Original Article
Value of ultrasound in diagnosis of diabetic mastopathy

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Abstract: Objective: The aim of the study is to reveal the value of ultrasonography (US), ultrasound elastosonography (UE) and contrast-enhanced ultrasonography (CEUS) in diagnosing or differentially diagnosing diabetic mastopathy (DMP). Methods: A retrospective analysis was performed to compare the image features of preoperative US, UE and CEUS in 19 DMP cases, 49 randomly selected cases with breast invasive ductal carcinoma (IDC) and 34 breast fibroadenoma (FA) cases. Results: In DMP group, the average age was larger than that in FA group ($P<0.05$), but was similar to that in IDC group ($P>0.05$); the average lesion diameter was greater than that in FA groups ($P<0.05$), but was similar to that in IDC group ($P=0.670$). The ultrasonograms of DMP group were characterized by unclear boundary, high echo halo, while the detection rates on rear echo attenuation and internal echo heterogeneity were similar to those in IDC group ($P>0.05$), but higher than those in FA group ($P<0.05$). The detection rates of internal calcified lesions and blood flow signals in DMP group were lower than those in IDC group ($P<0.05$). The average elasticity score of DMP group was similar to that in IDC group ($P>0.05$) but higher than that in FA group ($P<0.05$). The CEUSs of DMP group showed small enhancement of lesions and had higher probability of "late in and late back" pattern than those in IDC and FA groups ($P<0.05$), but a lower probability of twisted large blood vessels than those in IDC ($P<0.05$) and FA ($P<0.05$) groups. Conclusion: Preoperative US and UE have limited value in the differential diagnosis of DMP and breast IDC. CEUS is valuable for the differential diagnosis of DMP. The occurrence of DMP should be seriously considered when CEUS shows the following features in the masses of suspect breast tumors: few contrast agents enters the lesions; the signal is weaker in lesions than in surrounding normal breast tissues; no twisted large blood vessel is observed.

Keywords: Diabetic mastopathy, ultrasound, contrast-enhanced ultrasonography

Introduction

Diabetic mastopathy (DMP), also known as diabetic sclerosing lymphocytic lobulitis (DSLL) or fibrous mastopathy, is an abnormal fibrosis disease closely related to the long-term insulin therapy. It is often misdiagnosed as breast cancer by clinical and imaging diagnoses [1-3]. Currently, very limited studies are related to the ultrasonic diagnosis of DMP and most of them are single case reports [4-6]. Therefore, the current study retrospectively analyzed the preoperative features of ultrasonography (US), ultrasound elastosonography (UE) and contrast-enhanced ultrasonography (CEUS) in 19 DMP patients, which were compared with those features in two most common and typical diseases with benign or malignant breast lesions: invasive ductal carcinoma (IDC) and fibroadenoma (FA). Based on this information, we can reveal the value of US, UE and CEUS in diagnosing or differentially diagnosing DMP.

Materials and methods

Subjects

The 17 DMP patients with 19 lesions from January, 2008 to June, 2015 were selected. These subjects were pathologically confirmed as DMP patients after having surgeries in our hospital. They were all females, aged from 18 to 65 (50.2±10.5). Two of them had disease recurrence leading to both ipsilateral and contralateral DMPs. Sixteen cases (16/19, 84.2%) had diabetes before. We randomly selected 49 breast IDC cases and 34 breast FA cases and confirmed them by pathological examination, at the same period of DMP cases. These patients were also females. All patients completed pre-

Table 1. The comparison of ultrasonic diagnosis results in DMP, breast IDC and FA cases

Groups	Case Number	Ultrasonic diagnosis						
		Missed	Malignant	Hyperplasia	Fibroadenoma	Ductal tumor	Ductal ectasia	To be determined
DMP	19	0	18	0	0	0	0	1
IDC	49	0	47	0	1	0	1	0
FA	34	0	6	1	26	0	0	1

Table 2. The comparison of ultrasonic features in DMP, breast IDC and FA

Groups		Case Number	High echo halo		Clear boundary		Homogeneous internal echo	
			Yes	No	Yes	No	Yes	No
DMP ①		19	2	17	2	17	2	17
IDC ②		49	9	40	6	43	9	40
FA ③		34	25	9	27	7	23	11
P value	①:②		0.413		0.517		0.439	
	①:③		0.000		0.000		0.001	

Table 3. The comparison of other ultrasonic features in DMP, breast IDC and FA

Groups		Case Number	Posterior echo attenuation		Internal calcification in lesions		Blood flow signals in lesions	
			Yes	No	Yes	No	Yes	No
DMP ①		19	18	1	6	13	3	16
IDC ②		49	41	8	39	10	35	14
FA ③		34	6	28	13	21	19	15
P value	①:②		0.359		0.001		0.000	
	①:③		0.000		0.124		0.007	

operative US, UE and CEUS examination. IDC patients were aged from 30 to 81 (50.6±11.2), and FA patients were aged from 15 to 54 (35.8±10.4).

