Medicine®

OBSERVATIONAL STUDY

OPEN

Breast Sclerosing Adenosis and Accompanying Malignancies

A Clinicopathological and Imaging Study in a Chinese Population

Naisi Huang, MD, Jiajian Chen, MD, Jingyan Xue, MD, Baohua Yu, MD, Yanqiong Chen, MD, Wentao Yang, MD, Zhimin Shao, MD, and Jiong Wu, MD

Abstract: Sclerosing adenosis (SA) is a less common histopathological lesion of the breast that can coexist with proliferative lesions as well as malignancies. We aimed to analyze the clinicopathological characteristics of SA and to investigate the radiological features of SA.

Patients who underwent breast surgery at our institute from 2007 to 2013 were retrospectively reviewed. A total of 815 breasts (722 patients) were included in the final analysis. Synchronous bilateral SA was defined as the detection of another SA arising in the contralateral breast within 1 month after surgery for the initial breast lesion. Baseline characteristics, imaging records (ultrasonography, mammography, and magnetic resonance imaging [MRI]), and pathology were included in the analysis.

The median age at diagnosis was 47 years old. The majority of patients had unilateral non-Bc-SA (457/722). Among 102 patients with bilateral SA, 78.4% were diagnosed synchronously. In total, 26 patients suffered from synchronous bilateral breast cancer. Upon final pathological investigation, 226 cases were SA involving breast cancer (Bc-SA), most (56.2%) of which were ductal carcinoma in situ (DCIS). In addition, lobular carcinoma in situ (LCIS) and diseases that involved LCIS also comprised up to 11.1% of cases. The majority of SA cases (405; 49.7%) had no obvious symptoms except for imaging changes in mammography or ultrasound. Compared with non-Bc-SA cases, Bc-SA cases were more likely to exhibit features of mass (32.8% vs. 28.6%) and architectural distortion (20.4% vs. 13.0%) on mammography. Ultrasonography, mammography, and MRI revealed unsatisfactory sensitivity and specificity to differentiate Bc-SA from non-Bc-SA. MRI exhibited the highest sensitivity and lowest specificity, whereas the specificity of mammography was as low as 50.0%.

A tendency for synchronous bilaterality in both Bc-SA and non-Bc-SA was noted. DCIS was the most commonly observed malignancy involved in Bc-SA. Although most patients with SA were asymptomatic, the ability of imaging studies to accurately differentiate non-Bc-SA from Bc-SA remained unsatisfactory.

(*Medicine* 94(49):e2298)

Abbreviations: Bc-SA = SA involving breast cancer, BI-RADS = Breast Imaging Reporting and Data System, DCIS = ductal carcinoma in situ, FUSCC = Fudan University Shanghai Cancer Center, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, IQR = interquartile range, LCIS = lobular carcinoma in situ, MRI = magnetic resonance imaging, non-Bc-SA = SA not involving breast cancer, OR = odd ratio, SA = sclerosing adenosis.

INTRODUCTION

Sclerosing adenosis (SA) is a histopathological description of human breast that was first clearly described in 1968.[1] SA refers to proliferating fibrous and myoepithelial tissue that is disposed in whorls and distorts the normal architecture of the lobules accompanied by desmoplasia and epithelial hyperplasia.[2,3] SA can also be observed in other proliferative lesions, such as papilloma and fibroadenoma. The condition even coexist with both invasive and in situ breast malignancies.[4] Although SA is not a common condition, the number of cases has recently been increasing.[5]

SA is difficult to distinguish from breast carcinoma based on radiology and frozen sections.[1] SA mostly presents as a nonpalpable lesion with different mammographic and sonographic appearances, the features of which may occasionally mimic malignant conditions. Therefore, histopathologic examination is mandatory for definite diagnosis.[2]

The etiology of SA is not yet clear, but it is believed to be a benign lesion developing in response to an abnormal hormonal environment.[6] SA itself is an independent risk factor for subsequent breast cancer unassociated with atypical lobular hyperplasia.[7] Patients with SA have an increased risk for subsequent invasive breast cancer (range 1.7- to 3.7-fold), which is within the range of other benign proliferative lesions without atypia.[8]

Due to the relatively low incidence of SA, our knowledge of SA is limited. In the present study, a retrospective review was performed in a cohort of 815 SA cases, with 226 cases involving malignancies. We aimed to analyze the clinicopathological characteristics of SA, investigate the radiological features of SA, and assess the ability of imaging studies to differentiate SA not involving breast cancer (non-Bc-SA) from SA involving breast cancer (Bc-SA).

