

## Original Article

# Fine needle aspiration cytology of signet ring cells in breast carcinoma: a cytohistological study of 11 cases

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**Abstract:** Signet ring cell (SRC) carcinoma is a unique subtype of adenocarcinoma; however, the clinicopathological profiles of SRCs in breast carcinoma are yet to be determined. Here, we investigated cyto-histological findings of 11 breast carcinoma cases with SRCs comprising more than 20% of the tumor cells; invasive ductal carcinoma (IDC) (n=4), invasive lobular carcinoma (ILC) (n=4), pleomorphic lobular carcinoma (PLC) (n=1), and mucinous carcinoma (MC) (n=2). The mean age of the patients was  $60.2 \pm 13$  years, and the mean tumor size was  $2.0 \pm 0.8$  cm. Three cases of IDC, 1 PLC, and 1 of MC had grade 2 or 3 nuclear atypia, whereas 1 case of IDC, 4 of ILC, and 1 of MC had grade 1 nuclear atypia. Axillary lymph nodes were positive for metastatic carcinoma in 1 patient with IDC and 1 with ILC. In fine needle aspiration smears, intracytoplasmic lumen (ICL) type SRCs were found to be major constituents of SRCs in ILC and PLC, while non-ICL type SRCs were predominant in IDC. MC tumors had SRCs of both ICL and non-ICL types. During our follow-up period ranging from 97 to 3650 (mean  $1458 \pm 1055$ ) days, all the patients were alive without recurrence of the tumor. Our results indicate that the nature of SRCs may vary with the histological subtype of breast cancer, but its presence may not indicate poor prognosis. A large study with more cases of breast cancer with SRCs for a longer period may be needed to determine the clinical significance of SRCs.

**Keywords:** Signet ring cells, breast cancer, fine needle aspiration, cytology

## Introduction

Signet ring cell (SRC) carcinoma is a unique subtype of mucin-producing adenocarcinoma arising in various organs such as the stomach, colon, lungs, and prostate gland [1-4]. The presence of SRCs in breast cancer was first reported by Saphir more than half a century ago [5]. Steinbrecher et al later described 5 cases of SRC breast carcinoma as an uncommon type of breast cancer characterized by the presence of cells containing intracellular mucin without large amounts of extra-cellular mucin, clinically and pathologically distinct from breast mucinous carcinoma (MC) [6]. Hull et al found that breast cancer with SRCs comprised about 4.5% of all the breast tumors; however, breast cancers purely composed of SRCs are extremely rare [7-9]. In 2012, World Health Organization has included a section on 'carcinomas with SRC differentiation' in the chapter on MC; how-

ever, it remains undetermined whether breast carcinoma with SRCs should represent a distinct disease entity [10].

Histological characteristics of breast carcinoma with SRCs have been elusive because of conflicting results from earlier studies. Some have demonstrated that breast tumors with SRCs are generally invasive lobular carcinomas (ILC) [11, 12]. By contrast, a recent study by Kelten et al on 10 cases of breast carcinoma with SRCs revealed that 7 cases were invasive ductal carcinoma (IDC), 2 were ILC, and the remaining was a mixture of IDC and ILC [13]. Two previous studies found that the presence of SRCs has been noted with similar frequency in IDC and ILC [14, 15]. Regardless of the origin, breast carcinoma with SRCs behaves more aggressively than other breast cancers without SRCs [7, 11, 12]. Therefore, it is crucial to identify the presence of SRCs during histological

**Table 1.** Clinicopathological profiles of 11 patients with breast carcinoma with signet ring cells

Case	Age (years)	Dx	Side	Size (cm)	SRC (%)	NG	ly	v	N	M	FU (days)
1	48	IDC	R	1.7	80	2	-	-	-	-	97
2	57	IDC	R	1.8	20	3	+	+	+	-	3650
3	72	IDC	R	2.8	20	2	-	-	-	-	2020
4	74	IDC	R	2.2	40	1	+	-	-	-	901
5	85	ILC	L	3.5	40	1	+	+	-	-	1514
6	47	ILC	L	2.8	60	1	+	-	+	-	2153
7	52	ILC	R	1	30	1	+	-	-	-	365
8	57	ILC	R	1.8	20	1	+	-	-	-	2218
9	39	PLC	R	1.2	20	3	-	-	-	-	407
10	68	MC	R	2.5	40	2	-	-	-	-	473
11	63	MC	R	0.7	60	1	-	-	-	-	2250