Experimental apparatuses and methods

Philips Iu22, Logiq E9 and Philips Elite ultrasonographs were used to scan all lesions before operation. During grayscale ultrasonography, the default apparatus settings for breast examination were used. When lesions were found, depth, gain and focusing site were adjusted according to the specific circumstances of the lesions so that the images could achieve the best quality. Based on breast imaging-reporting and data system-ultrasound (BI-RADS-US), lesions were estimated by the following ultrasonic performances: mass number, size, morphology, boundary, internal echo, posterior echo, posterior halo and calcification. Color Doppler ultrasonography was applied to access the blood flow richness surround or inside the lesions.

The static pressure elastography in real-time double-image mode was used, which simultaneously displayed elastograph and grayscale image. Referencing the scoring criteria of elastography and according to the different colors of lesion regions, we graded the elastograms using the 5 points scoring method proposed by Baoming Luo [7]: 1 point, all or most parts of the lesions were in green; 2 points, the center of lesions was in blue and the periphery in green; 3 points, the lesion region showed a similar proportion of green and blue; 4 points, overall lesion color was blue but with a little green inside; 5 points, the lesions and surrounding tissues were in blue, and with or without green signals inside. Four to five points indicated the tissues with high hardness, which were diagnosed as malignant tissues.

The following parameters in Philips Iu22 were used: L9-3 broadband linear probe array, pulse inversion harmonic (PIH), mechanical index (MI)=0.06. The probe was fixed at the most appropriate tumor section. The patients were subjected with intravenous bolus injection of 5 mL conventional ultrasound contrast agent SonoVue, and then rapidly injected with 5 mL saline. The dynamic image was continuously captured for 3 min, and then stored in hard disk.

Statistical analysis

The statistical software SPSS17.0 was used to perform statistical analysis. The quantitative data were showed in means ± SD. Two groups
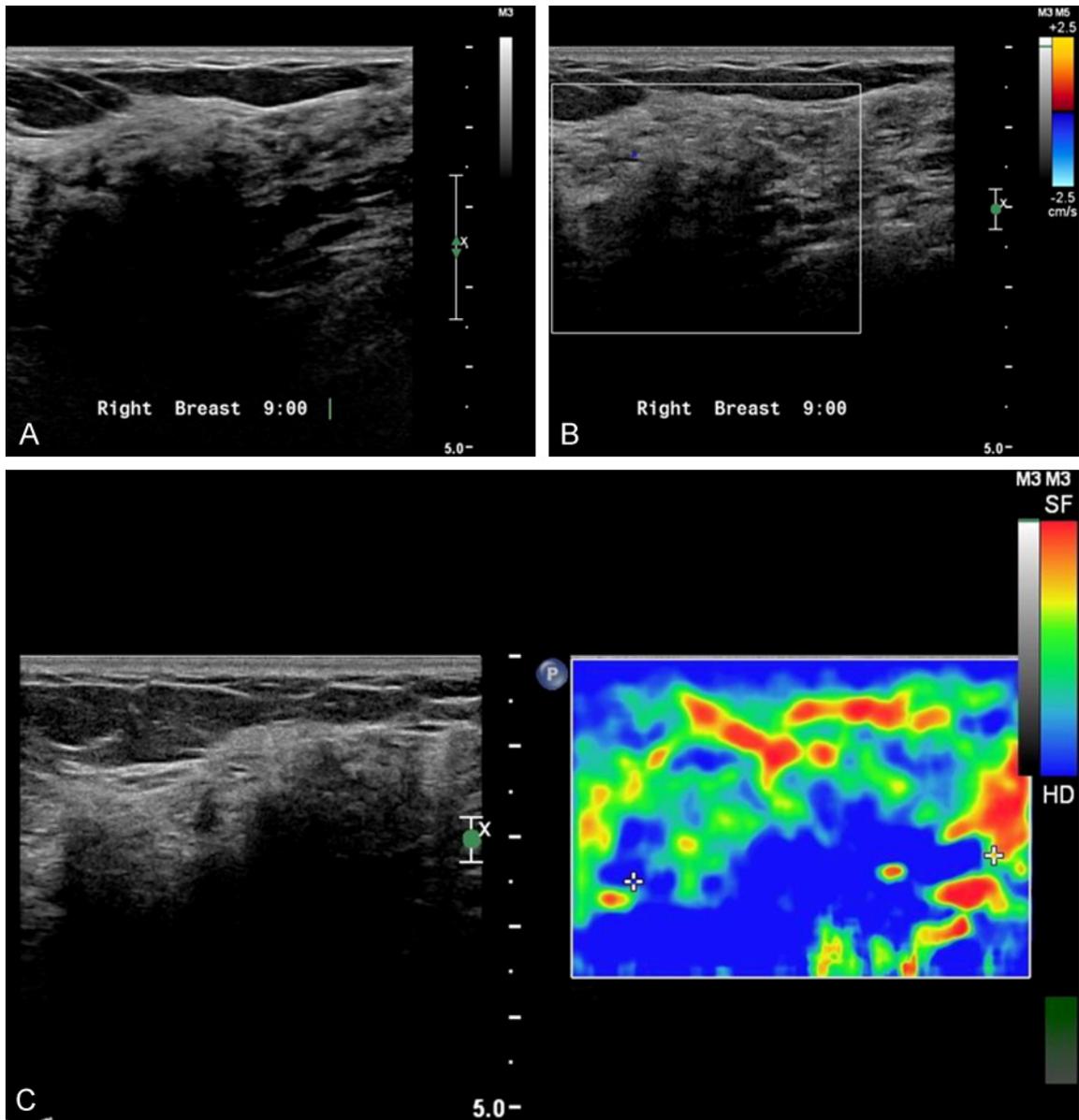
Figure 1. DMP ultrasonograms. A. Irregular mass morphology, unclear boundaries, high echo halo in anterior mass, heterogeneous inner echo, posterior echo attenuation. B. Dot-like color blood flow signals were surround but not inside the mass. C. In elastosonograph, the whole lesion was in blue, with green signals around it. The score was 4 points.