MATERIALS AND METHODS

Patients who underwent breast surgery at Fudan University Shanghai Cancer Center (FUSCC) from 2007 to 2013 were

Editor: Michael Masoomi.
Received: October 9, 2015; revised: November 15, 2015; accepted: November 20, 2015.
From the Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, China (NH, JC, JX, ZS, JW); Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China (BY, WY); Department of Diagnostic Radiology, Fudan University Shanghai Cancer Center, Shanghai, China (YC); Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China (NH, JC, JX, BY, YC, WY, ZS, JW); and Collaborative Innovation Center for Cancer Medicine, Guangdong, China (JW).
Correspondence: Jiong Wu, Fudan University Shanghai Cancer Center, Shanghai, China (e-mail: wujiong1122@vip.sina.com).
This study was supported in part by grants from the Youth Scientific Research Foundation of the Shanghai Municipal Health Bureau (no. 20124Y067) and the National Natural Science Foundation of China (no. 81302297). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Naisi Huang, Jiajian Chen, and Baohua Yu contributed equally to this work.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002298

TABLE 1. Baseline Characteristics of All SA Patients

Characteristics	N (%)
Median age at biopsy (IQR)	47 (41–52)
Sex (female)	722 (100%)
Site of SA	
Unilateral SA	620 (85.9%)
Non-Bc-SA	457
Bc-SA	125
Non-Bc-SA with contralateral malignancy not involving SA	26
Bc-SA with contralateral malignancy not involving SA	12
Bilateral SA	102 (14.1%)
Bilateral non-Bc-SA	25
Bilateral Bc-SA	24
Unilateral Bc-SA	53
Timing of bilateral SA	
Synchronous SA*	80 (78.4%)
Bilateral non Bc-SA	23
Bilateral Bc-SA	21
Metachronous SA	22 (21.6%)
Bilateral non Bc-SA	2
Bilateral Bc-SA	3
Family history (N = 494)	
Any malignancy	156 (31.6%)
Breast cancer	60 (12.1%)
Ovary cancer	5 (1.0%)
Other malignancy	107 (21.7%)
Previous benign breast disease confirmed by pathology (N = 101)	
Pathology type	
Fibroadenoma	53 (52.5%)
Papilloma	11 (10.9%)
Adenosis	27 (26.7%)
Dysplasia	4 (4.0%)
Others†	6 (6.0%)
Site of the disease	
Ipsilateral breast	52 (51.5%)
Contralateral breast	27 (26.7%)
Bilateral breast	22 (21.8%)

IQR = interquartile range; SA = sclerosing adenosis; Bc-SA = SA involving breast cancer; non-Bc-SA = SA not involving breast cancer.
* Synchronous SA is defined as SA of bilateral breasts that were diagnosed within 1 month.
† Six cases of other pathology type included 2 cases of mastitis, 1 case of breast cyst, 1 case of lipoma, 1 case of benign phyllodes tumor, and 1 case of SA.

retrospectively reviewed. A total of 771 cases were identified with SA as the final pathology. An additional pathologist reviewed the sections from all Bc-SA cases. Given that SA has a tendency for bilaterality, sections from breast cancer patients with non-Bc-SA in the contralateral breast were also reviewed by the pathologist to determine whether it was accompanied by previously undiscovered SA. After careful reexamination, the pathologist identified 48 additional SA cases. Among the 819 cases, 3 were excluded because they had their breasts removed in other hospitals, and no imaging studies were available for pre-operative evaluation. Another case who received neoadjuvant chemotherapy was also excluded from the study. Therefore, a total of 815 breasts were included in the final analysis. The protocol for the present study was approved by the Ethics Committee of FUSCC.

