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EPIDEMIOLOGY

Ultrasound characteristics of sclerosing adenosis mimicking breast carcinoma

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Abstract

Background Sclerosing adenosis (SA) is a benign lesion with complicated pathological components and could mimic breast carcinoma in both clinical palpation and medical imaging findings. The present study was conducted to assess the value of ultrasound (US) characteristics in diagnosing SA and their differentiation from breast carcinoma.

Methods We retrospectively reviewed the medical records of 305 women (347 lesions) with invasive ductal carcinoma (IDC) and 54 women with single SA lesion, who had breast excision between April 2016 and July 2018. US BI-RADS atlas and elastography were applied and their associated characteristics were compared between SA and IDC.

Results The mean age of SA was younger than that of IDC (43.6 ± 7.4 vs 53.2 ± 10.3, $P < 0.001$). Compared to IDC, SA had more frequency of parallel orientation (94.44% vs 71.76%, $P < 0.001$) and circumscribed margin (48.15% vs 4.90%, $P < 0.001$), less frequency of irregular shape (64.81% vs 95.97%, $P < 0.001$), hypoechoic echotexture (88.89% vs 98.27%, $P = 0.002$), calcification (12.96% vs 55.04%, $P < 0.001$), and posterior acoustic changes (3.70% vs 53.89%, $P < 0.001$) or associated features (architectural distortion, 3.70% vs 59.65%, $P < 0.001$; duct changes, 18.52% vs 63.40%, $P < 0.001$). Vascularity absence was more common in SA compared to IDC (35.19% vs 6.63%, $P < 0.001$). And the elasticity score was lower in SA (2.38 ± 0.60 vs 3.91 ± 0.81, $P < 0.001$). After adjusting for age, we found spiculated margin, posterior shadowing, calcification, architectural distortion, and vascularity could independently identify the differences between these two entities. After involving elasticity score, the calcification and vascularity could still be independent indicators for differential diagnosis.

Conclusion Understanding SA imaging features will enable radiologists to communicate results to the referring physician consistently, which could benefit a reliable assessment and specific management recommendations. A systematic evaluation of the US BI-RADS atlas together with breast elastography may be a powerful tool to identify SA and differentiate it from breast cancer.

Keywords Sclerosing adenosis · Breast carcinoma · Diagnostic ultrasound · Elastography

Introduction

Sclerosing adenosis (SA) is a proliferative benign lesion in breast, which demonstrate increased numbers of distorted lobules accompanied by stromal fibrosis on pathology [1, 2]. Since it is a histologically complex entity, some SA lesions could mimic invasive breast cancer on both clinical palpation and imaging presentation. Previous studies have described the radiological characteristics of mammography in SA lesions and find SA may present mainly microcalcifications, asymmetric focal density, or focal architectural distortion in some patients [3–5]. However, few studies investigate the ultrasonographic characteristics of SA [6]. As a non-invasive imaging technique, conventional ultrasound was the most efficient technique in detecting benign

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nodular or screening breast cancer, especially when we can acquire breast elastography. However, knowledge of both the conventional ultrasound and elastography in differentiating SA from breast cancer remains scarce [6]. A clear understanding of the ultrasound characteristics of SA is not only essential in differentiating this certain entity from breast carcinoma, but also crucial to improve benefit for clinical management [6].

Materials and methods

Study population

The study was approved by the Ethics Committee of Harbin Medical University. We retrospectively reviewed the medical records of consecutive 305 women (347 lesions) with non-treated invasive ductal carcinoma (IDC), and 54 women with single SA, between April 2016 and July 2018 in our hospital. All these patients were clinically suspicious of breast cancer and underwent surgical excision. Their final pathological results and preoperative imaging records of breast ultrasound were retrieved and analyzed.

Pathological findings

Sections from each breast lesion underwent hematoxylin and eosin (H&E) staining and evaluated by an experienced breast pathologist, who was unaware of the participant's clinical presentation or medical imaging findings. SA was defined as cellular lobulocentric proliferation of both epithelium and myoepithelium, as well as consisting of compressed and crowded gland-like acini [2]. IDC was determined as literature described [7], with heterogeneous growth patterns such as diffuse sheets, nests, cords, or single cells with ductal differentiation, and pleomorphic tumor cells that prominently have nucleoli and numerous mitoses, sometimes together with necrosis, calcification, squamous or apocrine metaplasia.