Table 4. The comparison of elasticity scores in DMP, breast IDC and FA

Groups	Case Number	Elasticity scores				
		1 point	2 points	3 points	4 points	5 points
DMP	19	0	0	0	12	7
IDC	49	0	0	7	20	22
FA	34	2	7	19	5	1

were compared using the two independent sample t-tests. The count data were analyzed by chi-square test or Fisher probabilities. $P<0.05$ denoted statistical difference.

Results

The average age of the DMP patients was 50.2±10.5, which was larger than that in FA group (35.8±10.4, $P<0.05$; But was similar to that in IDC group (50.6±11.2, $P>0.05$). The maximum and average lesion diameters in DMP patients were

Table 5. The CEUS features in DMP breast IDC

Groups	Case Number	Enhancement patterns		Disappear patterns		Enhancement degrees		Twisted large blood vessels	
		Early enhancement	Late enhancement	Early disappear	Late disappear	Strong enhancement	Weak enhancement	Yes	No
DMP ①	19	9	10	9	10	6	13	3	16
IDC ②	49	42	7	31	18	40	9	38	11
FA ③	34	24	10	11	23	28	6	8	26
P value ①:②		0.000		0.003		0.000		0.001	
①:③		0.004		0.219		0.000		0.042	

19-62 mm and 34.5±8.7 mm, respectively, which was greater than those in IDC group (11-42 mm and 31.2±8.4 mm, P=0.671) and FA group (7-58 mm, 23.2±11.3 mm, P=0.000).

The comparison of ultrasonic diagnosis results in DMP, breast IDC and FA groups were shown in **Table 1**.

An ultrasonography feature of the lesions in 19 DMP cases was the solid heterogeneous mass with low echo. The ultrasonograms of DMP group were characterized by unclear boundary and high echo halo, and the detection rates of rear echo attenuation and internal echo heterogeneity were similar to those in IDC group (P>0.05), but higher than those in FA group (P<0.05). The detection rate of internal calcified lesions in DMP group was lower than that in IDC group (P=0.001) but similar with that in FA group (P=0.124). The detection rate of internal blood flow signals in DMP group was lower than that in IDC and FA groups (P<0.05). The comparison of US features among DMP, IDC and FA groups was shown in **Tables 2** and **3**. The surrounding regions in 12 (12/19, 63.2%) DMP cases exhibited color blood flow signals (**Figure 1A** and **1B**).