The information regarding all study patients was obtained from the electronic medical history system in our institute and reviewed by researchers. Baseline characteristics (age, family history, and breast disease history), imaging records (ultrasonography, mammography, and magnetic resonance imaging [MRI]) with Breast Imaging Reporting and Data System (BI-RADS)[9] classification and lesion features, and pathology records were included in the analysis. In the subgroup analysis, patients were categorized into 3 groups according to BI-RADS classification to investigate the diagnosis of SA using imaging methods: BI-RADS 0, BI-RADS 1–3 and BI-RADS 4–5. Synchronous bilateral Bc-SA was defined as the detection of another SA/cancer arising in the contralateral breast within 1 month after surgery for the initial breast lesion.

We used SPSS version 20 (SPSS Inc., Chicago, IL.) for statistical analysis. For descriptive statistics, we used medians (interquartile range [IQR]), and for categorical variables, frequency was used. Comparative analysis was carried out using χ^2 test. P-value < 0.05 was considered to be statistically significant. Sensitivity and specificity were used to assess the imaging methods to differentiate non-Bc-SA from Bc-SA.

TABLE 2. Pathology Diagnosis Accompanied by SA in 815 Cases

Pathology Diagnosis	N (%)
Bc-SA, N = 226	
Ductal carcinoma in situ (DCIS)	127 (56.2%)
Invasive ductal carcinoma (IDC)	74 (32.7%)
Invasive lobular carcinoma (ILC)	1 (0.4%)
Other invasive carcinoma	8 (6.3%)
Lobular carcinoma in situ (LCIS) or diseases involve LCIS	25 (11.1%)
Non-Bc-SA, N = 588	
Fibroadenoma	145 (24.7%)
Papilloma	73 (12.4%)
Dysplasia	91 (15.4%)
Adenosis and other benign breast disease	279 (47.4%)
SA involving borderline phyllodes tumor, N = 1	

Bc-SA = SA involving breast cancer; DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LCIS = lobular carcinoma in situ; non-Bc-SA = SA not involving breast cancer; SA = sclerosing adenosis.

RESULTS

Baseline Characteristics

A total of 815 cases (722 Asian female patients) were included in the final analysis, among which 620 patients had unilateral SA and 101 patients had bilateral SA. In addition, 1 patient had synchronous bilateral SA, and her right breast developed SA again 1 year later. The baseline characteristics of all patients are summarized in Table 1. The median age at diagnosis was 47 years old (IQR: 41–52), and all patients were female. The majority of patients had unilateral non-Bc-SA (457/722). Among 102 patients with bilateral SA, 53 had unilateral Bc-SA, and 24 patients had bilateral Bc-SA. In total, 78.4% of bilateral SA cases were diagnosed synchronously. A total of 240 patients in our cohort had breast cancer, among whom 204 (85%) had unilateral breast cancer and 36 (15%) had bilateral breast cancer. Up to 26 patients suffered from synchronous bilateral breast cancer.

In terms of family history, 31.6% of patients had a family history of malignant tumors, and 12.1% had breast cancer family history. Previous surgeries for benign breast disease in these patients were also reviewed. Among a total of 14.0% of patients who had previous breast biopsy or surgery, fibroadenoma was the most common disease (52.5%) followed by adenosis (26.7%) and papilloma (10.9%). Most of the benign disease (51.5%) occurred in the ipsilateral breast, whereas 21.8% of cases occurred in bilateral breasts.

The Clinicopathological Study of SA Cases

The initial symptoms of SA cases varied: 361 cases (44.3%) presented with palpable breast lump; 41 cases (5.4%) had nipple discharge; 13 cases (1.6%) reported mastalgia as the chief complaint; and the majority of cases (405; 49.7%) had no obvious symptoms except for imaging changes in mammography or ultrasound. Upon final pathological investigation, 226 cases were classified as Bc-SA (Table 2), most (56.2%) of which were ductal carcinoma in situ (DCIS). Notably, lobular carcinoma in situ (LCIS) or diseases that involved LCIS accounted for 11.1% of all cases. For non-Bc-SA, the most common pathological description included fibroadenoma (24.7%), dysplasia (15.4%), and papilloma (12.4%).