Ultrasound protocol

Conventional two-dimensional B-mode breast ultrasound and elastography were performed by experienced sonographers and the characteristics of the lesions were carefully reviewed using a HITACHI HI-VISION Preirus System (Hitachi Ltd., Tokyo, Japan) with a EUP-L74 M linear array ultrasound transducer (5–13 MHz, center frequency 7.5 MHz). It also equipped the elastography module, which can acquire the elastographic images of the breast lesions. All patients were at their supine position with hands above the head for adequate exposure of the breast. The ultrasound characteristics of the breast lesions, such as shape, maximum diameter, orientation, margin, internal echotexture, posterior acoustic features, calcification, associated features of surrounding tissues, and vascularity condition were documented according to the recommendation of the 5th edition ACR BI-RADS Atlas Reporting System for breast ultrasound [8]. The elasticity score was queried if the elastographic images [9] were available at their initial presentation. All the images were reviewed by 3 experienced radiologists (ZW, ZL, and JT). In case of disagreement, final consensus was reached through discussion. The shape was interpreted as round/oval vs. irregular. Orientation was depicted as whether the breast lesion was parallel to the chest wall or not. The margin was defined as the morphological features of the boundary between breast lesions and surrounding tissues, which was classified as circumscribed or not circumscribed, and the not circumscribed was further stratified by indistinct, spiculated, angular, or microlobulated. Internal echo pattern was classified as hyperechoic, hypoechoic, and complex cystic and solid. Posterior acoustic features included no posterior features, enhancement, and shadowing. Associated features were defined as architectural distortion, duct changes, or skin changes. The blood flow distribution within and at the rim of the lesions were recorded as recommended by Adler's method [10] into four levels: absent (grade 0), minimal (grade 1), moderate (grade 2), or marked (grade 3), and pulse wave Doppler resistive index (RI) was documented if available. In elastographic imaging, the red–green–blue color map at the left upper corner referred to a color overlay based on the conventional ultrasound image. During the elastographic procedure, stiffer tissues were coded as dark blue which indicating their less deformation compared to the medium soft and most soft ones which were coded as green and red, respectively. With a regular and small perpendicular pressure over the breast skin by using the transducer, a stable and reliable elastography image will show up along with a pressure-amplitude monitor bar with white borderlines at the bottom or a color bar on the left. The elasticity score was evaluated as described in a previous study [11].

Statistical analysis

Data were summarized as means ± standard deviations for continuous variables, and numbers and frequencies for categorical variables. We used chi-square tests to compare SA and IDC differences across categorical ultrasound characteristics (including shape, size, orientation, margin, echo pattern, posterior features, calcification, associated features, and vascularity). We use the student *t*-test to compare the continuous variables between these two entities. Multivariate regression analysis was conducted after univariate analysis to assess the value of ultrasound characteristics in differentiating SA from IDC. The analysis was conducted using JMP

Pro 14.1.0 (SAS Institute, Inc). A 2-tailed *P* value less than 0.05 was considered statistically significant.

Results

The baseline characteristics are shown in Table 1. The median age of the whole study cohort was 51 years old. SA patients were younger than IDC patients (43.6 ± 7.4 vs. 53.2 ± 10.3, $P < 0.001$) at the initial presentation. Forty (74.07%) SA appeared as a nodular lesion on ultrasound imaging. SA lesion was more frequently with regular shape, smaller size (maximum diameter ≤ 1 cm), with more parallel orientation, circumscribed margin, complex cystic and solid internal echotexture, and less calcification, posterior acoustic changes or associated features, as well as less blood flow signals. The elasticity score of SA was significantly lower compared to IDC, as well as the US BI-RADS level. Characteristics such as angular margin, hyperechoic, combined posterior acoustic pattern could not be helpful in differentiating diagnosis. However, in terms of SA features alone, a certain number of lesions may present diverse ill manifestations that could mimic breast carcinoma, such as the higher frequency of irregular contour (64.81%), indistinct margin (51.85%), spiculated margin (9.26%), hypoechoic in-mass echotexture (88.89%), in-mass calcification (12.96%), accompanied duct changes (18.52%), as well as more internal blood flow ≥ moderate grade (18.52%).

