disease have been poorly studied. The heterogeneity of metaplastic carcinoma also makes investigations difficult. Since no specific systemic treatment for SpCC has been established in clinical practice, patients with SpCC are given the same treatment as for invasive ductal carcinoma.[2,5] We hypothesized that spindle cell and epithelial lesions differ biologically, such as in tumour grade and chemo-effect. Such differences have not well been investigated.[7,8] Therefore, we retrospectively investigated SpCC cases, focusing on the differences of spindle cell and epithelial components.

Methods

Clinical samples

In total, 10 patients with SpCC were surgically treated at our hospital from January 2007 to December 2018. Clinicopathological features were retrospectively assessed. In the analysis of patient outcomes, we used 283 TNBC patients as controls with infiltrating duct carcinoma NOS (not otherwise specified) who underwent curative surgery from 2007 to 2018. Clinicopathological features of the 283 patients are shown in Supplementary Table 1. The basic adjuvant chemotherapy regimen was 4 cycles of CE (C: cyclophosphamide 500 mg/m^2, E: epirubicin 75 or 100 mg/m^2) and taxane (4 cycles of docetaxel: 75 mg/m^2).

This study was carried out with approval from the ethics committee of our hospital (no: 19-289), and the research plan is presented on the homepage of our hospital. All patients were offered the choice to opt out of the study at any time.

Pathological examination and immunohistochemistry

Pathological examination was carried out for surgical specimens by 2 experienced pathologists at our hospital, based on the 5th edition of the WHO classification of tumours of the breast.[1] Tumour grade was judged based on the modified Bloom-Richardson histological grading system.[9] For patients who received neoadjuvant chemotherapy (NAC), treatment effects were evaluated from surgical specimens. In this study, we defined pathologic complete response as the disappearance of invasive nest based only on the primary breast tumour, that is, without lymph node evaluation.

Oestrogen receptor (ER) and progesterone receptor (PgR) status were assessed semiquantitatively with IHC and reported as positive when at least 1% of the nuclei of cancer cells showed staining. HER2 was considered positive if strong staining of the complete membrane in >10% of tumour cells was observed. Ki67 labelling index was determined from a hot spot chosen under 200× magnification and counting cells positive for nuclear Ki67. For programmed death ligand 1 (PD-L1), membrane staining of tumour cells was determined semiquantitatively in 10% increments, employing mAb SP142 (Spring Bioscience). PD-L1 on immune cells could not be assessed in this study because it was difficult to distinguish whether those immune cells belonged to spindle or epithelial components. Other antibodies used for immunohistochemistry (IHC) were anti-CK5/6 mAb D5/16 B15 (Dako), anti-AE1/3 mAb AE1/AE3 (Dako), and anti-p63 mAb DAK-p63 (Dako).

Microsatellite instability testing

DNA extraction and microsatellite instability (MSI) tests were conducted as previously described.[10] DNA was extracted from paraffin blocks of tissue sections from surgical specimens, without separating by spindle cell and epithelial components. Microsatellite instability testing was outsourced to TaKaRa Bio Inc. Using a Promega MSI Multiplex System, 5 spots from the DNA sequence for microsatellite markers (BAT-25, BAT-26, NR-21, NR-24, and MONO-27) were amplified, and MSI status was determined based on the revised Bethesda Guidelines.[11]

Statistical analysis

Statistical analyses were performed using JMP 14.2 statistical software (SAS Institute, Inc., Cary, NC, USA). To compare mean values, such as those for age, unpaired data were examined using the 2-sided Student *t*-test.

To assess the outcomes of patients with spindle carcinoma, we matched propensity scores. To calculate these, we selected age, pathological tumour size, lymph node metastasis, and treatment with (neo-)adjuvant chemotherapies, if applicable. For matching, 0.20 was employed as the calliper width, with logit transformation of the data. Kaplan-Meier curves were estimated and the log-rank test was applied for comparisons of the survival distributions of the 2 patient groups. Furthermore, hazard ratios and their 95% confidence intervals were estimated employing the Cox regression hazard model. A $P < .05$ was considered statistically significant.

Results

Clinical findings

Clinicopathological features of the 10 cases are presented in Table 1. All patients were Japanese females ranging in age from 47 to 86 years (median 64 years). Pathological state was as follows: stage I (6 cases), stage II (3 cases), and stage III (1 case). Nine cases had hormone-receptor-negative tumours, and the other case had a luminal HER2 tumour. Five cases received perioperative systemic chemotherapies, of which 4 cases received NAC. During the median 66-month follow-up period, 4 patients developed distant metastasis. Among them, 2 patients died due to breast cancer.

