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## CASE REPORT

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# Sclerosing Adenosis: Should We Still Regard It as a Simple Benign Disease? Report of Two Patients with Subsequent Development of Invasive or In-situ Breast Cancer

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### ABSTRACT

*Sclerosing adenosis belongs to the group of benign proliferative breast diseases. The imaging and histological findings of sclerosing adenosis can mimic invasive ductal carcinoma. The diagnosis of sclerosing adenosis is challenging, and requires the combination of clinical, radiological, and pathological findings. Sclerosing adenosis is associated with a small risk of subsequent breast carcinoma. This report is of two patients with incidentally detected and biopsy-proven sclerosing adenosis. The clinical history, serial mammogram, breast ultrasonography, and preoperative breast magnetic resonance imaging findings are reviewed and the histological slides of the biopsy and surgical specimens are presented. In both patients, serial follow-up ultrasonography 7 years after the initial diagnosis showed mild increase in vascularity in the lesions. Repeat biopsies were performed, which showed invasive ductal carcinoma and ductal carcinoma in situ in patient 1 and patient 2, respectively. The authors recommend long-term follow-up for a sclerosing adenosis because of the risk of breast carcinoma with a long latency period. If any suspicious feature or change in morphology is detected in follow-up imaging, a biopsy should be performed to exclude carcinoma.*

*Key Words: Breast neoplasms; Fibrocystic breast disease; Mammography; Ultrasonography, mammary*

## 中文摘要

### 硬化性腺病：是否依然視作單純良性病變？兩名硬化性腺病患者後期發展為侵襲性或原位乳腺癌的報告

王馨藝、角田博子、松田直子、鈴木高佑、李治平、霍泳珊、趙朗峰、陳慈欽

硬化性腺病屬於良性乳腺增生病變，其影像和組織學檢查結果與浸潤性導管癌相似。硬化性腺病的診斷具挑戰性，須結合臨床、影像學和病理結果。硬化性腺病與未來發展成乳腺癌的風險有少許相關。本文報告兩名意外發現並獲活檢證實的硬化性腺病病例。回顧病人的臨床病史、乳腺X光檢查、乳腺超聲檢查和術前乳腺磁共振成像的結果並展示活檢的組織切片和手術標本。兩名病人於首次診斷硬化性腺病後連續超聲隨訪，七年後發現病灶有輕微的血流增加。重複進行活檢發現兩名患

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者分別有浸潤性導管癌和導管原位癌。由於乳腺癌有很長的潛伏期，我們建議為硬化性腺病患者進行長期隨訪。如果隨訪影像發現有任何可疑的徵狀或形態學上的變化，便應替病人進行活檢以排除癌症的可能性。

## INTRODUCTION

Sclerosing adenosis (SA) belongs to the group of proliferative breast diseases, which also include typical ductal hyperplasia, intraductal papilloma, multiple papilloma, radial scar, and fibroadenoma.<sup>1</sup> Sclerosis means proliferation of stromal cells, and adenosis means proliferation of glands. SA describes the condition of increased acini in the terminal duct lobular unit that is surrounded by abundant stromal cells.

SA is benign in nature. The lobular architecture is retained, but becomes exaggerated and distorted, and the acini may be compressed, or even obliterated, by stromal fibrosis.<sup>2</sup> No treatment is required for SA, but it is associated with a small risk of subsequent breast carcinoma.<sup>3-5</sup> The diagnosis of SA requires the combination of clinical, radiological, and pathological findings. This report is of two patients, one with invasive ductal carcinoma (IDC) and one with ductal carcinoma in situ (DCIS) of the breast detected 7 years after the diagnosis of SA.

