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ORIGINAL ARTICLE

A clinico-pathological study on cancer in sclerosing adenosis

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Abstract
Background Cancer in sclerosing adenosis includes the following 2 types: cancer genuinely arising from sclerosing adenosis and cancer arising near a sclerosing adenosis lesion and infiltrating into it. This study aimed to elucidate the features of the former by comparing both types.
Methods This study included 28 lesions in 27 cases of cancer in sclerosing adenosis for which surgery was performed during a 2-year period from January 2006 at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. We determined the proportions of cancer in sclerosing adenosis relative to the overall lesion of ductal carcinoma in situ. They were compared for 13 clinico-pathological factors by dividing the lesions into 2 groups: those involving cancer in 50 % or more (cancer in sclerosing adenosis predominant type—inner type) and those involving cancer in less than 50 % (cancer out of sclerosing adenosis predominant type—outer type).
Results There were 20 lesions (71 %) of the inner type and 8 lesions (29 %) of the outer type. The comparison between the 2 types revealed significant differences in the following 3 factors. Bilateral breast cancer was observed in 5 cases (26 %) of the inner type and in none (0 %) of the outer type, indicating that there were significantly more cases of bilateral breast cancer for the inner type ($p = 0.04$). Regarding the subtypes of ductal carcinoma in situ, there were significantly more cases of the non-comedo type for the inner type ($p = 0.002$). Significantly fewer cases were positive for human epidermal growth factor receptor type 2 (HER2) for the inner type ($p = 0.007$).
Conclusion The results of this study suggest that cancer genuinely arising in sclerosing adenosis may often have biological features of bilateral breast cancer, non-comedo type in subtype, and being negative for HER2.

Keywords Cancer in sclerosing adenosis · Bilateral breast cancer · Non-comedo type · HER2

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Introduction

In the mammary gland, the peculiar pathological conditions of cancer arising within a benign lesion are cancer in fibroadenoma [1–3], cancer in intraductal papilloma [4–6], and cancer in sclerosing adenosis [7–17]. Although they are all rare pathological conditions, the number of cases of cancer in sclerosing adenosis has recently been increasing.

Cancer in sclerosing adenosis includes the following 2 types: cancer genuinely arising from sclerosing adenosis and cancer arising near a sclerosing adenosis lesion and infiltrating into it. Although cancer similarly exists in a sclerosing adenosis lesion in these 2 types, they may differ

in biological conditions. This study compared these types to elucidate the features of cancer genuinely arising in sclerosing adenosis.

Materials and methods

At the Cancer Institute Hospital of Japanese Foundation for Cancer Research, surgery was performed for 2,042 lesions in 1,990 breast cancer cases during a 2-year period from January 2006 to December 2007. After excluding 331 lesions in 321 cases in which preoperative chemotherapy was performed, this study included 28 lesions (1.6 %) in 27 cases (1.6 %) of cancer in sclerosing adenosis (Figs. 1, 2) selected from 1,711 lesions in 1,669 cases.

In these 28 lesions, we determined the proportions of cancer in sclerosing adenosis relative to the overall lesion of ductal carcinoma in situ. Then, the lesions were divided into 2 groups: those involving cancer in sclerosing adenosis in 50 % or more (cancer in sclerosing adenosis predominant type) and those involving cancer in less than 50 % (cancer out of sclerosing adenosis predominant type). In this article, for the sake of convenience, the former was considered as the inner type, and the latter as the outer type (Fig. 3). These 2 types were compared for the following 13 clinico-pathological factors: age, presence or absence of bilateral breast cancer, past history of other cancer, family history of breast cancer and other cancer, factors leading to detection, and remarks from mammography.

For the pathological factors, pathological features and protein expression were examined. The pathological features were the presence or absence of invasion, subtypes of ductal carcinoma in situ, apocrine metaplasia, and a concomitant radial sclerosing lesion based on hematoxylin–eosin (HE) staining. Regarding protein expression, representative blocks of cancer in sclerosing adenosis were immunohistologically examined for the expression of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor type2 (HER2). Representative blocks were stained with ER (Dako monoclonal mouse anti-human estrogen receptor α 1D5), PgR (Dako monoclonal mouse anti-human progesterone receptor 636), and HER2 (Dako HercepTest™), according to the manufacturer's manuals. A lesion was determined to be positive for ER or PgR if positive cells accounted for 10 % or more of cancer cells [18, 19]. According to the criteria of the American Society of Clinical Oncology/College of American Pathologists [20], a lesion with 0–2+ was determined to be negative for HER2, and that with 3+ to be positive.