Table 1 Baseline conventional ultrasound and elastography characteristics of the study cohort

Baseline variables	SA $N=54$	IDC $N=347$	*P*
Age	43.6 ± 7.4	53.2 ± 10.3	< 0.001
Age (≥ 51 vs < 51)	6 (11.11)	206 (59.37)	< 0.001
Shape (irregular)	35 (64.81)	333 (95.97)	< 0.001
Size (> 1 cm)	29 (53.70)	316 (91.07)	< 0.001
Orientation (not parallel)	3 (5.56)	98 (28.24)	< 0.001
Margin			
Circumscribed	26 (48.15)	17 (4.90)	< 0.001
Indistinct	28 (51.85)	330 (95.10)	< 0.001
Spiculated	5 (9.26)	150 (43.23)	< 0.001
Angular	2 (3.70)	42 (12.10)	0.10
Microlobulated	0	192 (55.33)	< 0.001
Echo pattern			
Hyperechoic	1 (1.85)	1 (0.29)	0.21
Complex cystic and solid	5 (9.26)	5 (1.44)	0.01
Hypoechoic	48 (88.89)	341 (98.27)	0.002
Posterior features			
No posterior features	52 (96.30)	160 (46.11)	< 0.001
Enhancement	1 (1.85)	37 (10.66)	0.04
Shadowing	1 (1.85)	132 (38.04)	< 0.001
Combined pattern	0	18 (5.19)	0.15
Calcifications			
In mass	7 (12.96)	191 (55.04)	< 0.001
Associated features			
Architectural distortion	2 (3.70)	207 (59.65)	< 0.001
Duct changes	10 (18.52)	220 (63.40)	< 0.001
Vascularity			
Absent	19 (35.19)	23 (6.63)	< 0.001
Internal (≥ moderate)	10 (18.52)	238 (68.59)	< 0.001
Rim (≥ moderate)	8 (14.81)	240 (69.16)	< 0.001
RI	0.60 ± 0.35	0.79 ± 0.10	< 0.001
Elasticity score	2.38 ± 0.60	3.91 ± 0.81	< 0.001
US-BI-RADS	3.00 ± 0.00	5.18 ± 0.63	< 0.001

SA sclerosing adenosis, *IDC* invasive ductual carcinoma, *RI* resistive index

In univariate regression analysis (Table 2), age ≥ 51, irregular shape, indistinct or spiculated margin, hypoechoic internal echotexture, posterior shadowing, calcification in mass, architectural distortion, vascularity grade ≥ moderate, and higher RI were all imaging indicators for suspicious IDC, whereas circumscribed margin, complex cystic and solid echotexture, and absence of vascularity were more related to SA. Elastography could help distinguish the borderline of the lesions and also the stiffness of the lesion tissues. The conventional ultrasound and corresponding elastography of SA or breast carcinoma are shown in Figs. 1 and 2, respectively, and Fig. 3 depicts the H&E staining of these two distinct entities.

In multivariate regression analysis (Table 3), after adjusting for age, the spiculated margin, posterior shadowing, calcification in mass, architectural distortion, and vascularity were all predominant characteristics in differentiating SA from IDC. After involving the elastography into the multivariate regression model, the elasticity score, together with calcification, and vascularity could all be independent supporters for the final differentiation diagnosis.