## CASE REPORT

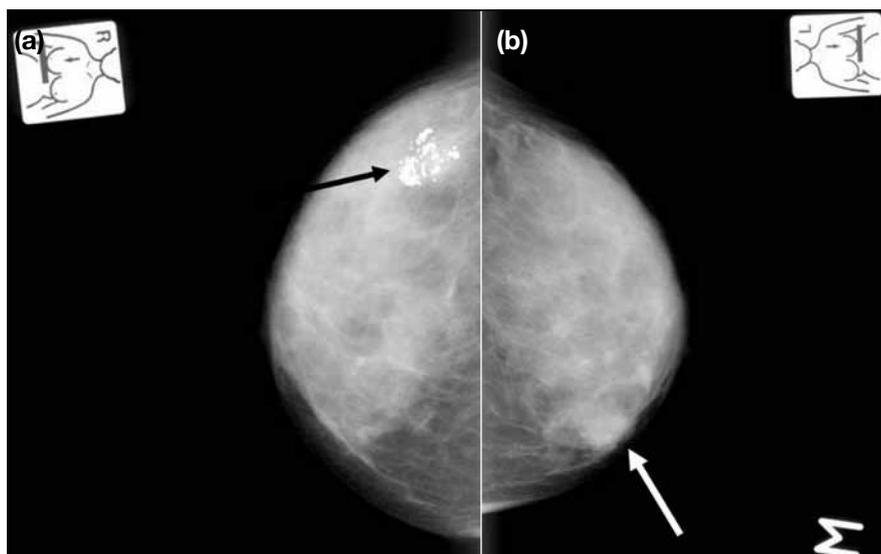
### Patient 1

In January 2005, a 43-year-old woman with right breast fibroadenoma for more than 20 years presented with new-onset right breast pain. Initial mammogram showed

a 2-cm oval lesion with a circumscribed border and coarse calcifications in the right upper outer quadrant, compatible with fibroadenoma (Figure 1a). Incidentally, there was focal asymmetric density (FAD) of breast parenchyma, about 1.5 cm in size, in the lower inner quadrant of the left breast (Figure 1b). The FAD was seen in the craniocaudal view, but was not obvious in the mediolateral view. No discrete mass or suspicious microcalcifications were seen in the left breast.

Breast ultrasonography showed a hypoechoic mass with coarsened calcification in the right breast, corresponding to the fibroadenoma seen in the mammogram. There was a 1.5-cm hypovascular hypoechoic area with an indistinct border at the 9 o'clock position of the left breast, probably corresponding to the FAD seen in the mammogram. Since DCIS could not be excluded based on the radiological findings, ultrasound-guided biopsy of the hypoechoic area was performed. Pathology revealed SA. There was no evidence of malignancy.

The patient underwent annual screening mammogram and ultrasonography. On the follow-up ultrasonography performed 7 years later, the index hypoechoic lesion at the 9 o'clock position of the left breast had increased in size from 1.5 cm to 2.7 cm, and showed peripheral hypervascularity in colour Doppler mode (Figure 2). In



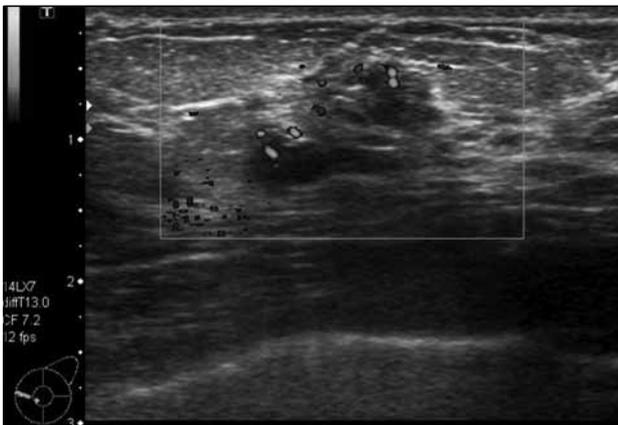
**Figure 1.** Craniocaudal mammography views of both breasts of patient 1 at presentation show (a) typical fibroadenoma (black arrow) with coarse calcifications in the upper outer quadrant of the right breast, and (b) focal asymmetric density in the lower inner quadrant of the left breast (white arrow), which is superficial and measured about 1.5 cm in length. The lesion was found to be sclerosing adenosis by core needle biopsy.

elastography, the fat-lesion ratio of the mass was 9.65 (Figure 3), which indicated malignancy; a fat-lesion ratio below 4.8 is considered benign and above 4.8 is considered malignant.<sup>6</sup> Core biopsy of the lesion showed a scirrhous type of IDC against a background of SA.