JMP® Statistical Discovery Software was used for statistical analysis. χ^2 test was performed for analysis. $p < 0.05$ was considered significant.

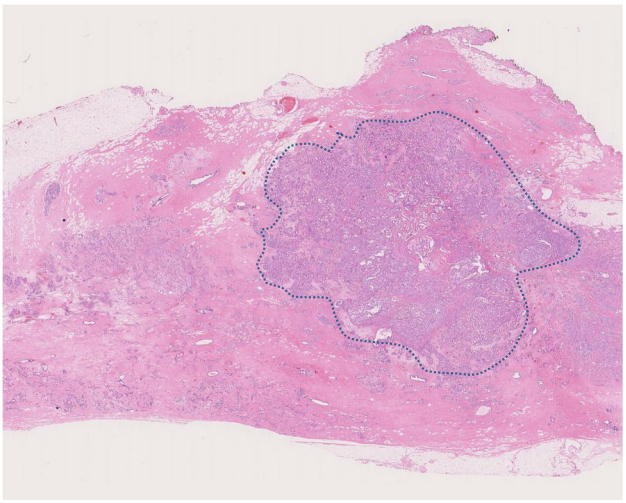

Fig. 1 Cancer in sclerosing adenosis; sclerosing adenosis has spread to the entire mammary gland. Outstanding ducts affected by cancer in sclerosing adenosis are observed inside the *dots*, in the mammary gland in the center of sclerosing adenosis (H&E staining, low magnification)

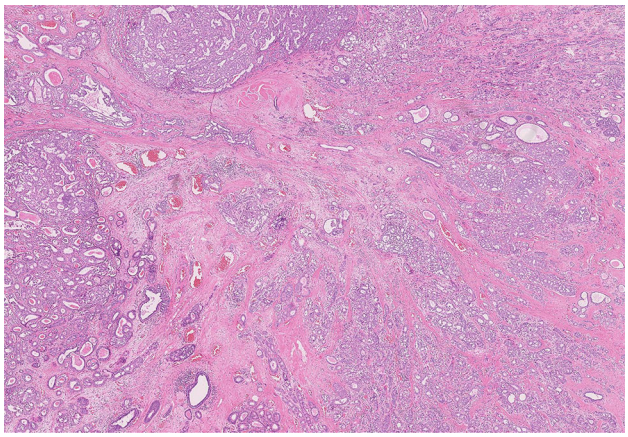

Fig. 2 Cancer in sclerosing adenosis; the outstanding mammary gland in Fig. 1 is magnified. The *right* of the image shows sclerosing adenosis, and the *left* of the image shows ductal carcinoma in situ in sclerosing adenosis (H&E staining, high magnification)

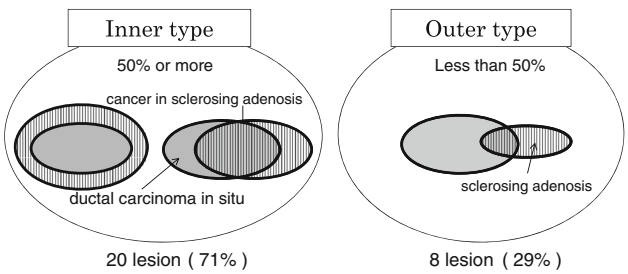

Fig. 3 Topography; image shows the relationship between ductal carcinoma in situ and sclerosing adenosis. *Stripes* show sclerosing adenosis, *gray area* shows ductal carcinoma in situ, and *striped gray area* shows cancer in sclerosing adenosis. *Inner type*, i.e., those involving cancer in 50 % or more in sclerosing adenosis relative to the overall lesion of ductal carcinoma in situ; *outer type*, i.e., those involving cancer in less than 50 %

Results

Proportions of inner and outer type

Among the 28 lesions, there were 20 lesions of the inner type (71 %) and 8 lesions of the outer type (29 %).