Abbreviations: Dx, histological diagnosis; SRC, signet ring cell; NG, nuclear grade; ly, lymphatic invasion; v, venous invasion; N, lymph node metastasis; M, distant metastasis; FU, follow-up period; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; PLC, pleomorphic lobular carcinoma; MC, mucinous carcinoma.

diagnosis of breast cancers. Accordingly, it is important to recognize SRCs in fine needle aspiration (FNA) cytology smears as well, which is usually performed prior to surgical resection of the breast tumor.

In the present study, we investigated the clinicopathological features of breast carcinomas with SRCs. The SRCs were classified into intra-cytoplasmic lumen (ICL) type and non-ICL type according to the definition described previously [10, 16]. We also retrospectively reviewed FNA findings of each case to describe cytomorphological characteristics of breast carcinoma with SRCs.

## Materials and methods

### Case selection

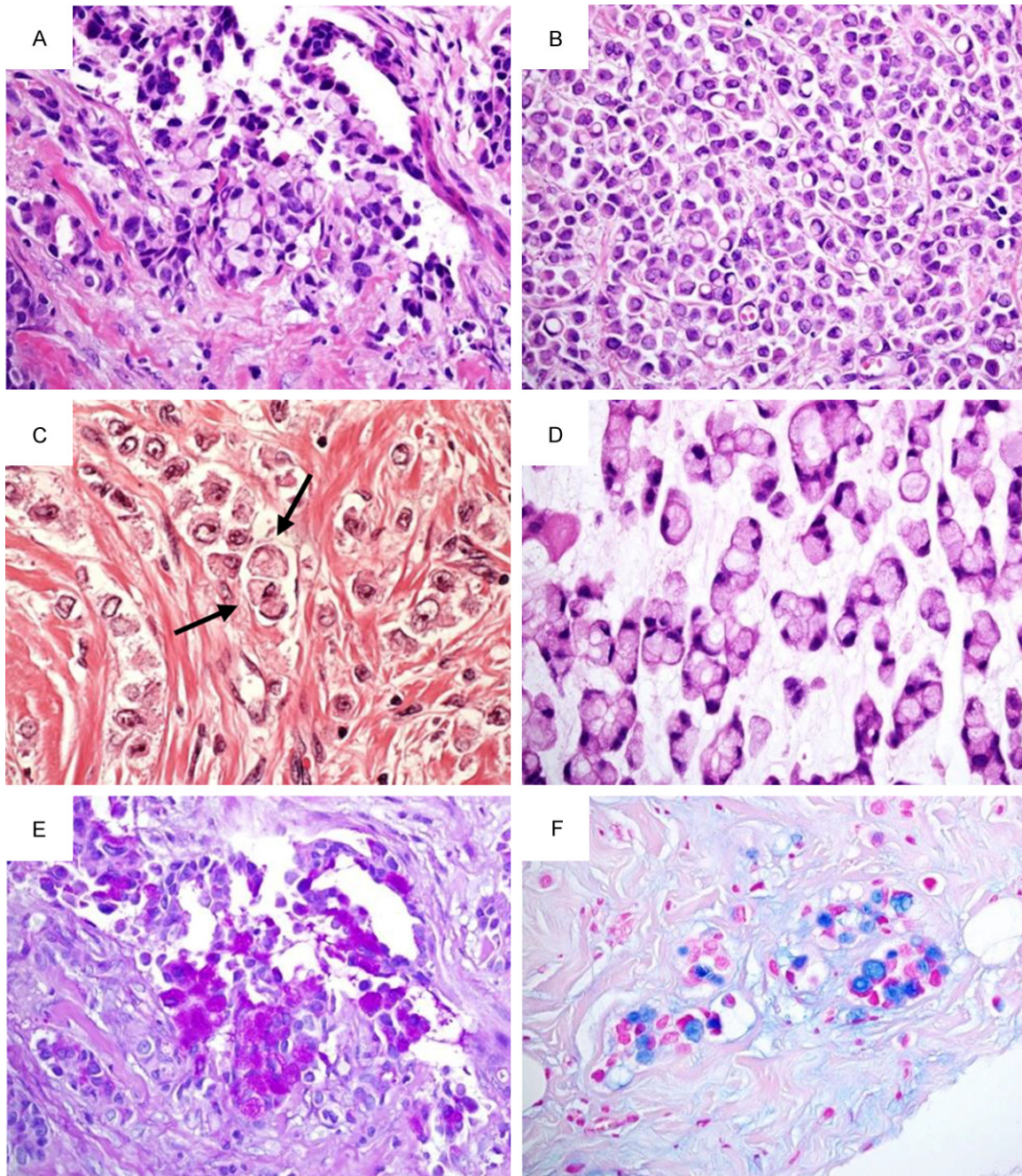
We searched the archives at the Department of Diagnostic Pathology, Nippon Medical School Hospital (Tokyo, Japan) between January 2004 and August 2013. We found 25 cases with "SRC" in the diagnostic lines and/or histological description. Patients with tumors in the breast metastasized from primary carcinomas in other organs (gastrointestinal system or lung) were excluded. We chose 11 cases that had undergone FNA cytology examination before excisional biopsy or operation. We reviewed all the histological sections of each case to confirm that at least 20% of the tumor