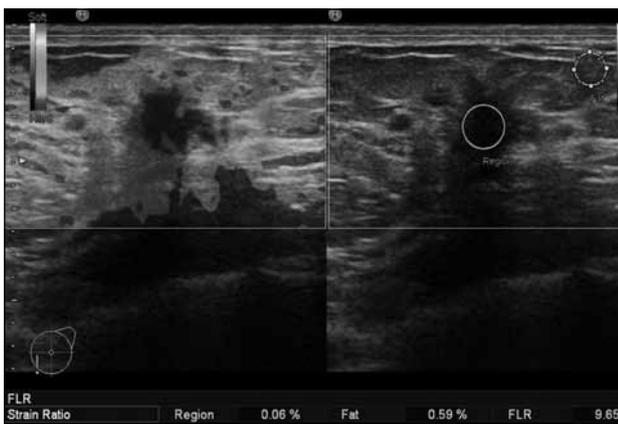
Preoperative magnetic resonance imaging (MRI) of the left breast showed a 1-cm mass with an irregular border at the 9 o'clock position (Figure 4). The lesion had slightly high T2-weighted signal and demonstrated restricted diffusion (high signal in diffusion-weighted

image [DWI] and loss of signal in apparent diffusion coefficient [ADC]). There was rapid enhancement in the early phase and plateau enhancement in delayed phase, demonstrating a type 2 kinetic curve. Around the mass, there was tiny nodular and non-mass-like enhancement with segmental distribution in the left lower inner quadrant, likely representing the background SA.

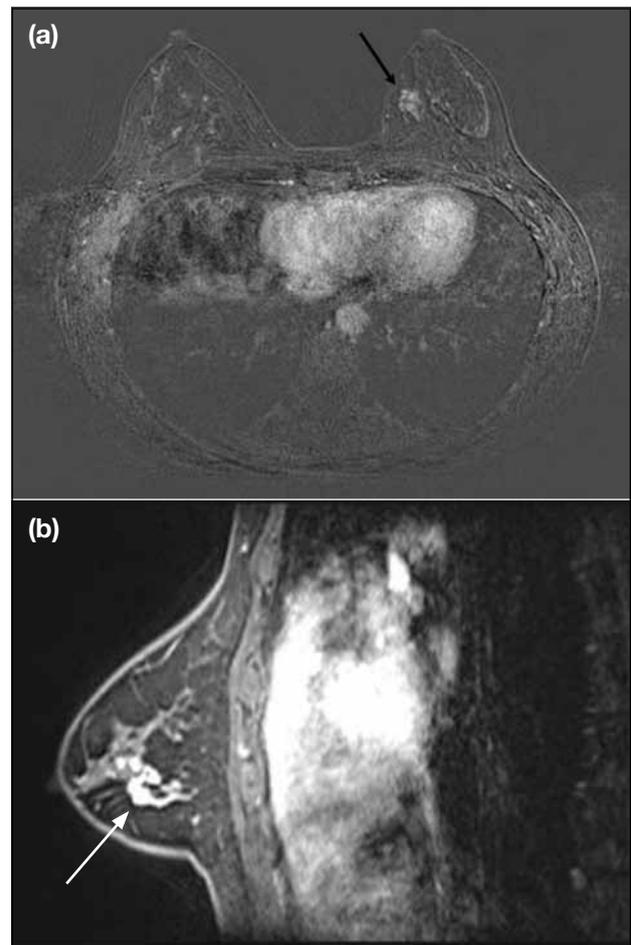
The pathology results for the surgical specimen revealed IDC of scirrhous type surrounded by background SA (Figure 5).



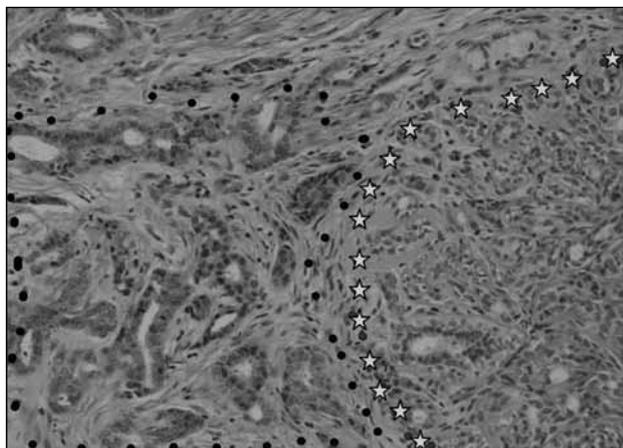
**Figure 2.** Follow-up ultrasonography of the breast 7 years after initial examination of patient 1 shows an ill-defined hypoechoic area in the 9 o'clock position of the left breast, measuring about 2.7 x 0.9 cm. This lesion corresponds to the focal asymmetric density detected on mammography. Colour Doppler mode shows increased peripheral vascularity in the lesion, and repeat biopsy confirms invasive ductal carcinoma.