Clinical factors

Regarding the clinical factors, as shown in Tables 1, 2, a significant difference between the 2 types was observed only in the presence or absence of bilateral breast cancer. Among the 27 cases, there were 5 cases of bilateral breast cancer (19 %), which included 2 cases of synchronous bilateral breast cancer (including 1 case of synchronous bilateral breast cancer in sclerosing adenosis) and 3 cases of metachronous bilateral breast cancer. Bilateral breast cancer was observed in 5 cases of the inner type (26 %) but none of the outer type (0 %)[1]. Comparison between the 2 types revealed that there were significantly more cases of bilateral breast cancer for the inner type ($p = 0.04$).

The details of follow-up of other lesions were as follows: 3 lesions were detected by examination of contralateral breast cancer (1 lesion synchronous and 2 lesions metachronous), 1 lesion was detected by examination of nipple discharge, and 2 lesions were other lesions not related to cancer.

Pathological factors

Regarding the pathological factors, as shown in Table 3, invasive carcinoma was observed in 11 (39 %) of the 28 lesions, and all of the 11 lesions were invasive ductal carcinoma with a predominant intraductal component. Invasive carcinoma was observed in 8 (40 %) of the 20 lesions of the inner type and 3 (38 %) of the 8 lesions of the outer type, indicating no significant difference between the 2 types ($p = 0.90$). Carcinoma in situ was observed in 17 lesions (61 %), all of which were ductal carcinoma in situ.

Regarding the subtypes of ductal carcinoma in situ, there were 9 lesions (32 %) of the comedo type and 19 lesions (68 %) of the non-comedo type in the 28 lesions. Out of the 20 lesions of the inner type, there were 3 lesions (15 %) of the comedo type and 17 lesions (85 %) of the non-comedo type. Out of the 8 lesions of the outer type, there were 6 (75 %) and 2 lesions (25 %), respectively. The non-comedo type was significantly more frequently observed for the inner type ($p = 0.002$).

Out of the 28 lesions, apocrine metaplasia was observed inside the 12 lesions (43 %), and 17 lesions (61 %) were accompanied by a radial sclerosing lesion. However, no significant difference was observed in either apocrine metaplasia or radial sclerosing lesion between the 2 types ($p = 0.63$ and $p = 0.47$, respectively).

Out of the 28 lesions, 14 (50 %) were positive for ER, and 11 (39 %) were positive for PgR. No significant difference was observed between the 2 types. For HER2, 5 (18 %) of the 28 lesions were positive. HER2-positive lesions were observed in 1 (5 %) of the 20 lesions of the inner type and 4 (50 %) of the 8 lesions of the outer type, indicating that there were significantly fewer HER2-positive lesions for the inner type ($p = 0.007$).

Discussion

Although many studies have examined the development of breast cancer including gene disorder [21, 22], the development mechanism has not been elucidated, yet. Cancer genuinely arising in sclerosing adenosis is breast cancer developing in a benign lesion as a site of origin. We conducted this study with the expectation that a study on such a peculiar biological condition would be helpful for elucidation of the mechanism of development of breast cancer.

Sclerosing adenosis is one of the components of mastopathy, a benign lesion developing owing to an abnormal hormonal environment [23]. Cancer in sclerosing adenosis is a lesion including cancer cells within sclerosing adenosis. According to the literature, the lesion is common in premenopausal women [7], is pathologically easy to confuse with invasive ductal carcinoma [8, 9], develops into the solid or cribriform type [7], and is often considered to be a hormone-positive case [10].

Cancer in sclerosing adenosis may include the following 2 types: cancer genuinely arising from sclerosing adenosis and cancer arising near a sclerosing adenosis lesion and infiltrating into it. Differentiation between these types may occasionally be difficult. Moritani et al. [10] reported 24 cases and classified them into the following 2 types: those where the area of cancer is entirely surrounded by sclerosing adenosis and the others. In this study, while considering that the inner type included many cases of the former and that the outer type included many cases of the latter, we developed a study design to compare these 2 types. Although cancer develops in the mammary gland with a hormonal environment including sclerosing adenosis of both types, they are different in terms of whether sclerosing adenosis cells have become malignant.