Discussion

SA is a benign but complex lesion for it combines the proliferation of epithelial, myoepithelial, and mesenchymal cells [1, 2, 12], which may set the stage for a higher likelihood of subsequent malignancy. And there may have some phenotypic changes resulting from microenvironmental signals that stimulate progression to more advanced stages of carcinoma [13]. Research from Mayo Clinic had reported that SA as a single feature, may convey an approximate doubling of breast cancer risk [2]. Those may be the plausible reason why SA could mimic the clinical palpation and even the imaging presentation of a malignant lesion [5, 14]. As such, a consistent ultrasound report or note of this entity may aid

Table 2 Univariate regression between ultrasound characteristics and pathology results, the ORs were for diagnosis of IDC

Baseline variables	OR	*P*
Age	1.11 (1.07–1.15)	< 0.001
Age (≥ 51 vs < 51)	11.69 (4.87–28.05)	< 0.001
Shape (irregular)	12.91 (5.96–27.98)	< 0.001
Size (> 1 cm)	8.79 (4.59–16.83)	< 0.001
Orientation (not parallel)	6.69 (2.04–21.94)	< 0.001
Margin		
Circumscribed	0.06 (0.03–0.11)	< 0.001
Indistinct	18.03 (8.75–37.14)	< 0.001
Spiculated	7.46 (2.90–19.19)	< 0.001
Angular	3.58 (0.84–15.24)	0.10
Echo pattern		
Hyperechoic	0.15 (0.01–2.49)	0.21
Complex cystic and solid	0.14 (0.04–0.51)	0.01
Hypoechoic	7.10 (2.20–22.91)	0.002
Posterior features		
No posterior features	0.03 (0.01–0.14)	< 0.001
Enhancement	6.33 (0.85–47.09)	0.04
Shadowing	32.54 (4.45–238.09)	< 0.001
Calcifications		
In mass	8.22 (3.61–18.70)	< 0.001
Associated features		
Architectural distortion	38.44 (9.21–160.40)	< 0.001
Duct changes	7.62 (3.71–15.67)	< 0.001
Vascularity		
Absent	0.13 (0.06–0.26)	< 0.001
Internal (≥ moderate)	9.61 (4.66–19.80)	< 0.001
Rim (≥ moderate)	12.90 (5.89–28.26)	< 0.001
RI	2.13 (1.0003–4.54)	< 0.001
Elasticity score	16.14 (8.05–32.35)	< 0.001

OR odds ratio, *IDC* invasive ductual carcinoma, *RI* resistive index

risk prediction efforts for women with benign breast lesions. However, knowledge of the ultrasound characteristics of SA, as well as the differences between SA and breast cancer has not been fully explored [15]. So we try to assess the clinical value of conventional ultrasound and elastography in diagnosing SA and also try to evaluate their capacity in differentiating SA from breast carcinoma.

In our cohort, the mean age of patients with SA (43.6 years old) was younger than those with breast cancer (53.2 years old), and only 6 (11.11%) patients were older than or equal to the median age (51 years old) of the whole study population, which was consistent with previous studies [5, 15, 16]. Compared to IDC, SA tends to have a less frequent irregular shape, smaller lesion size, more parallel orientation, more circumscribed margin, less hypoechoic pattern, less posterior acoustic changes or associated features, as well as less blood flow and lower RI. Despite SA had relatively less prevalence of all those malignancy-related ultrasound appearances compared to IDC, these characteristics still presented with a higher prevalence in SA to help this entity mimic breast cancer.

In terms of each component of the US BI-RADS lexicon, SA could present different manifestations mimic breast carcinoma, which was consistent with previous studies [5, 15]. There were 29 (53.70%) lesions had a maximum diameter larger than 1 cm, and 35 (64.81%) SA lesions were irregularly contoured, which was similar to a previous study [5]. As for the lesions with not circumscribed margin, 28 (51.85%) lesions were indistinct, 5 (9.26%) lesions were spiculated, and 2 (3.70%) were angular. Hypoechoic internal echotexture was seen in 48 (88.89%) patients. Calcification was detected in 7 (12.96%) lesions, which was consistent with a previous study about the calcification is common in mammographic findings of SA [15]. Of note, the finding of microcalcification was suggesting a biopsy [17]. As for the associated features, some studies found some SA may present architectural distortion in ultrasound [5, 18]. In our study, only 2 (3.70%) SA patients appeared architectural distortion, but 10 (18.52%) patients accompanied by duct changes. One plausible reason was some proliferative SA lesions may contain atypical ductal or lobular hyperplasia [19]. There were 3 (5.56%) SA lesions had not parallel orientation, and 5 (9.26%) SA had complex cystic and solid internal echotexture. A plausible reason may be SA could have fibrocystic changes, which may sometimes present as complex cystic and solid masses [18]. SA with microlobulated margin or combined posterior acoustic pattern was not seen in the current study. Only one SA patient had posterior enhancement or shadowing, respectively. Although SA was more associated with the absence of blood signal in Doppler ultrasound, the more than moderate grade of blood flow distribution pattern could still be seen in a certain number of patients, either for the internal or the rim vascularity. And in that situation, RI may be very helpful in differentiating the two entities, with a specificity of lower RI indicating a SA entity.