**Figure 3.** Elastography of the left breast lesion in patient 1: the region of interest as circles of the hypoechoic lesion and in fatty tissue are measured respectively, and the value of fat-lesion ratio (FLR) is calculated. The result of FLR is 9.65 and the lesion is considered to be malignant.



**Figure 4.** Magnetic resonance imaging of the breast of patient 1: (a) axial post-contrast subtraction T1-weighted fat-saturated image shows an irregular mass (black arrow) in the left breast in the 9 o'clock position, which has rapid early enhancement corresponding to the biopsy-proven invasive ductal carcinoma, and (b) sagittal post-contrast T1-weighted image shows tiny nodular and non-mass-like enhancement (white arrow) in the 9 o'clock position in the inner part of the breast, with segmental distribution representing the background sclerosing adenosis.



**Figure 5.** A histology slide of the surgical specimen after mastectomy. The area marked by black dots is invasive ductal carcinoma composed of angular glands and the area marked by stars represents sclerosing adenosis with preservation of myoepithelial cells (H&E).

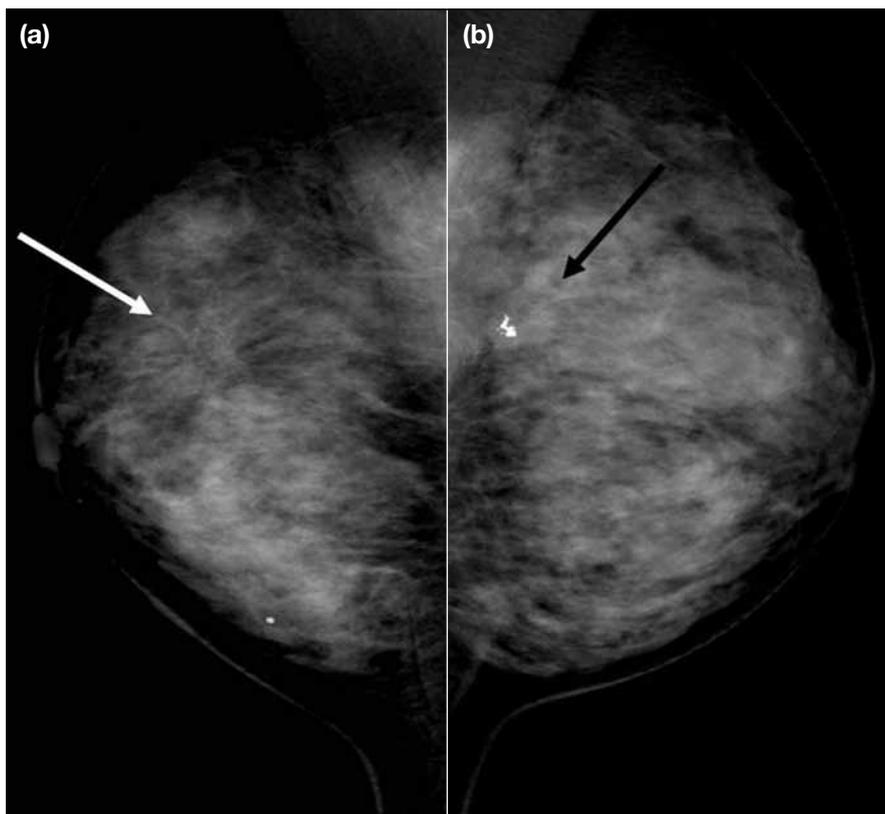
### Patient 2

In March 2005, a 61-year-old woman had her screening mammogram, and was found to have architectural distortion in the upper inner quadrant of the right breast in mammogram (Figure 6).

Ultrasonography of the breast showed a hypoechoic lesion, about 2.5 cm in size, with an indistinct border in the right breast at the 2 o'clock position, corresponding to the architectural distortion seen in the mammogram. Ultrasound-guided core needle biopsy of the hypoechoic lesion showed SA without evidence of malignancy.