Regarding the clinical factors, this study revealed a significant difference between the inner and outer types only in bilateral breast cancer. As the development of bilateral breast cancer is reported to be associated with hormonal environment or gene disorder [24, 25], malignant

[1] Bilateral breast cancer was observed in 122 cases out of 1,669 cases in total.

Table 1 Clinical findings of age, bilateral breast cancer, past and family history (27 cases)

Clinical findings	Total		Inner type		Outer type		*p* value
	No. of cases	%	No. of cases	%	No. of cases	%	
Age							0.40
Mean ± SD	52.2 ± 8.8		53.0 ± 2.0		50.0 ± 3.1		
Range	39–78		39–78		40–60		
Bilateral breast cancer							0.04
Yes	5	19	5	26	0	0	
No	22	81	14	74	8	100	
Past history of cancer							0.28
Yes	7	26	6	32	1	13	
No	20	74	13	68	7	87	
Family history of breast cancer							0.23
Yes	2	7	2	11	0	0	
No	25	93	17	89	8	100	

Table 2 Clinical findings of opportunity for detection and remarks from mammography (28 lesions)

Clinical findings	Total		Inner type		Outer type		*p* value
	No. of lesions	%	No. of lesions	%	No. of lesions	%	
Opportunity for detection							0.43
Tumor (self-diagnosis)	9	32	5	25	4	50	
Screening	13	46	10	50	3	37	
Mammography	7		5		2		
Ultrasonography	5		4		1		
CT	1		1		0		
Follow-up of other lesions	6	22	5	25	1	13	
Mammography remarks							
Mass							0.10
Yes	5	18	2	10	3	38	
No	23	82	18	90	5	62	
Calcification							0.14
Yes	15	54	9	45	6	75	
No	13	46	11	55	2	25	
Architectural findings							0.55
Yes	13	46	10	50	3	38	
No	15	54	10	50	5	62	

transformation of sclerosing adenosis cells is suggested to be associated with these two factors.

Regarding the pathological factors, although cases of lobular carcinoma have been reported in the literature [9, 11–13, 15, 16], the 28 lesions included in our study were all ductal carcinoma. Our study revealed a significant difference in the subtypes of ductal carcinoma in situ, indicating that there were significantly more cases of the non-comedo type for the inner type. As pre-existing sclerosing adenosis is accompanied by fibrous sclerosis around the ducts, there may be more cases of the non-comedo type than those of the comedo type showing expanding growth.

Regarding protein expression, there was a significant difference in HER2. The inner type had significantly fewer HER2-positive cases, suggesting that cancer genuinely arising in sclerosing adenosis is characterized by low HER2 expression. Although many cases of cancer arising in sclerosing adenosis are also reported to be positive for ER/PgR [10], our study did not show any significant difference.

Table 3 Pathological findings of pathological features and protein expression (28 lesions)

Pathological findings	Total		Inner type		Outer type		*p* value
	No. of lesions	%	No. of lesions	%	No. of lesions	%	
Invasion							0.90
Yes/IDC	11	39	8	40	3	38	
No/DCIS	17	61	12	60	5	62	
Subtype of intraductal carcinoma							0.002
Comedo	9	32	3	15	6	75	
Non-comedo	19	68	17	85	2	25	
Apocrine metaplasia							0.63
Yes	12	43	8	40	4	50	
No	16	57	12	60	4	50	
Radial sclerosing lesion							0.47
Yes	17	61	13	65	4	50	
No	11	39	7	35	4	50	
ER							0.40
Positive	14	50	11	55	3	38	
Negative	14	50	9	45	5	62	
PgR							0.32
Positive	11	39	9	45	2	25	
Negative	17	61	11	55	6	75	
HER2							0.007
Positive	5	18	1	5	4	50	
Negative	23	82	19	95	4	50	

IDC invasive ductal carcinoma, *DCIS* ductal carcinoma in situ

In conclusion, this study suggests that cancer genuinely arising in sclerosing adenosis often has biological features of bilateral breast cancer, the non-comedo type in subtype, and being negative for HER2. Sclerosing adenosis is a lesion arising in the terminal duct-lobular unit (TDLU). Cancer arising there may be expressing the features of breast cancer arising in TDLU.

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Conflict of interest The authors declare that they have no conflict of interest.

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