Immunohistochemical features of both spindle and epithelial components

The immunohistochemical features of all cases are presented in Table 2. The spindle cell component in the lesion varied from 30% to 100% where Case 7 only had a spindle component. The spindle cell component was positive for vimentin, mesenchymal marker, in 90% (9/10) of patients. In contrast, AE1/3, epithelial marker, was positive in all epithelial components (9/9), but some tumours were also AE1/3 positive in the spindle component. Comparisons in tumour grade, Ki67 labelling index and PD-L1 expression on tumour cells between spindle and epithelial components are shown in Figure 1. Seventy percent spindle lesions were high-grade tumours, while 56% of epithelial lesions were high grade ($P = .65$). The mean Ki67 labelling index was 63% (range: 30-100) in spindle lesions and 58% (range: 10-100) in epithelial lesions ($P = .71$). Mean PD-L1 expression on tumour cells reached 11% in spindle lesions and 1% in epithelial lesions ($P = .20$). Representative images of PD-L1 in both components are shown in Supplementary Figure 1. Spindle cell components showed higher values in all examined factors, but there was no statistically significant difference.

Changes in the proportion of spindle cell component during NAC

Next, we investigated 4 patients who received NAC. No patient had achieved pathologic complete response. We compared the proportion of spindle cell component between pre-NAC and post-NAC (Figure 2). In 3 cases, the proportions of spindle cell component in post-NAC were higher than those in pre-NAC ($P = .06$), while no case showed a decrease in proportion.

Table 1. Clinicopathological features of the 10 patients.

CASE	AGE	CSTAGE	PSTAGE	SUBTYPE	SYSTEMIC TREATMENT	DISTANT METASTASIS	OUTCOME	DFS (M)	OS (M)
1	49	T1cN0, IA	T1aN0, IA	TN	CT(A)[a]	Bone, pleura	Death	10	17
2	51	T1cN0, IA	T1bN0, IA	TN	None	None	Survival	75	75
3	76	T1cN0, IA	T1bN0, IA	TN	None	None	Survival	119	119
4	61	T2N0, IIA	T1cN0, IA	TN	None	None	Survival	47	47
5	64	T1cN0, IA	T1cN0, IA	TN	None	None	Survival	116	116
6	74	T2N0, IIA	T1cN0, IA	TN	CT(T)[a]	Lung, mediastinal LN	Survival	91	123
7	86	T2N0, IIA	T2N0, IIA	TN	None	None	Survival	42	42
8	65	T2N1, IIB	T2N2a, IIIA	TN	CT(A + T)	None	Survival	95	95
9	67	T4bN3a, IIIB	T3N0, IIB	TN	CT(A + T)[a]	Contralateral axillary LN	Death	4	7
10	47	T3N0, IIB	T2N0, IIA	Luminal-HER2	CT(A + T)[a], HT	Liver	Survival	55	57

Abbreviations: A, anthracycline; CT, chemotherapy; DFS, disease-free survival; HT, hormone therapy; LN, lymph node; m, months; OS, overall survival; T, taxane; TN, triple negative.
[a]Neoadjuvant chemotherapy.

Table 2. Immunohistochemical features of spindle and epithelial components.

CASE	1	2	3	4	5	6	7	8	9	10
Proportion of spindle/ epithelial components	60/40	50/50	70/30	90/10	30/70	80/20	100/0	80/20	90/10	60/40
Vimentin	+/–	+/–	+/–	+/+	+/–	–/–	+/n.e.	+/–	+/–	+/–
CK5/6	–/–	–/+	–/–	+/+	–/+	–/+	+/n.e.	–/+	–/–	–/–
AE1/3	+/+	+/+	–/+	–/+	–/+	+/+	+/n.e.	–/+	+/+	+/+
p63	–/–	–/–	–/–	–/–	–/+	–/–	+/n.e.	–/–	–/–	–/+
Tumour grade	3/3	3/2	3/3	3/3	2/2	3/3	2/n.e.	3/3	3/2	2/2
Ki-67 L.I.	70/70	90/100	30/30	70/80	50/70	90/10	50/n.e.	50/50	100/100	30/10
PD-L1 (TC)	0/0	70/10	10/0	0/0	10/0	0/0	0/n.e.	0/0	20/0	0/0

Abbreviations: L.I., labelling index; n.e., not evaluated; TC, tumour cell.