The patient underwent follow-up mammogram and ultrasonography of the breast annually. On the surveillance ultrasonography performed 7 years later, the hypoechoic area remained similar in size and morphology in B-mode. However, in colour Doppler mode, there was a significant increase in peripheral vascularity compared with the previous studies (Figure 7). In elastography, the elasticity had decreased with a high fat-lesion ratio of 7.11, which signified a solid lesion (Figure 8).

Further examination with breast MRI demonstrated a T2-weighted slightly hyperintense area associated with segmental non-mass-like enhancement and architectural distortion in the upper inner quadrant of the right breast (Figure 9). There was restricted diffusion as the signal rose in DWI and dropped in ADC images. There were two small enhancing foci, about 0.4 cm in size,



**Figure 6.** Mediolateral oblique mammography views of both breasts of patient 2 at presentation show (a) architectural distortion (white arrow) in the upper inner quadrant of the right breast; no discrete mass or nipple retraction is noted, and (b) a fibroadenoma with coarse calcifications (black arrow) in the upper outer quadrant of the left breast.

within the architectural distortion. The enhancement pattern of the lesions was for a type 2 kinetic curve (Figure 10). Combined with the mammographic and ultrasonographic findings, the MRI features were highly suggestive of DCIS within the area of SA.

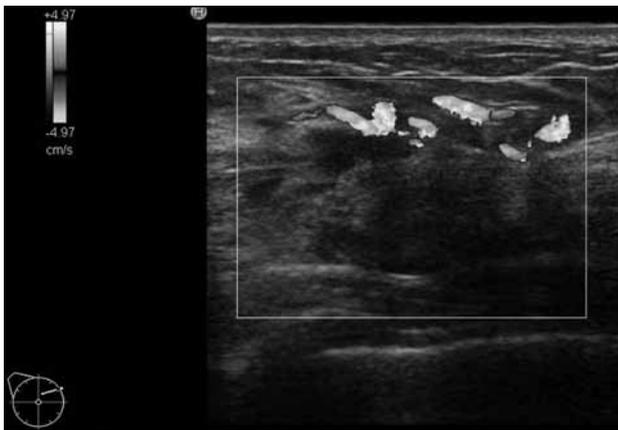
The patient received breast conservation surgery after the suspicion of DCIS was confirmed by biopsy. The histological findings for the final surgical specimen showed DCIS against a background of SA (Figure 11).

## DISCUSSION

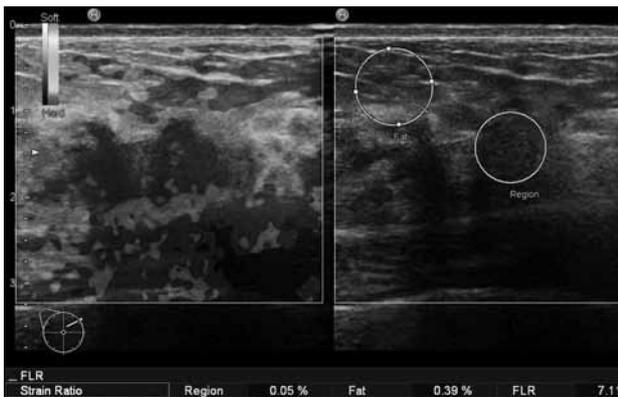
SA is usually asymptomatic and presents as an

incidental finding on screening mammogram. Sometimes, SA can present with mastalgia, but it is often non-palpable on physical examination.