In the univariate regression analysis, multiple imaging features could serve as indicators to differentiating SA from carcinoma. In the multivariate regression analysis, after adjusting for age, the spiculated margin, posterior shadowing, calcification, architectural distortion, and vascularity could identify the differences between these two entities. After involving the elastography, the elasticity score, together with calcification, and vascularity could all be contributors for the final differentiation diagnosis. As such, elastography could act as a powerful complementary tool in achieving a diagnosis of complicated SA, especially when there are multiple imaging manifestations mimic malignancy on conventional ultrasound. In addition, the elastographic images could also clearly show the

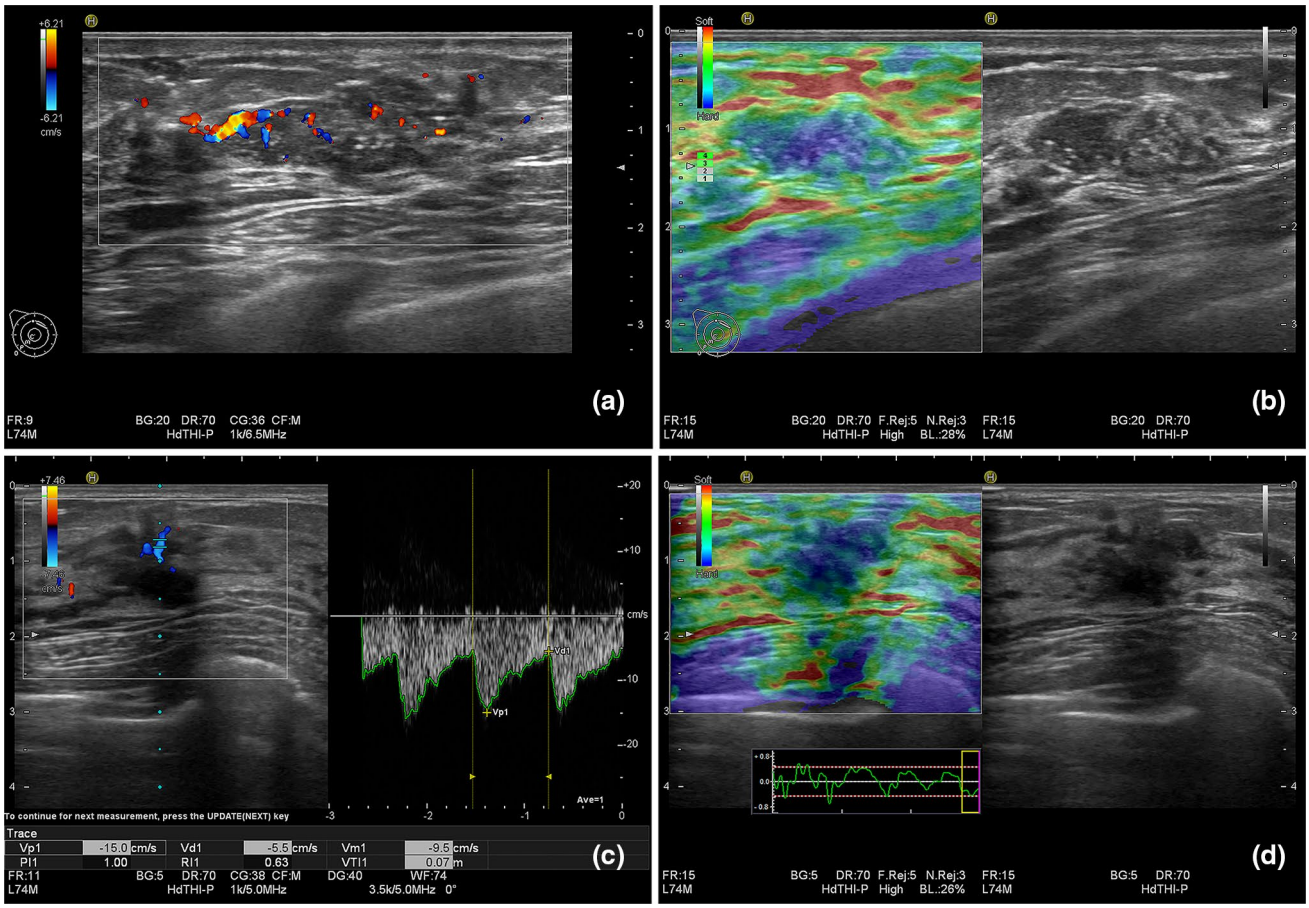

Fig. 1 The SA lesions presented different ultrasound features. In one patient, it appeared with parallel orientation, irregular shape, multiple microcalcifications, posterior acoustic enhancement, and marked blood flow (**a**). Its elastography more clearly showed the lesion contour with a color code pattern of central blue surrounded by green, indicating its stiffness distribution with an elasticity score of 3 (**b**). In another case, the lesion was ill-defined, with architectural distortion, posterior shadowing, a central blood flow pattern with relative lower RI = 0.63 (**c**); however, its elastographic color features were similar to the first case with an elasticity score of 3 points (**d**)

borderline of the breast lesion, especially for those that could not be easily distinguished from their surrounding tissues, or even for some deeply located lesions which could not present in clinical palpation.