Comparisons in the proportion of components between primary and lymph node metastatic lesions

We further examined pathological findings of lymph node metastases in 2 cases. Case 8 had axillary lymph node metastasis and underwent axillary dissection with mastectomy for the primary lesion. The spindle component constituted 80% of the primary tumour, but axillary lymph node metastasis was composed of only epithelial component. Case 9 developed contralateral axillary lymph node metastasis, and core needle biopsy was performed. The patient's metastatic lymph node comprised only spindle component, while some epithelial component was observed in the primary tumour.

MSI status in SpCC

Finally, we examined MSI status. All 10 samples were microsatellite stable. All 5 microsatellite markers were negative in all cases.

Patient outcomes compared with usual TNBC

During the 66-month median follow-up period, 4 of the 10 patients developed distant metastases. Median disease-free survival (DFS) was 32.5 (4-91) months. Metastatic sites varied among patients, and included bone, pleura, lungs, and liver (Table 1). Two patients died due to breast cancer. Since 9 of the

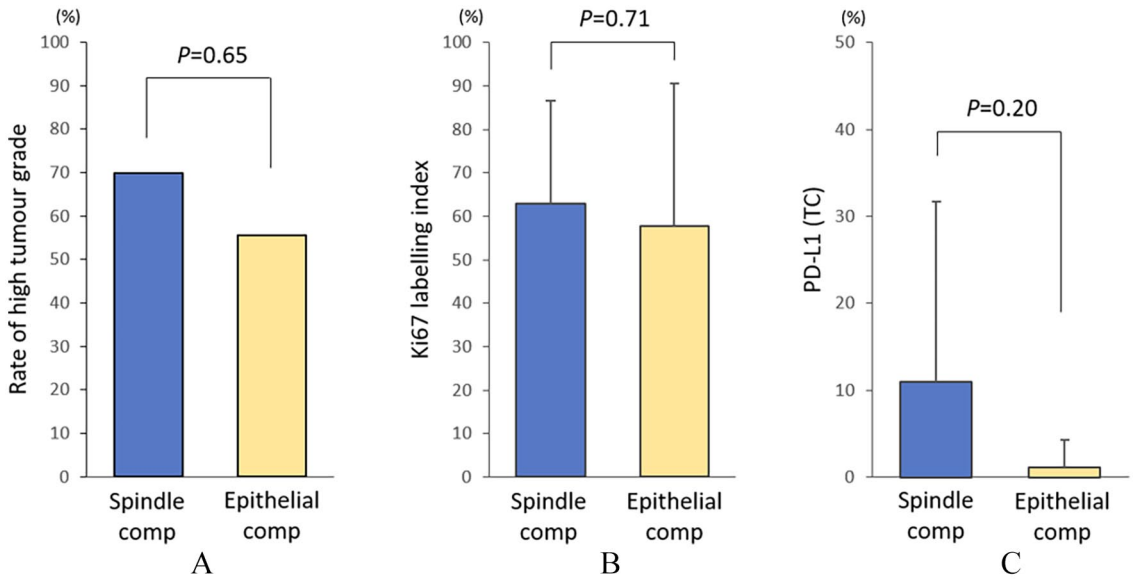

Figure 1. Comparison of spindle and epithelial components ($n = 10$). Comparisons of tumour grade (A), Ki67 labelling index (B), and PD-L1 (C) expression between spindle and epithelial components.

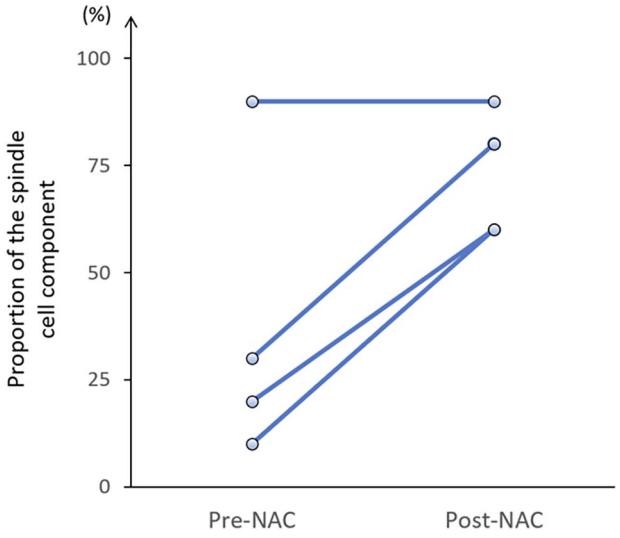

Figure 2. Changes in the proportion of the spindle cell component during neoadjuvant chemotherapy. Comparisons of the proportion of spindle cell component between pre-NAC and post-NAC.
NAC indicates neoadjuvant chemotherapy.