cells consisted of SRCs, based on a previous report that stated that the presence of SRCs accounting for more than 20% of the tumor should have clinical significance [11]. FNA cytology was performed by a number of experienced surgeons by using a 20-gauge needle attached to a 20 mL syringe. Clinical data were extracted and reviewed from medical charts and pathology reports. This study was conducted in accordance with the principles embodied in the Declaration of Helsinki and informed consent was obtained from each patient for the use of their tissues samples.

### Special and immunohistochemical stainings

Specimens were smeared on glass slides and immediately fixed with solution containing 95% ethanol. Subsequently, the cytological slides were stained according to the routine Papanicolaou method. Formalin-fixed histological sections of the tumors were stained with alcian blue (AB) (pH 2.5) and periodic acid-Schiff (PAS) to reveal both acidic (blue) and neutral (red) mucins [17]. Immunohistochemical staining was performed with primary antibodies by using the standard avidin-biotin-peroxidase complex technique. The following antibodies were used: E-cadherin (NCH-38, dilution 1:50; DAKO, Denmark), GCD-FP-15 (NCL-GCDFP15, dilution 1:20; Novocastra Laboratories, UK), monoclonal rabbit anti-human estrogen receptor (ER) (SP1, dilution 1:1; Ventana Medical Systems, USA), monoclonal rabbit anti-human progesterone receptor (PgR) (1E2, dilution 1:1; Ventana Medical Systems), monoclonal rabbit anti-human HER2/neu (4B5, dilution 1:1; Ventana Medical Systems), monoclonal mouse anti-human Ki67 (M7240, dilution 1:100; DAKO, Denmark), polyclonal rabbit anti-human chromogranin A (A0430, dilution 1:100; DAKO, Denmark) and monoclonal mouse anti-human synaptophysin (NCL-SYNAP-299, dilution 1:100; Novocastra, UK). Positive and negative controls for each antibody were used. Positivity for ER and PgR was graded according to the guidelines established at the St Gallen Consensus Conference [18]. Briefly, ER and PgR status should be judged as positive (+) if any positive cells are detected within the tumor. Assessment of





**Figure 1.** Signet ring cells (SRCs) of invasive ductal carcinoma (IDC) (A), invasive lobular carcinoma (ILC) (B), pleomorphic lobular carcinoma (PLC) (C, arrows), and mucinous carcinoma (MC) (D). The tumor cells of IDC and MC are cohesive and form clusters, whereas those of ILC and PLC are relatively dispersed with less cohesiveness. The entire cytoplasm of SRCs of IDC (case 1) stained positive for periodic acid-Schiff (E), and the intracytoplasmic lumen (ICL) of SRCs in ILC (case 5) specifically stained positive for alcian blue (F). Hematoxylin and eosin staining (A-D). Original magnification  $\times 600$  (A-F).