The Diagnosis of SA by Ultrasonography, Mammography, and MRI

In 815 SA cases, 759 were subject to breast ultrasonography, 623 were subject to mammography, and 434 were subject to MRI (Table 3). For ultrasonography, 71.9% cases presented with a solid mass, and 6.1% presented a shadow

TABLE 3. Imaging Features of SA Cases With Ultrasonography, Mammography, and MRI

Imaging Features	All SA Cases, N = 815	Non-Bc-SA Cases, N = 588	Bc-SA Cases,* N = 227	*P*-Value†
Ultrasonography, N = 759				
Solid mass	546 (71.9%)	382 (71.3%)	164 (72.2%)	0.581
Shadow without mass	46 (6.1%)	31 (5.8%)	15 (6.6%)	
Others‡	167 (22.0%)	123 (22.9%)	44 (19.7%)	
Mammography, N = 623				
Calcification	237 (38.0%)	175 (40.0%)	62 (33.3%)	0.051
Mass ± calcification	186 (29.9%)	125 (28.6%)	61 (32.8%)	
Architectural distortion	95 (15.2%)	57 (13.0%)	38 (20.4%)	
Asymmetric density	47 (7.5%)	34 (7.8%)	13 (7.0%)	
Negative or not specified	58 (9.3%)	46 (10.5%)	12 (6.5%)	
Magnetic resonance imaging, N = 434				
Enhancing mass	213 (49.1%)	142 (49.5%)	71 (48.3%)	0.950
Non-mass enhancement	143 (32.9%)	94 (32.8%)	49 (33.3%)	
Structure distortion	23 (5.3%)	14 (4.9%)	9 (6.1%)	
Negative or not specified	55 (12.7%)	37 (12.9%)	18 (12.2%)	

Bc-SA = SA involving breast cancer.
* One case of borderline phyllodes tumor was also grouped into malignant SA cases in the analysis.
† *P*-value was calculated by Pearson χ^2 test.
‡ Other ultrasound characteristics included cyst formation, structure distortion, and cases with no specific characteristics described.