All the above evidence suggested that diagnosing SA and differentiating it from breast carcinoma is not easy by only a few ultrasound features. The US BI-RADS atlas provides standardized breast imaging terminology, report organization, assessment structure, and a classification system. In the current study, we found the US BI-RADS atlas could be a powerful tool in demonstrating the SA lesion, and also in differentiating SA from IDC lesions. Most of these conventional ultrasound characteristics could be helpful for a consistent differential diagnosis between SA and IDC. Moreover, the US BI-RADS atlas, together with elastography should be combined to provide quality and standard diagnose comments to improve the quality of patient care. Younger radiologists should take training before clinical practice in order to magnify the benefit of these diagnosing tools.

The strength of the study was that it assessed the capacity of the US BI-RADS atlas and elastography in detecting SA features as well as differentiating it from breast carcinoma. However, our study also had some intrinsic limitations as a retrospective observation. The sample size was small for SA lesions and they underwent surgical excision owing to suspicious malignancy on clinical presentation. That was also the plausible reason for the majority of SA lesions were nodular on ultrasound images and so we still lack the information regarding the disparity between nodular and non-nodular SA. Considering the non-nodular SA may also challenge the final diagnosis, further larger sample studies are needed to explore more imaging atlas of this complicate entity.

In summary, SA is a complicated entity that may present diverse ultrasound characteristics, so that awareness of the possible imaging features will enable radiologists