The average elasticity score of DMP lesions was 4.36±0.27, which was similar to that in IDC lesions (4.35±0.29) (P=0.82), but was higher than that in FA lesions (2.88±1.49) (P=0.000) (**Table 4** and **Figure 1C**).

The probability of later enhancement in DMP CEUS was higher than that in IDC CEUS (52.6% VS 14.3%, P=0.000) and FA CEUS (52.6% VS 29.4%, P=0.004). The probability of later disappear in DMP CEUS was higher than that in IDC CEUS (52.6% VS 36.7%, P=0.003), but a bit lower than that in FA CEUS (52.6% VS 67.6%, P=0.104). The probability of low enhancement in DMP CEUS was higher than that in IDC

(68.4% VS 18.4%, P=0.000) and FA (68.4% VS 17.6%, P=0.000) CEUSs. The probability of twisted large blood vessels in DMP CEUS was lower than that in IDC CEUS (15.8% VS 77.6%, P=0.000), and a bit lower than that in FA CEUS (15.8% VS 23.5%, P=0.042) (**Table 5** and **Figure 2A-C**).

Under the pathological light microscope, DMP cases showed mature lymphocytes, infiltration of plasma cells, and infiltration of lymphocytes at acini and duct epitheliums. Fibrosis and hyaline degeneration were obvious in the mesenchyme, which was accompanied by different numbers of epithelioid cells. Small blood vessels were also obviously infiltrated by lymphocytes. There was lymph cell infiltration in the lobuli. Lobular crypts were disappeared. Different degrees of lymphocyte infiltrations were around mesenchymal capillaries (**Figure 3**). Immunohistochemistry results: α-SMA: (++)-(+++), CD34: (-)-(+).

Discussion

The incidence of DMP is about 0.06%-3% [2]. There were 2034 breast mass excision cases at the same period recorded by the pathology database of our hospital. Among them, 19 cases were DMP so that the DMP incidence in our database was 0.9%, which was similar to the data in the literatures. Previously studies demonstrate that DMP recurrence can occur at new regions of ipsilateral or contralateral breast after excision [4]. In our DMP cases, 2 patients had DMP recurrence: one at ipsilateral breast and the other one at contralateral breast.

The histopathological changes of mammary gland are the basis of imaging diagnosis. The US diagnosis features of mammary gland include unclear mass boundary, high echo halo and posterior echo attenuation. Previously studies attribute these three pathological
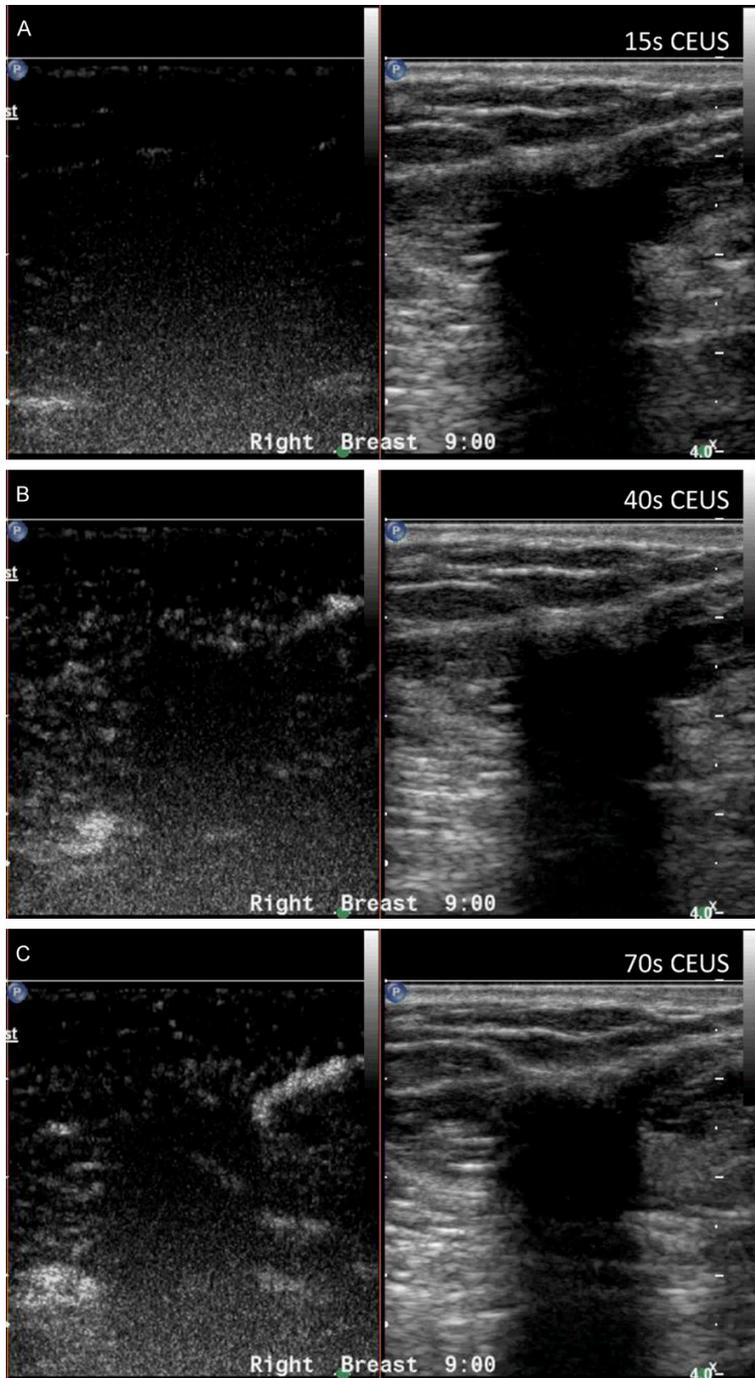
Figure 2. DMP CEUS. A. The entrance of contrast reagent to lesions was revealed by 15 s CEUS. B. 40 s CEUS exhibited the entrance of few contrast reagents inside the lesion, which is less than the surrounding tissues. C. 70 s CEUS showed the entrance of contrast reagent inside the lesion, which is also significantly less than surrounding tissues. No signal of twisted large blood vessels.