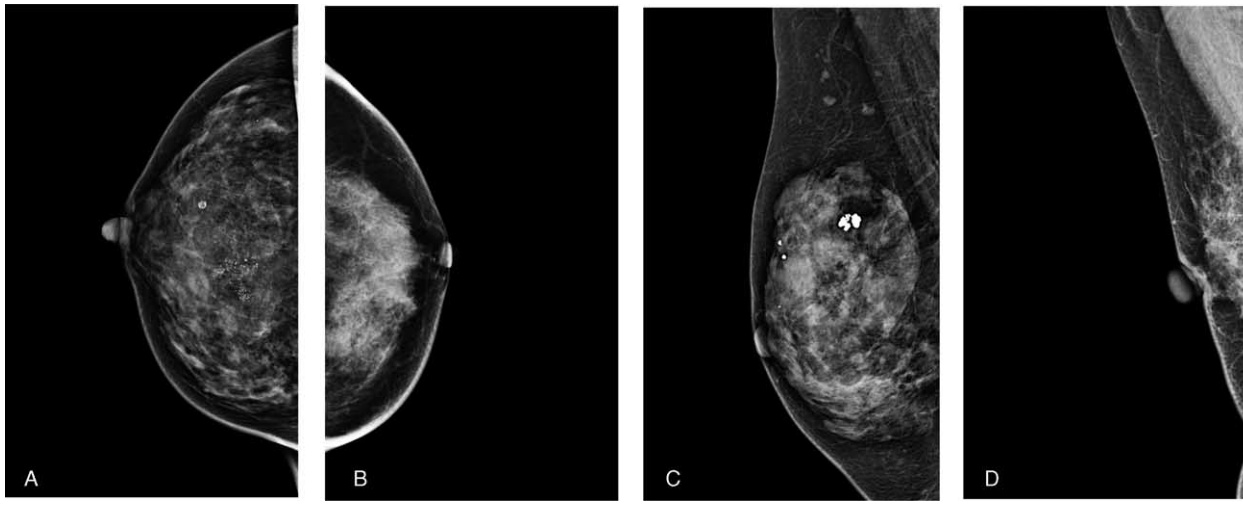

FIGURE 1. SA features on mammography. (A) Mammography depicts an 11 mm × 12 mm mass in the outer upper quadrant of the left breast, with part of the margin ill-defined. BI-RADS 4A. Pathology: SA with ductal hyperplasia. (B) Segmental fine pleomorphic calcifications were detected in the inner upper quadrant, BI-RADS 4B. Pathology: DCIS arising from SA. (C) Architectural distortion with coarse, lucent-centered, and fine calcifications is noted. BI-RADS 4B. Pathology: SA with dysplasia. (D) Mammography reveals an asymmetry with grouped amorphous calcifications behind the nipple in the right breast. BI-RADS 4A. Pathology: SA with focal DCIS.

without mass. For mammography, the percentages of calcification, mass, architectural distortion, and asymmetric density were 38.0%, 29.9%, 15.2%, and 7.5%, respectively. For MRI, the 2 most commonly reported features were enhancing mass (49.1%) and nonmass enhancement (32.9%). Some of the typical features of SA in mammography and MRI were illustrated in Figures 1 and 2. Compared with non-Bc-SA cases, Bc-SA cases were more likely to have features of mass (32.8% vs. 28.6%) and architectural distortion (20.4% vs. 13.0%) on mammography with a tendency for significance ($P = 0.051$). However, no significant differences were detected in imaging features of ultrasonography ($P = 0.581$) or MRI ($P = 0.950$).

BI-RADS classification was used to categorize breast lesions in 756 (99.6%) ultrasonography cases, 580 (93.1%) mammography cases, and 431 (99.3%) MRI cases (Table 4). Moreover, 4.2% cases assessed by ultrasonography, 15.3% assessed by mammography, and 0.5% assessed by MRI were reported as BI-RADS 0, which required further investigation. The sensitivities of the 3 imaging methods to differentiate non-Bc-SA from Bc-SA were 66.3%, 72.8%, and 88.4%, respectively. The specificities of the three imaging methods were 64.1%, 50.0%, and 41.5%, respectively. MRI had the highest sensitivity and lowest specificity, whereas the specificity of mammography was as low as 50.0%.

DISCUSSION

The median age at diagnosis of SA was 47 years old in patients in this study, which is younger than the median age of breast cancer diagnosis in China.[10] Previous studies also revealed that DCIS arising from SA occurred on average at the age of 42.6 years old, which is younger than the average age of breast cancer diagnosis.[11,12] Up to 14.0% of patients in this cohort had previous benign breast disease confirmed by pathology, and 12.1% had a family history of breast cancer. These features correlated with a previous study from Mayo Clinic that found that SA was more common in women with a strong family history of breast cancer.[13] The etiology of SA and its role in carcinogenesis remains elusive. Some suggested that SA might result from age-related regression or abnormality after lactation.[7]