HER2 follows the guidelines defined by American Society of Clinical Oncology/College of American Pathologists [19]. Positivity for PAS, AB, and other immunohistochemical staining was expressed as negative (-), mild (+), moderate (++) , or strong (+++).

#### Review of FNA cytology smears

We examined FNA smears to assess the morphological features of SRCs. An SRC was defined as a cell with a single large vacuole within the cytoplasm. We further classified

**Table 2.** AB and PAS stainings, and immunohistochemical profiles

Case	ER	PgR	HER2	Ki67 (%)	PAS	AB	GCDFP15	CGA	SYN
1	-	-	-	5	+++	++	++	-	-
2	+	+	-	15	++	+	+	-	-
3	-	-	+	10	++	+	+++	-	-
4	+	-	-	5	+++	++	-	-	-
5	+	+	-	10	+	++	-	-	-
6	+	+	-	10	+	+++	+	-	-
7	+	+	-	5	+	++	+++	-	-
8	+	+	-	10	+	++	+	-	-
9	-	-	-	20	+	+	+++	-	-
10	+	-	-	5	+++	+++	-	++	-
11	-	-	-	10	+++	+++	++	-	-

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; PAS, Periodic acid-Schiff; AB, alcian blue; GCDFP, gross cystic disease fluid protein; CGA, chromogranin A; SYN, synaptophysin.

SRCs into ICL type and non-ICL type based on the definition described previously [10, 16]. Specifically, ICL type SRCs are characterized by a “target” appearance owing to the presence of a large ICL containing PAS or AB positive globules. Non-ICL type SRCs contain acidic muco-substance that diffusely fills the cytoplasm and dislodges the nucleus to one pole of the cell, as seen in gastric carcinoma. The presence of ICL or non-ICL type SRCs was recorded as present (+) or absent (-). Cells with multiple vacuoles or bubbles were excluded since degenerative cells can also resemble SRCs. The smears were also evaluated for the following cytomorphological features: cellularity-low (+), moderate (++), or high (+++); nuclear size-small (+), moderate (++), or large (+++); nuclear atypia-mild (+), moderate (++), or severe (+++); chromatin-fine (+) or coarse (++); nucleolus-distinct (+) or indistinct (-); nuclear pleomorphism-mild (+), moderate (++), or severe (+++); background necrosis-present (+) or absent (-); and discohesiveness-mild (+), moderate (++), or severe (+++). The size of nucleus was determined in comparison with that of red blood cells (RBC) as mild: less than 2 × RBC, moderate: 2-3 × RBC, and large: greater than 3 × RBC as described elsewhere [20]. A review of the cytological diagnosis and cytohistological specimens was performed by two pathologists (R.O and T.S).

## Results

### *Clinicopathological profiles of breast carcinoma with SRCs*

**Table 1** summarizes patient and tumor characteristics of 11 patients with breast cancer with SRCs. The diagnosis of lobular carcinoma was confirmed by detecting the loss of E-cadherin expression. Histological variants of the tumors consisted of IDC of no special type (n=4), ILC (n=4), pleomorphic lobular carcinoma (PLC) (n=1), and MC (n=2) (**Figure 1A-D**). The patients' age ranged from 39 to 85 (mean 60.2 ± 13) years. The tumor size ranged from 0.7 to 3.5 (mean 2.0 ± 0.8) cm. Three cases of IDC, 1 PLC and 1 of MC had grade 2 or 3 nuclear atypia, whereas 1 case of IDC, 4 of ILC, and 1 of MC had grade 1 nuclear atypia. Lymphovascular invasion was observed in 2 patients with IDC, 4 with ILC patients, and in none with PLC and MC. Axillary lymph nodes were positive for metastatic carcinoma in 1 patient with IDC and in 1 with ILC. None exhibited distant metastatic carcinoma in other organs. During the clinical follow-up period that ranged from 97 to 3650 (mean 1458 ± 1055) days, all the patients stayed alive, with no recurrence of the tumors.