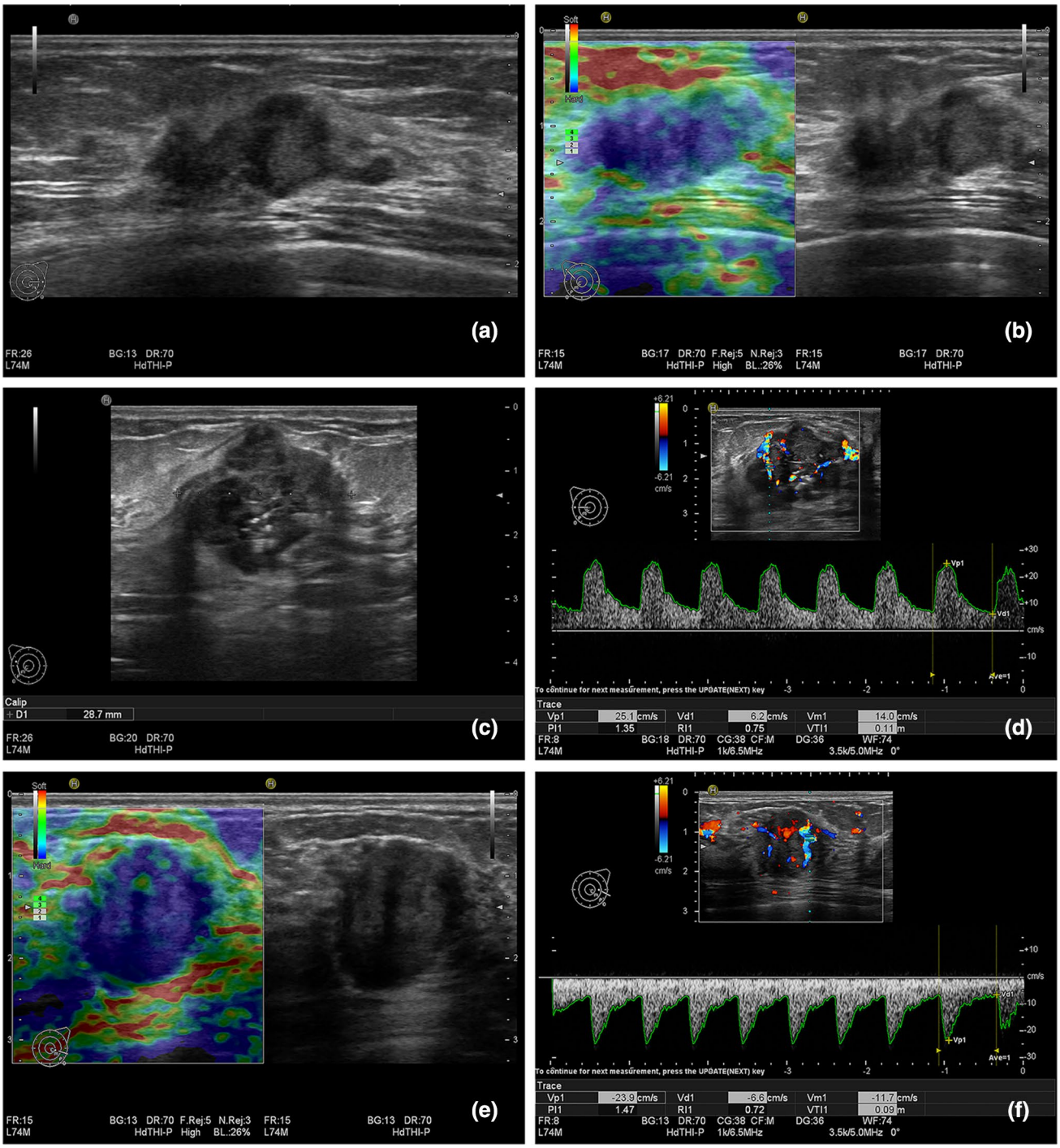

Fig. 2 The ultrasound characteristics of IDC in three patients were differently presented. The mass of the first patient showed a lesion with rat-like shape (**a**) which probably indicates its anisotropy growth pattern and associated duct changes. Its elastography was coded as dark blue for its advance stiffness and the elasticity score should be 4 points (**b**). In the second patient, the lobulated lesion had micro-calcifications in the center, posterior enhancement, and apparent blood flow inside and surrounding the mass with a relatively higher RI = 0.75 (**c**, **d**). In the third patient, the mass had a non-parallel orientation, speculated and indistinct margin, combined posterior acoustic pattern, advance central blood flow with an RI of 0.72, and a dark blue coded elastography (**e**, **f**)

to consider sclerosing adenosis in the final diagnosis. US BI-RADS atlas and elastography are powerful tools in the decision making progress. However, since there are multiple imaging features of SA that could mimic malignancy, the histopathologic examination may be mandatory for a definite diagnosis.