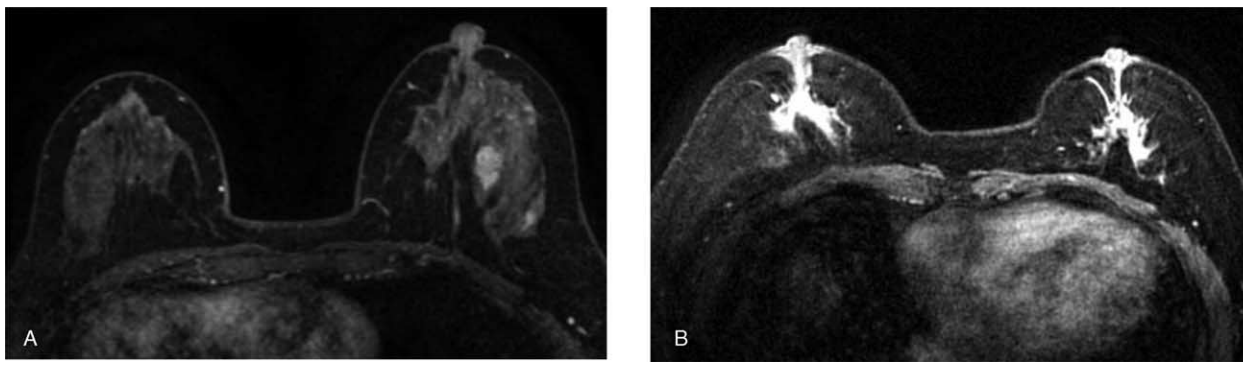

FIGURE 2. SA features on magnetic resonance imaging (MRI). (A) Irregular even enhancement mass of 26 mm × 21 mm in lateral to the middle of the right breast is noted. BI-RADS 4B. Pathology: DCIS arising from SA. (B) MRI reveals non-mass enhancements inferior to the lateral of both nipples. BI-RADS 4B. Pathology: IDC with DCIS arising from SA.

TABLE 4. Comparison of the Sensitivities and Specificities of Imaging Methods for Differentiating Non-Bc-SA From Bc-SA

Method/BI-RADS	All SA Cases, N = 815	Non-Bc-SA Cases, N = 588	Bc-SA Cases,* N = 227	Sensitivity	Specificity
Ultrasonography, N = 756					
BI-RADS 0	32 (4.2%)	19 (3.6%)	13 (5.9%)	66.3%	64.1%
BI-RADS 1–3	401 (53.0%)	331 (61.9%)	70 (31.7%)		
BI-RADS 4–5	323 (42.7%)	185 (34.6%)	138 (62.4%)		
Mammography, N = 580					
BI-RADS 0	89 (15.3%)	60 (14.9%)	29 (16.5%)	72.8%	50.0%
BI-RADS 1–3	212 (36.6%)	172 (42.6%)	40 (22.7%)		
BI-RADS 4–5	279 (48.1%)	172 (42.6%)	107 (60.8%)		
Magnetic resonance imaging, N = 431					
BI-RADS 0	2 (0.5%)	2 (0.7%)	0	88.4%	41.5%
BI-RADS 1–3	134 (31.1%)	117 (41.2%)	17 (11.6%)		
BI-RADS 4–5	295 (68.4%)	165 (58.1%)	130 (88.4%)		

Bc-SA = SA involving breast cancer; BI-RADS = Breast Imaging Reporting and Data System.
* One case of borderline phyllodes tumor was also grouped into malignant SA cases in the analysis.

As noted in previous studies, SA was reported to have tendency for bilaterality.[14,15] The frequency of bilateral breast cancer in all breast cancer patients was 1.6% to 7%,[16,17] whereas the frequency of bilateral breast cancer in Bc-SA was as high as 27%.[17] In a retrospective study analyzing 117 synchronous bilateral breast cancer and 7400 unilateral breast cancer patients, the author indicated that the presence of SA was a risk factor for developing synchronous bilateral breast cancer (hazard ratio: 11.8; 95% confidence interval: 5.3–26.3; $P < 0.001$).[16] Our cohort also revealed a tendency for bilaterality in SA, among which 78.4% were synchronous.

Some studies suggested that invasive lobular carcinoma (ILC) and LCIS presented in the majority of Bc-SA,[18,19] which might explain the increased frequency for bilateral breast cancer. However, in our series, only 1 case of SA was associated with ILC, which was unilateral breast cancer. Moreover, 11.1% cases were associated with LCIS, 9 of which were bilateral. In contrast, DCIS (56.2%) and invasive ductal carcinoma (IDC) (32.7%) were the most commonly observed pathology types. Another hypothesis is that there is a strong association with hormonal environment or gene disorder in bilateral breast cancer, and the association is especially strong for synchronous tumors occurring within 1 month (odd ratio (OR) = 25.9). Therefore, it is possible that malignant SA is also related to these factors.[20,21] Some studies have previously demonstrated that SA cases are often considered to be hormone positive.[22]