### *AB, PAS, and immunohistochemical stainings*

**Table 2** summarizes special staining and immunohistochemical profiles of 11 patients with breast cancer with SRCs. As for the hormonal status of the tumor cells, 1 patient with IDC, 1 with PLC and 1 with MC showed a triple negative phenotype, 1 patient with IDC showed HER2 type, and all the others showed type A. SRCs of all the cases showed positive PAS staining with predominance in IDC cases (**Figure 1E**). By contrast, AB staining was more conspicuous in SRCs of ILC compared with those of IDC (**Figure 1F**). SRCs of PLC and MC displayed similar staining intensity for PAS and AB. GCDFP-15 expression was focally or diffusely identified in 3 patients with IDC, 3 with ILC, 1 with PLC, and in 1 with MC. Chromogranin A was focally positive in SRCs of 1 patient with MC, but none showed significant expression of synaptophysin.



**Table 3.** Cytomorphology of fine needle aspiration cytological samples

Case	SRC type		Cellularity	Nuclear size	Atypia	Chromatin	Nucleous	Pleomorphism	Necrosis	Discohesiveness
	ICL	Non-ICL								
1	+	+	++	++	+++	++	-	+	-	+
2	-	+	++	++	++	+	-	+	-	++
3	-	+	+	++	++	++	-	++	-	++
4	+	-	++	++	++	++	-	+	-	++
5	+	-	+++	++	+	+	+	+	-	+++
6	+	+	+++	++	+	+	-	+	-	++
7	+	-	+++	++	+	+	+	+	-	++
8	+	-	+++	+	+	+	+	+	-	+++
9	+	-	++	+++	+++	+	+	+++	+	+++
10	+	+	+++	+++	++	++	-	++	-	+++
11	+	+	++	+++	++	++	-	+	-	+++

Abbreviations: SRC, signet ring cell; ICL, intracytoplasmic lumen.