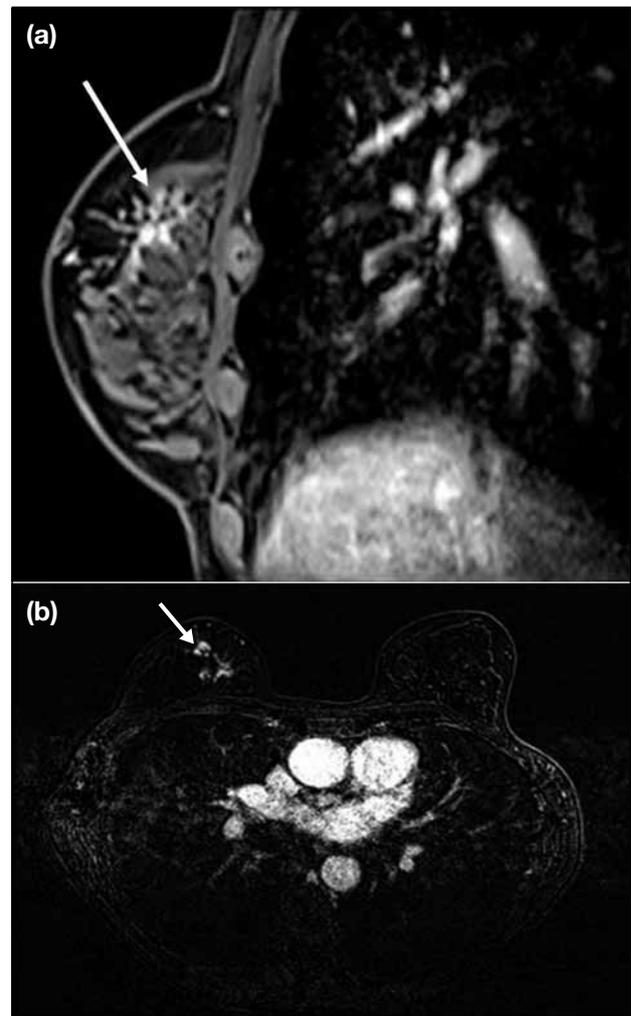
The mammographic findings of SA vary widely. In Günhan-Bilgen et al's study,<sup>7</sup> 55.8% of patients had microcalcifications that were clustered, diffuse, punctate, or amorphous. Less commonly, SA presents with pleomorphic microcalcifications or masses.<sup>8</sup> The pattern of microcalcifications in SA is indistinguishable from breast malignancy. Around 11.6% of SA is detected as a mass on mammogram, which is a subtype called 'nodular SA', with areas of SA forming a mass.