Given that most SA cases were asymptomatic, imaging studies were essential to diagnose and differentiate the disease. Our results revealed no differences in imaging features between non-Bc-SA and Bc-SA in terms of ultrasonography ($P = 0.581$), mammography ($P = 0.051$), or MRI features ($P = 0.950$). Nevertheless, architectural distortion was more commonly observed in Bc-SA on mammography (20.4% vs. 13.0%), and calcification was more commonly observed in non-Bc-SA (40.0% vs. 33.3%). This result was consistent with a study of 43 non-Bc-SA cases in which 24 (55.8%) had microcalcifications in mammographic findings.[2] In addition, several studies reported that architectural distortion was more often associated with Bc-SA. Yoshida et al[15] reported that architectural distortion was more frequent in patients with SA-DCIS compared with those with non-SA DCIS (15, 54% vs. 5, 2%, $P < 0.01$) on mammography; Ogura et al[5] reported 13 (46%) cases with architectural distortion in a study of 28 Bc-SA cases. One possible explanation was that architectural distortion became apparent as cancer developed or grew into the sclerotic stroma of SA.[17] On ultrasound, non-Bc-SA presented as a focal, ill-defined mass with acoustic shadowing or a circumscribed mass with a well-defined, microlobulated, or irregular margin, which shared numerous features with breast cancer.[2,23]

All the above evidence suggested that non-Bc-SA lesions might mimic malignancy on ultrasound, mammography, and MRI,[24–27] which correlated with our findings that BI-RADS had a relatively low accuracy to differentiate non-Bc-SA from malignant cases. In our cohort, ultrasonography had the highest specificity and was adopted in nearly all cases (99.6%). The sensitivity of MRI was the highest among the three methods (88.4%), whereas the specificity was as low as 41.5%. Although all three methods exhibited unsatisfactory sensitivity and specificity to differentiate Bc-SA from non-Bc-SA, ultrasound and mammography might be considered as the initial diagnostic methods; or the combination of ultrasound and mammography might be considered to increase sensitivity. MRI must be used with caution because of its low specificity and high cost.

The strengths of the study includes that it reported a relative large cohort of patients in a less common breast disease relating to breast cancer. This is also the first study to compare the accuracy of different imaging methods to differentiate Bc-SA from non-Bc-SA using BI-RADS. Nevertheless, it is a retrospective study and no radiologist reviewed the imaging studies of SA cases, so that it was impossible to make direct connections of certain imaging features with specific pathological conditions. Future prospective studies are awaited to directly evaluate the diagnostic value of ultrasound, mammography, and MRI in SA.

CONCLUSIONS

The current study demonstrated that 240 out of 722 SA patients had Bc-SA. A tendency for synchronous bilaterality was noted in both Bc-SA and non-Bc-SA. The frequency of synchronous bilateral breast cancer in all Bc-SA patients was as high as 10.8%. Moreover, 56.2% of Bc-SA was DCIS, and 11.1% involved LCIS. Most patients with SA were asymptomatic. The sensitivity and specificity of the imaging studies to differentiate non-Bc-SA from Bc-SA were unsatisfactory.

ACKNOWLEDGMENT

The authors would like to thank the patients for their willingness to participate in our study.