#### Review of FNA cytology reports and detailed characteristics of FNA smears

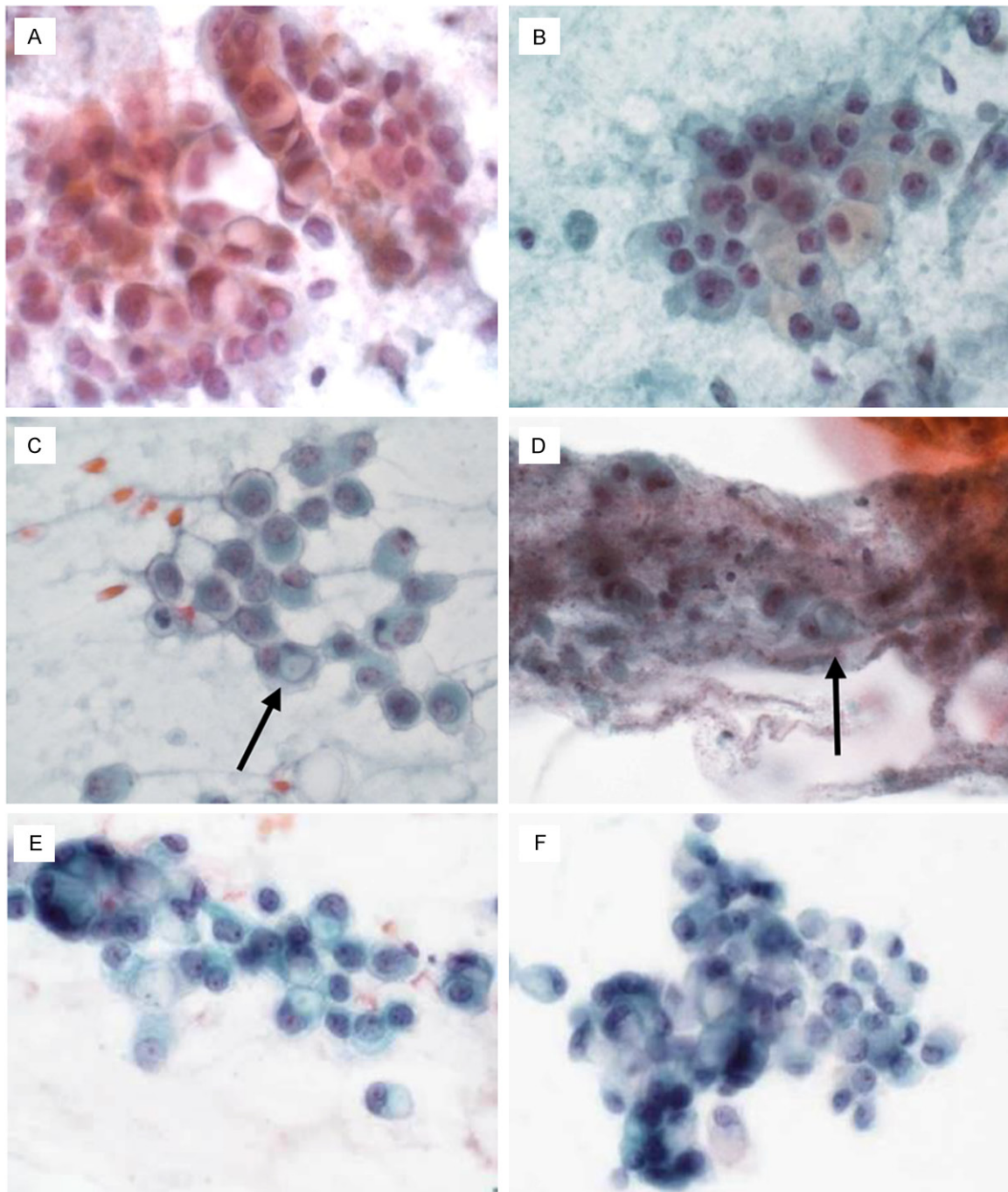
**Table 3** summarizes cytological findings of the FNA smears. ICL type SRCs were seen in all the ILC and PLC cases, and in 2 of the 4 IDC cases (**Figure 2A-E**). Non-ICL type SRCs were present in 3 IDC cases, but were identified in only 1 ILC case, and were absent in the PLC case (**Figure 2B, 2F**). MC cases had both ICL and non-ICL type SRCs. These findings suggest that ICL type SRCs are more commonly seen in ILC than in IDC, consistent with the findings of a previous report [16]. All the patients showed moderate or high degree of cellularity, except for one patient with IDC who showed low cellularity. Nuclear size was moderate in all IDC cases, large in all MC and PLC cases, and mild to moderate in ILC cases. Nuclear atypia was severe in 1 IDC and 1 PLC cases, moderate in 3 IDC and 2 MC cases, and mild in all ILC cases. Fine chromatin was seen in all ILC cases, while coarse chromatin was predominant in the other cases. Nucleolus was distinct in 3 ILC cases and 1 PLC case, and indistinct in the other cases. Pleomorphism was severe in the PLC case, and moderate in 1 IDC case and 1 MC case, and mild in all the other cases. Necrosis was identified only in the background of PLC case. Discohesiveness was severe in all MC cases and 2 ILC cases, and either mild or moderate in the other cases.

#### Discussion

SRCs are one of the morphological findings commonly encountered in the aspirates of the breast tumors, defined as cells containing intra-

cytoplasmic vacuoles inducing peripheral displacement and indentation of nuclei. Other studies revealed that SRCs contain secretory products, such as mucin, as seen in adenocarcinoma in other organs [21]. Despite the recognition of SRCs in breast tumors, the origin of SRCs has been a matter of debate over the last few decades. Previous studies have found that a vast majority of SRCs in the breast cancer originate from ILC [11, 12]. Contrary to these reports, other studies have revealed that the presence of SRCs has been noted with similar frequency in IDC and ILC in the histological specimens, suggesting that the presence of SRCs does not necessarily predominate in ILC [14, 15]. We assume that the above-mentioned differences in the presence of SRCs may be due to the different definition of SRCs used by each study. To delineate the cytological features of SRCs, Kamiya et al subgrouped SRCs into ICL type and non-ICL type cells [16]. ICL type cells had large ICL with a varying amount of mucin, while non-ICL cells had wide amorphous cytoplasm diffusely dispersed with mucin. In the present study, we chose SRCs based on the criteria put forth by Kamiya et al and found 4 cases of IDC and 4 cases of ILC, suggestive of no significant difference in the frequency of SRC presence in IDC and ILC. However, given that IDC and ILC account for 80% and 15%, respectively, of the breast carcinomas treated at our institution, it is difficult to estimate the percentage of SRCs contained in ILC and IDC.