10 patients with *SpCC* were triple-negative, we compared these 9 patients with a control TNBC cohort comprising 283 TNBC patients with infiltrating duct carcinoma NOS, as described in the Methods section. Propensity score matching was conducted based on age, pathological tumour size, lymph node metastasis, and whether (neo-)adjuvant chemotherapies were being administered. Eighteen patients were matched in 9 pairs, and the clinicopathological features of these patients are shown in Supplementary Table 2. Of these 18 patients, 6 developed distant metastasis during the 61-month median follow-up period (range: 7-123 months). Supplementary Figure 2 shows Kaplan-Meier curves of DFS and overall survival (OS). There was no statistically significant difference between the *SpCC* and control TNBC groups ($P = .835$ and 1.000, respectively). Furthermore, the effect size and 95% confidence interval were estimated. As shown in Supplementary Table 3, the hazard ratios for both DFS and OS were close to 1.0, although the confidence interval was relatively wide due to small sample size (Figure 3).

Discussion

SpCC is frequently TNBC.[2,4,5] Nine of 10 cases in our cohort were TNBC, which was consistent with previous reports. The frequency of lymph metastasis is low in SpCC, potentially behaving similarly to sarcoma;[2] however, the frequency varied from 5% to 50% across reports. In our cohort, 3 patients (30%) had lymph node metastasis. Our findings from Case 9 indicate the epithelial components of SpCC do not necessarily metastasize, although the proportion of the 2 components in the primary tumour will vary between cases.

Metaplastic carcinoma is reported to have poor prognosis.[12-14,15] However, there are major limitations in the interpretation of these results. For instance, in analysis of data from the Surveillance, Epidemiology, and End Results (SEER) conducted by Nelson et al,[15] details of metaplastic carcinoma were not defined, and there were no data on whether patients received chemotherapy. Meanwhile, the prognosis in *SpCC* has been examined in some case series.[2,5,12] Khan et al and Carter et al observed distant metastasis in 63% and 46% in their cohorts, respectively, and they both concluded *SpCC* to be a highly aggressive histological type.[2,5] However, none of these studies employed a control group to compare patient outcomes. We compared patient outcomes with control TNBC cohort and found no statistical difference between these 2 groups, although our sample size was clearly not large enough to obtain conclusive evidence. The poor prognosis of