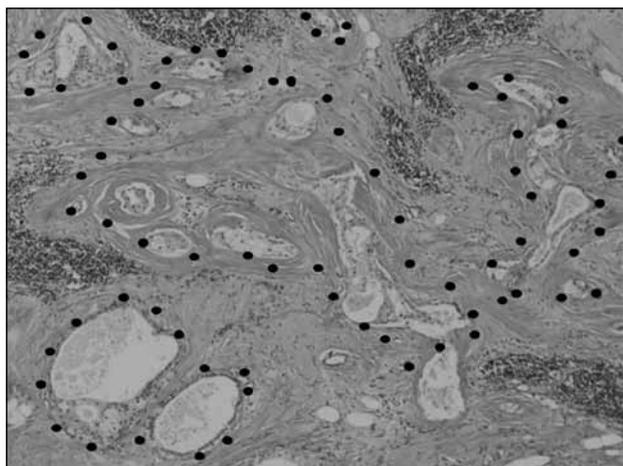
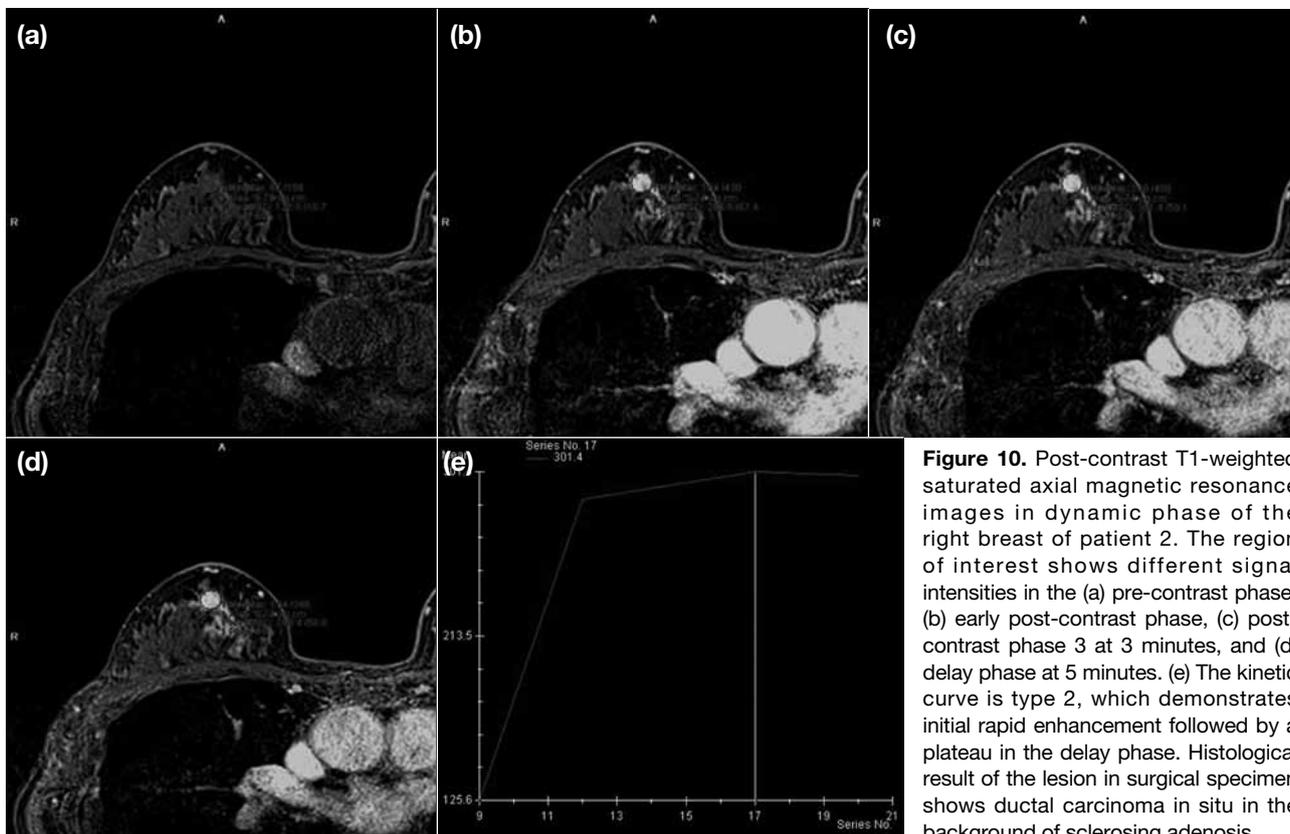
**Figure 7.** Follow-up ultrasonography of the right breast in colour Doppler mode 7 years after initial examination in patient 2 shows a hypoechoic lesion with an ill-defined border and peripheral hypervascularity in the 2 o'clock position, corresponding to the region of architectural distortion detected in mammography.



**Figure 8.** Elastography of the right breast lesion 7 years after initial examination in patient 2: the region of interest as circles in centre of the lesion and in fatty tissue are measured respectively, and the value of fat-lesion ratio is calculated to be 7.11, which falls into the category of solid lesion. The lesion is diagnosed to be ductal carcinoma in situ in subsequent repeated biopsy.



**Figure 9.** Preoperative magnetic resonance images of patient 2: (a) a sagittal post-contrast T1-weighted image of the right breast shows architectural distortion and non-mass-like enhancement (arrow) in the upper inner quadrant, and (b) an axial post-contrast subtraction T1-weighted fat-saturated image shows two small foci (arrow) with rapid early enhancement in the background of non-mass-like enhancement; the findings are suspicious to be malignancy. They are further evaluated with dynamic phase and findings are shown in Figure 10.



**Figure 11.** A histology slide of the surgical specimen: the areas circled by dots represent ductal carcinoma in situ tissue, which has apocrine metaplasia. The background tissue is sclerosing adenosis with strong fibrosis (H&E).

Another 6.9% of SA shows FAD, and 6.9% shows architectural distortion.<sup>7</sup>

On breast ultrasonography, the features of SA are non-specific. Most of the types are ultrasonographically negative except nodular SA, which may be observed as

a solid mass. For SA manifesting as focal symmetric density or architectural distortion on mammography, it can appear as acoustic shadowing or ill-defined hypoechoic areas on ultrasonography.

Since the radiological features of SA mimic malignancy, histological examination is mandatory for a definitive diagnosis. Microscopically, SA is characterised by proliferation of the epithelial elements of the terminal ductal lobular unit and stroma. SA appears as multiple foci with distinct round borders, each around a terminal duct. These foci retain the lobular architecture, but the architecture becomes exaggerated and distorted. The crowded ductules or acini may be compressed or even obliterated by stromal fibrosis.