A notable finding in our study is the case of PLC with SRCs. The PLC was first described by Dixon et al [22]. It exhibits the infiltrating patterns of



**Figure 2.** Cytomorphology of signet ring cells (SRCs) in invasive ductal carcinoma (A, B), invasive lobular carcinoma (C, arrow), pleomorphic lobular carcinoma (D, arrow), and mucinous carcinoma (E, F) identified in fine needle aspiration biopsy smears. SRCs were categorized into intracytoplasmic lumen (ICL) type (A, C-E) and non-ICL type (B and F). ICL type SRCs are characterized by a “target” appearance because of the large ICL. Non-ICL type SRCs have an acidic muco-substance that diffusely fills the entire cytoplasm and displaces the nucleus to one edge of the cell, as seen in gastric carcinoma. Papanicolaou staining (A-F). Original magnification  $\times 600$  (A-F).

classic ILC with pleomorphic nuclei and often shows aggregation of tumor cells. Compared with the FNA smears of conventional ILC, those

of PLC are more cellular, with 2 or 3 times larger nuclei, showing irregular contours, prominent nucleoli, hyperchromasia, and high mitotic

activity [23-25]. These cytological features often overlap with those of IDC, resulting in erroneous diagnoses [26]. Clinically, patients with PLC tend to have a poor prognosis, explained by the advanced stage at presentation, and they are more likely to develop distant metastasis and recurrence than those with the classical form of ILC [27, 28]. In our case of PLC, irregular contours, prominent nucleoli, and hyperchromasia were noted, as reported previously. In addition to these features, our PLC case presented with SRCs. To our knowledge, there are only a few reports of the presence of SRCs in PLC; thus, the presence of SRCs in PLC remains under-recognized [29, 30]. Our study indicates that PLC should be included in the differential diagnoses when SRCs are identified in FNA smears.

Regardless of the primary organs affected, carcinomas with SRCs tend to have an aggressive clinical course due to frequent metastasis to lymph nodes [1-4]. However, the prognosis of breast carcinoma with SRCs varies depending on the study, probably because the diagnostic criteria for SRC carcinoma have not been strictly defined. Merino et al demonstrated that ILC in which SRCs account for more than 20% of the tumor cells showed a poor prognosis: 60% of the patients died within 7 years, and some of them exhibited unusual metastatic pattern, with a propensity to involve serosal surfaces of gastrointestinal tracts [11]. Frost et al showed that the presence of 10% or more SRCs represents a poor individual prognostic factor in patients with ILC due to frequent recurrence or distant metastasis [21]. In our study, only 2 of the 11 patients evaluated showed lymph node metastasis even though SRCs accounted for more than 20% of tumor cells in all the patients. Based on our results, we are unable to conclude that the presence of SRCs could be an adverse prognostic factor for breast cancer. A study evaluating a higher number of SRC cases, with a longer follow-up period, is needed to determine the clinical significance of SRCs in breast cancer.

In our study, 2 cases exhibited histological features of MC. One may argue that these cases should not be considered as carcinoma with SRCs, as some studies have suggested that carcinoma with SRCs should be distinguished from MC [6, 31]. In contrast, Kuroda et al pro-

pose that there should be a distinct type of MC characterized by the presence of SRCs, apart from MC lacking the presence of SRCs [32]. Although it remains controversial how these cases should be categorized, further studies using a larger number of similar cases with correlations to clinical profiles are needed to clarify the clinical significance of SRCs in MC.

In summary, we examined the clinicopathological features of 11 cases with breast carcinoma containing SRCs, consisting of 4 cases of IDC, 4 of ILC, 1 of PLC and 2 of MC. In FNA smears, while ICL type SRCs were predominant in ILC, non-ICL type SRCs were conspicuous in IDC. MC showed SRCs of both ICL and non-ICL types. During our follow-up period, no patient exhibited clinical signs of recurrence. We assume that the nature of the SRCs may differ depending on the histological subtype of breast cancer; however, their clinical significance remained undetermined.

## Disclosure of conflict of interest

None.

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