tumor mesenchyme [8]. As shown in **Table 2**, our study also demonstrates that these three features mainly exist in DMP cases, which is very similar to IDC cases. Thus, DMP is usually misdiagnosed as malignant pathological changes by preoperative US. Under light microscope, DMP lesions were broadly infiltrated by inflammatory lymphocyte; mesenchyme obviously had fibrosis and hyaline degeneration. We consider that these phenomena indicate the occurrence of acute or chronic inflammation and fibrosis in DMP lesions. The central tissues of DMP lesions may have potential necrosis and therefore showed low echo, while repeatedly reparative hyperplasia happens in the junctures between lesions and normal tissues. Thus, DMP ultra sonogram exhibits unclear boundaries. The anterior region of DMP lesions showed high echo halo, which is similar to the "malignant halo" in malignant tumors. Thus, DMP is frequently misdiagnosed as malignant tumors. However, their nature is not the same. FA hardly has this feature. Some studies indicate that the microenvironment around breast cancer cells is different from normal mesenchymal environment [9-11]. A large number of fibroblasts are activated by the increase of extracellular matrix and microvessel density, the infiltration of inflammatory cells. These activated fibroblasts are called cancer-associated fibroblasts (CAFs). During the inflammatory pathogenesis of normal breast tissue, the accompanied fibrosis leads to the hyperplasia of myofibroblasts, which is named as normal fibroblasts (NFs) comparing to CAFs. Both of them are muscle fiber cells with the
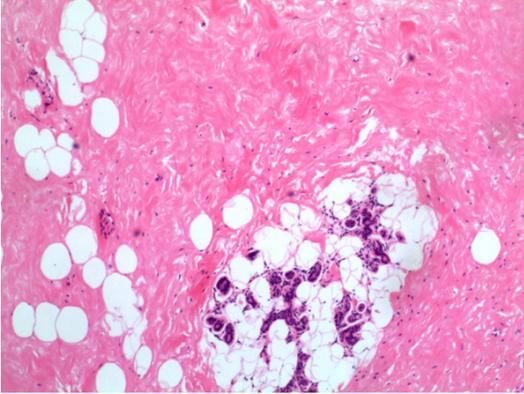
changes to the infiltration of breast IDC parenchyma to surrounding tissues, the accompanied mesenchymal reactions, and the increase of fibrosis and disordered arrangement in