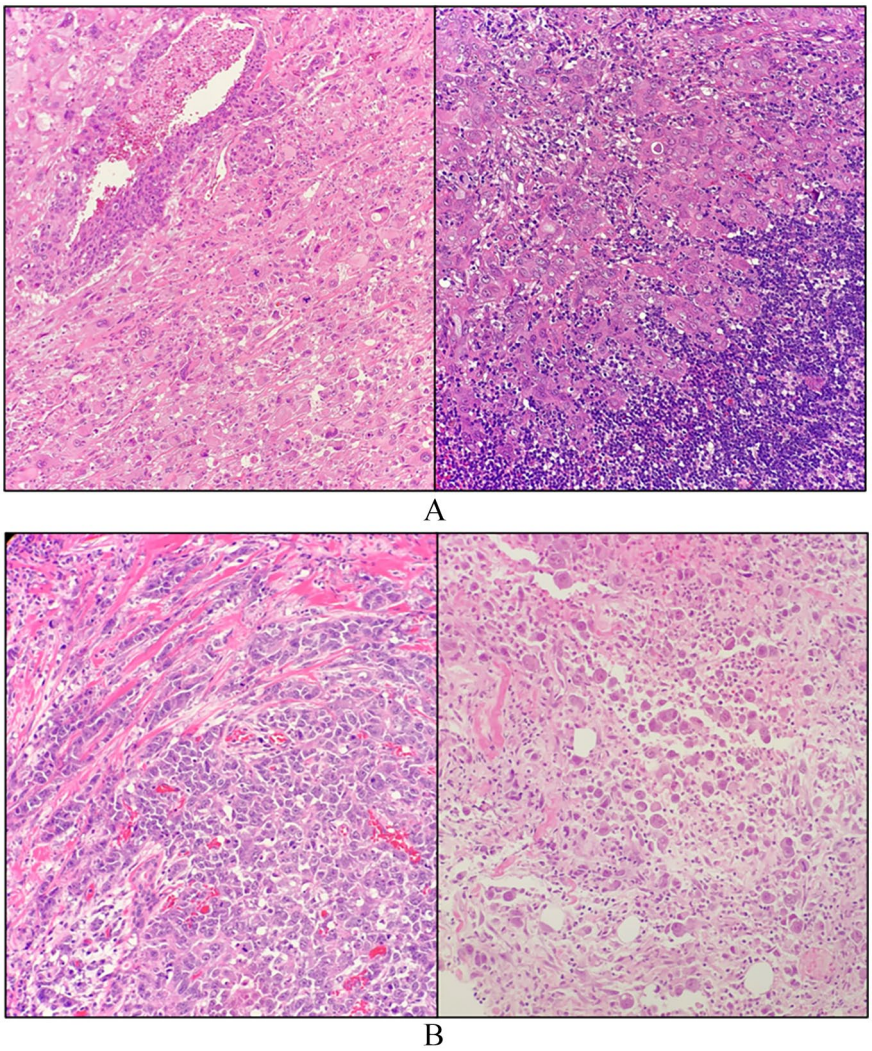

Figure 3. Comparison of histology of primary and lymph node metastasis. (A) In Case 8, 80% of the primary lesions consisted of spindle cell components (left), while lymph node metastasis was occupied only with epithelial components (right). (B) In Case 9, epithelial component was observed in 10% of primary tumours (left). On the contrary, only spindle cell component was seen in contralateral lymph node metastasis (right) (×200).

SpCC in previous reports might be due to a high proportion of TNBC in these cohorts, and we believe that this issue merits further investigations.

We compared tumour grade and Ki67 labelling index between spindle and epithelial components. Both were higher in the spindle component, suggesting the spindle cell component to be of more malignant nature. There were no statistical differences in our cohort, but it is obvious that the number of cases was too small for statistical comparison. This was a major limitation of this study, and it is necessary to conduct further studies employing more SpCC cases to draw conclusions.

Of the 4 patients who received NAC, including 3 TNBC patients, no case had achieved pathologic complete response. In most cases, the proportions of spindle cell component in post-NAC were higher than those in pre-NAC, although it must be kept in mind that the entire tumour could not be evaluated when biopsy specimens were assessed. Moreover, in Case 9 (who received NAC), the metastatic lymph node was composed only of spindle cell component. Taken together, our data indicate that the spindle cell component is more resistant to chemotherapy.

We further investigated MSI status and PD-L1 protein expression to explore potential targets for immune checkpoint inhibitors (ICIs) in SpCC. All 10 cases were microsatellite stable, although we could not evaluate MSI status within each component. Both breast cancer and soft tissue sarcoma have few high-MSI tumours.[10,16] Some case series of SpCC revealed a very low frequency of high MSI.[17-19] Taken together, it seems that high-MSI tumours cannot be expected in SpCC. As Latham et al[20] suggested, MSI status in breast cancer may largely depend on the presence of Lynch syndrome. As to PD-L1, recent reports revealed frequent overexpression of PD-L1 in metaplastic breast carcinoma.[17,21] Recently, ICIs have been approved for patients with PD-L1-positive metastatic TNBC. Notably, some reports of metaplastic breast cancer showed a good response to ICI.[22,23] We revealed that the spindle cell component tends to have higher PD-L1 expression

than the epithelial component, though we could not determine whether the former is more susceptible to ICI.

A number of molecular pathological studies have investigated the cell of origin of metaplastic carcinoma and the genomic relationship with co-existing epithelial cancer components. Major findings of these reports consistently indicate that both the sarcomatous and epithelial components are evolved from a single common stem cell and the sarcomatous component is assumed to be secondarily derived from the preceding cancer, in agreement with the so-called combination tumour theory.[24-28] A recent study, which employed whole-exome sequencing, also indicated monoclonality of *SpCC* with an adjacent epithelial carcinoma component.[29] However, either component can be subject to genetic progression, thus it may not be possible to determine which component is responsible for tumour behaviour.

In conclusion, our data reveal a possibility that the spindle cell component and epithelial component of SpCC may be of different biological nature and that assessment of each component might merit further investigation to better understand this disease.

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Author Contributions

Y.I. and Y.H. designed the study. Y.I., Y.H., and K.N. provided clinical information. Y.H. and A.A. performed pathological assessment. Y.I. and Y.H. analysed the data. Y.I. and Y.H. wrote the paper. M.S. reviewed and revised.

Ethical Approval and Consent to Participate

This study was carried out with approval from the ethics committee of our hospital (no: 19-289). All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent from participants were obtained in an opt-out manner. The research plan is presented on the homepage of our hospital and all patients were offered the choice to opt-out of the study at any time.

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Supplemental Material

Supplemental material for this article is available online.

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