SA poses a diagnostic challenge both for radiologists and for pathologists because it may mimic infiltrating carcinoma. The presence of myoepithelial cells and intact basement membrane are characteristic of SA. Staining of smooth muscle actin to demonstrate myoepithelial cells, or staining of collagen type IV or lamina to demonstrate preservation of the basement membrane is helpful. Infiltrative cancer, however, lacks these two features.<sup>9-11</sup>

Several studies have suggested that SA is a risk factor for breast carcinoma.<sup>3-5</sup> Authors have reported an overall relative risk ranging from 1.7 to 2.5.<sup>12-14</sup> When atypical hyperplasia is also present, the relative risk rises markedly to 6.7.<sup>12</sup> The study by Moritani et al<sup>15</sup> found that most carcinomas in situ involving SA arise within the ductules of SA rather than intruding from outside, although there was insufficient evidence to draw conclusions on the pre-cancerous potential of SA. Moritani et al<sup>15</sup> hypothesised that, in cases of carcinoma in situ entirely surrounded by SA, the closely associated SA might be the precursor of low-nuclear-grade breast carcinoma. In their study, five of 23 patients had synchronous or metachronous contralateral breast carcinoma; therefore, the cancer risk of SA may involve both breasts. The contralateral breast should also be checked carefully in patients with a large focus of SA or carcinoma in situ against the background of SA.<sup>15</sup>

Lobular carcinoma in situ (LCIS) is more commonly found than DCIS in areas of SA. Since SA develops from a mammary lobule, it is not surprising that LCIS is the most common neoplasm to develop from SA.<sup>2</sup>

Sloane and Mayers<sup>16</sup> suggested that the size of the SA and the patient's age correlate with the risk of carcinoma. Older women (of over 50 years old) have a higher risk of cancer developing from SA. A large focus of SA might carry a higher risk of cancer than a small one. In patients with a large area of SA, e.g. more than 3 cm, follow-up imaging is necessary. Ultrasonography is the modality of choice for follow-up because it has no radiation hazard and is useful for detecting small nodules in dense breasts. Elastography can help to differentiate between benign and malignant lesions by measuring the rigidity.

Careful review of the imaging and histological findings is required after a diagnosis of SA is made by core needle biopsy. For lesions with radiological features highly suggestive of malignancy, e.g. spiculated masses, or branching or fine linear calcifications, the findings can be regarded as radiopathological discordance. Excision may be appropriate to obtain more tissue for a definitive diagnosis.

For lesions that show an increase in size, change in morphology, or suspicious characteristics in follow-up imaging, a repeat biopsy or excision is warranted because of the potential association of SA with DCIS and invasive cancer. When SA shows no significant

interval change in size and morphology in the B-mode of ultrasonography, radiologists need to note the colour Doppler signal because a mild increase in vascularity can be the first ultrasonographic sign of malignant change. Correlation of mammogram, ultrasonography, and MRI findings is essential in depicting the overall picture of SA and its risk of malignancy.

No guideline for follow-up of SA could be found in the English literature. In the two patients presented here, the invasive and in-situ breast carcinoma developed 7 years after the initial diagnosis of SA. We suggest long-term follow-up with bilateral mammography and breast ultrasonography in view of the long latent period for cancer development in SA. In the future, more data for and experience of SA will be accumulated to determine the follow-up strategy.

In view of the clinical, radiological, and pathological characteristics of SA, thorough explanation of the condition to the patient is important. Patients should be informed that, although SA is a benign disease, it is associated with a small risk of developing malignancy in both breasts; therefore, regular follow-up with ultrasonography and mammography is necessary. When there are suspicious features on follow-up imaging, a repeat biopsy or excision is mandatory even if the patient is clinically asymptomatic.

## CONCLUSION

This report is of two patients with SA with subsequent development of invasive or in-situ breast cancer 7 years after the initial diagnosis. Histologically, the carcinoma cells were surrounded by background SA. Given the evidence of increased risk of bilateral breast carcinoma in SA, long-term follow-up of patients with SA is necessary. Any suspicious finding or change in morphology detected on follow-up imaging warrants a repeat biopsy or excision to exclude malignancy.

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