Figure 3. DMP pathological section. Infiltration of mature lymphocytes and plasma cells (HE × 40). Acini and duct epitheliums were also infiltrated by lymphocytes. Fibrosis and hyaline degeneration were obvious in the mesenchyme, which was accompanied by different numbers of epithelioid cells. Small blood vessels were also obviously infiltrated by lymphocytes. There was lymph cell infiltration in the lobuli. Lobular crypts were disappeared. Different degrees of lymphocyte infiltrations were around mesenchym capillaries.

characteristics of both fibroblasts and smooth muscle cells, which make it hard to distinguish them under light microscope. We think that the ultrasonography features "unclear mass boundary, high echo halo and posterior echo attenuation" are caused by the fibrosis of mammary gland cells and glandular tissues after the appearance of broad inflammatory response in DMP lesions. The blood flow signals in the DMP lesions were only detected in 3 cases (15.8%) by color Doppler ultrasonography. This detection rate was significantly lower than those in IDC (71.4%) and FA (55.9%) lesions (P<0.05). Thus, compared with breast IDC, the lack of blood supply is one of the DMP characteristics. Blood flow signals were detected in the border of lesions in 12 DMP cases (12/19, 63.2%), which might be caused by reparative hyperplasia in surrounding regions leading to the increase of vascular permeability and blood flow, as well as vascular dilatation. On the contrary, vascular occlusions were present inside the lesions, which might be due to inflammation-induced necrosis.

Previous studies demonstrate that breast elastosonogram can show the distribution of muscle fiber cells in the breast mass, which can be revealed by the distribution of α-SMA. Our study suggests that the expression of α-SMA is positively correlated with UE score. In DMP lesions, the scores of α-SMA expression were (++)-

(+++), denoting high expression level. Thus, the UE scores were also high. UE diagnosis was based on the hypothesis "The benign one is soft and the malignant one is hard". As we discussed above, DMP lesions are consist of NFs and with no malignant component. The UE scores of DMP group are similar to those of IDC group. Thus, UE cannot accurately differentiate DMP and breast IDC.

CEUS can sensitively reveal the features of blood supply and perfusion in breast mass, including vascular shape and distribution, enhancement pattern, enhancement intensity, and several quantitative indexes acquired in time-intensity curve. In the current study, the CEUS patterns of IDC lesions were "early in and early out", higher signals in lesions than in surrounding tissues, "high enhancement", visible twisted large blood vessels. On the contrary, the CEUS patterns of DMP lesions were "late in and late out", lower signals in lesions than in surrounding tissues, "low enhancement", with low probability of twisted large blood vessels. These two groups showed statistically difference. The CEUS signals are closely related to microvessel density (MVD) in the lesions. In this study, the immunohistochemistry scores of CD34 in DMP lesions were (-)-(+), suggesting low MVD in the lesions. Thus, the lesions showed a "low enhancement" pattern. Previously studies [13, 14] use "twisted large blood vessels" as a CEUS feature of breast carcinoma. However, DMP lesions are benign. Although this feature could also be observed in DMP lesions (3/19, 15.8%), its probability was significantly lower than that in IDC lesions (P<0.05). Saracco et al. [15] report that the imaging patterns of atypical and typical breast carcinoma were similar. Their imaging patterns are both characterized by "early in and early out" while the perfusion pattern of DMP lesions in our study was characterized by "slow in and slow out". Thus, the CEUS features are valuable to for the differential diagnosis of DMP and breast carcinoma.

As showed in **Tables 1** and **4**, preoperative DMP diagnosis is hard to be misdiagnosed as breast FA. The UE score of DMP is significantly higher than FA, which suggests that US and UE are valuable for the differential diagnosis of DMP and breast FA.

When comparing the randomly selected ultrasonograms of 19 DMP cases and 49 breast ID cases, they showed evident similarities on

boundary clarity, high echo halo, internal echo homogeneity, posterior echo attenuation and elasticity scores, which often make DMP be misdiagnosed as malignant pathological changes by preoperative ultrasonography. In this study, the misdiagnosing rate of DMP by US is 100%, which is caused by its low occurrence and the insufficient understanding by ultrasonography operators. Besides, it may be caused by the difficulty in accurately distinguishing DMP and breast carcinoma just based on ultrasonic imaging features. In addition, our study supports the value of CEUS in differentially diagnosing DMP. The occurrence of DMP should be seriously considered when CEUS shows the following features in the masses of suspect breast tumor: few contrast agent enters the lesions; the signal is weaker in lesions than in surrounding normal breast tissues; no twisted large blood vessel is observed. Further pathological examination should be performed to make a definite diagnosis.

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Disclosure of conflict of interest

None.

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