REFERENCES

1. Preece PE. Sclerosing adenosis. *World J Surg.* 1989;13:721–725.
2. Gunhan-Bilgen I, Memis A, Ustun EE, et al. Sclerosing adenosis: mammographic and ultrasonographic findings with clinical and histopathological correlation. *Eur J Radiol.* 2002;44:232–238.
3. Davies JD. Neural invasion in benign mammary dysplasia. *J Pathol.* 1973;109:225–231.
4. Gill HK, Ioffe OB, Berg WA. When is a diagnosis of sclerosing adenosis acceptable at core biopsy? *Radiology.* 2003;228:50–57.
5. Ogura K, Horii R, Oosako T, et al. A clinico-pathological study on cancer in sclerosing adenosis. *Breast Cancer.* 2014;21:732–737.
6. Shoker BS, Jarvis C, Clarke RB, et al. Abnormal regulation of the oestrogen receptor in benign breast lesions. *J Clin Pathol.* 2000;53:778–783.
7. Jensen RA, Page DL, Dupont WD, et al. Invasive breast cancer risk in women with sclerosing adenosis. *Cancer.* 1989;64:1977–1983.
8. Bodian CA, Perzin KH, Lattes R, et al. Prognostic-significance of benign proliferative breast disease. *Cancer.* 1993;71:3896–3907.
9. Obenauer S, Hermann KP, Grabbe E. Applications and literature review of the BI-RADS classification. *Eur Radiol.* 2005;15: 1027–1036.
10. Fan L, Strasser-Weippl K, Li JJ, et al. Breast cancer in China. *Lancet Oncol.* 2014;15:e279–e289.
11. Ichihara S, Aoyama H. Intraductal carcinoma of the breast arising in sclerosing adenosis. *Pathol Int.* 1994;44:722–726.
12. Sloane JP, Mayers MM. Carcinoma and atypical hyperplasia in radial scars and complex sclerosing lesions: importance of lesion size and patient age. *Histopathology.* 1993;23:225–231.
13. Visscher DW, Nassar A, Degnim AC, et al. Sclerosing adenosis and risk of breast cancer. *Breast Cancer Res Treat.* 2014;144: 205–212.
14. Guray M, Sahin AA. Benign breast diseases: classification, diagnosis, and management. *Oncologist.* 2006;11:435–449.
15. Yoshida A, Hayashi N, Akiyama F, et al. Ductal carcinoma in situ that involves sclerosing adenosis: high frequency of bilateral breast cancer occurrence. *Clin Breast Cancer.* 2012;12:398–403.
16. Chen JJ, Wang Y, Xue JY, et al. A clinicopathological study of early-stage synchronous bilateral breast cancer: a retrospective evaluation and prospective validation of potential risk factors. *PLoS ONE.* 2014;9:e95185.
17. Oiwa M, Endo T, Ichihara S, et al. Sclerosing adenosis as a predictor of breast cancer bilaterality and multicentricity. *Virchows Arch.* 2015;467:71–78.
18. Eusebi V, Collina G, Bussolati G. Carcinoma in situ in sclerosing adenosis of the breast: an immunocytochemical study. *Semin Diagn Pathol.* 1989;6:146–152.
19. Oberman HA, Markey BA. Noninvasive carcinoma of the breast presenting in adenosis. *Mod Pathol.* 1991;4:31–35.
20. Shahedi K, Emanuelsson M, Wiklund F, et al. High risk of contralateral breast carcinoma in women with hereditary/familial non-BRCA1/BRCA2 breast carcinoma. *Cancer.* 2006;106:1237–1242.
21. Huo DZ, Melkonian S, Rathouz PJ, et al. Concordance in histological and biological parameters between first and second primary breast cancers. *Cancer.* 2011;117:907–915.
22. Moritani S, Ichihara S, Hasegawa M, et al. Topographical, morphological and immunohistochemical characteristics of carcinoma in situ of the breast involving sclerosing adenosis. Two distinct topographical patterns and histological types of carcinoma in situ. *Histopathology.* 2011;58:835–846.
23. Chen JH, Nalcioglu O, Su MY. Fibrocystic change of the breast presenting as a focal lesion mimicking breast cancer in MR Imaging. *J Magn Reson Imaging.* 2008;28:1499–1505.
24. Cyrlak D, Carpenter PM, Rawal NB. Breast imaging case of the day. Florid sclerosing adenosis. *Radiographics.* 1999;19:245–247.
25. Nielsen NS, Nielsen BB. Mammographic features of sclerosing adenosis presenting as a tumour. *Clin Radiol.* 1986;37:371–373.
26. Gity M, Arabkheradmand A, Taheri E, et al. Magnetic resonance imaging features of adenosis in the breast. *J Breast Cancer.* 2015;18:187–194.
27. Oztekin PS, Tuncbilek I, Kosar P, et al. Nodular sclerosing adenosis mimicking malignancy in the breast: magnetic resonance imaging findings. *Breast J.* 2011;17:95–97.