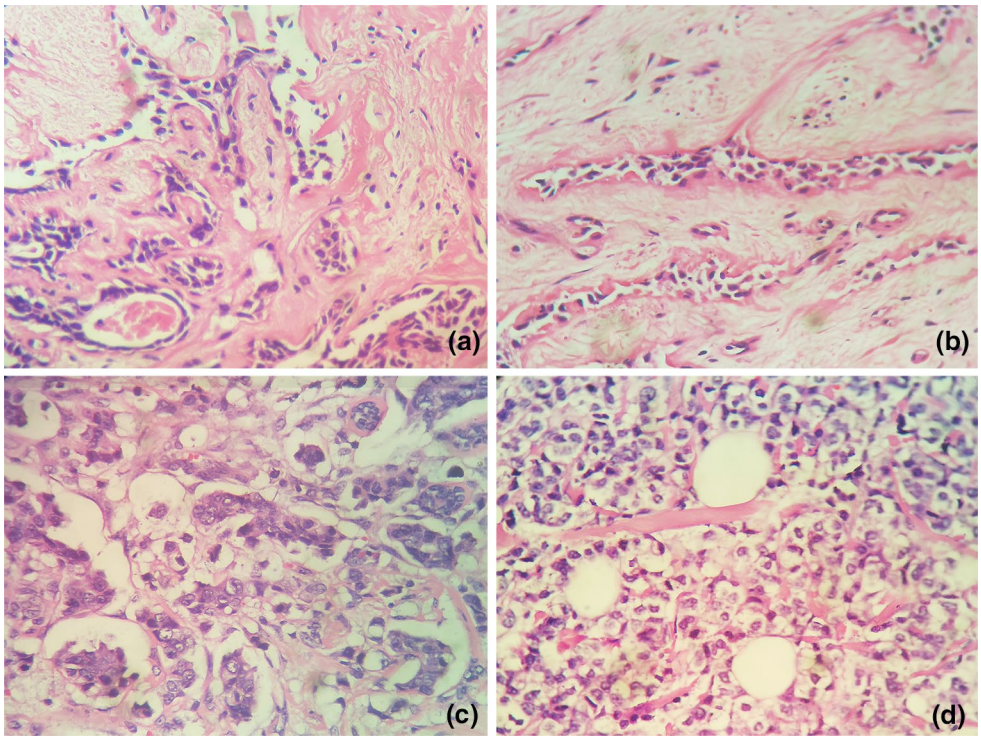

Fig. 3 H&E staining of SA and IDC as two distinct entities. H&E staining shows that the SA lesion was characterized as consisting of compressed and crowded gland-like acini with the proliferation of distorted stromal fibrosis (**a**, **b**), whereas an IDC lesion was presenting diffuse cords and nests of pleomorphic tumor cells, which prominently had nucleoli and numerous mitoses (**c**, **d**)

Table 3 Multivariate regression analysis for identifying predominant ultrasound characteristics for differentiating IDC from SA; ORs were for diagnosing IDC

Indicators	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.13 (1.08–1.19)	< 0.001	1.12 (1.06–1.18)	< 0.001
Shape (irregular)	2.79 (0.98–7.95)	0.053	0.58 (0.15–2.20)	0.42
Orientation (not parallel)	1.80 (0.40–8.11)	0.43	0.84 (0.16–4.46)	0.84
Margin (spiculated)	3.68 (1.13–11.96)	0.02	1.98 (0.54–7.22)	0.29
Hypoechoic echo pattern	2.05 (0.24–17.23)	0.50	4.17 (0.38–45.95)	0.24
Posterior shadowing	20.48 (2.01–208.43)	0.001	5.59 (0.57–55.00)	0.09
Calcification in mass	5.37 (1.87–15.43)	0.001	4.47 (1.24–16.04)	0.01
Architectural distortion	6.37 (1.36–29.83)	0.005	3.33 (0.55–19.99)	0.16
Vascularity (absent)	0.19 (0.06–0.53)	0.001	0.18 (0.05–0.71)	0.01
Elasticity score	–		7.82 (3.05–20.07)	< 0.001

SA sclerosing adenosis, *IDC* invasive ductual carcinoma, *OR* odds ratio

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Compliance with ethical standards

Conflict of interest The corresponding author Zhenzhen Wang has received a research grant from Harbin Science and Technology Bureau (CN). All the co-authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of our institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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