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ORIGINAL PAPER

Mammographically non-calcified ductal carcinoma *in situ*: sonographic features with pathological correlation in 35 patients

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AIM: To present the sonographic findings of mammographically non-calcified ductal carcinoma *in situ* (DCIS) with histopathologic correlation.

MATERIALS AND METHODS: The mammographic and ultrasonographic presentations of 47 radiographically non-calcified DCIS lesions in 35 patients were retrospectively analysed. Histological characteristics (architectural appearance, nuclear grade, percent of involved lobules, and presence of necrosis) were reviewed.

RESULTS: Seventeen lesions were not mammographically visible (17/47, 36%). Ultrasonographically, these lesions showed an irregular shape (28/47, 60%), microlobulated margins (34/47, 72%) and abrupt interfaces (42/47, 90%). Only 11% (5/47) displayed posterior shadowing. The echotexture of these lesions was most frequently complex (29/47, 62%); therefore, they were divided into two types: type I (24 cases), which were predominantly solid with cystic components, and type II (five cases), which were predominantly cystic with a solid intra-cystic component. A trend to have greater than 50% DCIS cells in cancerous lobules was observed in masses displaying type I echotexture (difference = 36%, 95% confidence interval 10.6–62.5) and microlobulated margins (difference = 32%, 95% confidence interval 5.1–58.7).

CONCLUSION: Ultrasonographically detected radiographically non-calcified DCIS commonly displays an irregular shape, microlobulated margins, and complex echotexture, giving a ''pseudomicrocystic'' appearance. Microlobulated margins and ''pseudomicrocystic'' echotexture seem to be associated with a cancerization of the lobules.

Introduction

Although ductal carcinoma *in situ* (DCIS) is commonly characterized by the presence of microcalcifications on mammograms,[1] less frequently DCIS may present as a non-calcified radiographic abnormality.[2,3] Reported sonographic features of DCIS are usually aimed at the identification of mammographically detected microcalcifications.[4–8] There is minimal literature describing the sonographic features of mammographically non-calcified DCIS.[2,4] In addition, although hypotheses have been propounded,[4,5] no study has correlated sonographic features with pathological characteristics, particularly regarding the involvement of the terminal ductolobular units.

The purpose of this study was to describe the sonographic appearance of mammographically non-calcified DCIS according to the Breast Imaging Reporting and Data System (BI-RADS),[9] and to

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correlate the sonographic features with pathological characteristics.

Materials and methods

The research ethics board did not require approval for this retrospective review of images and data. Permission was obtained from the hospital for review of the patients' medical records.

Patient recruitment

A retrospective review identified 697 (41.3%) malignant lesions from 1688 consecutive lesions biopsied under sonographic guidance in our hospital from January 2002 to December 2005. Among that group, 104 lesions were selected where the most suspicious histological diagnosis was DCIS (65 lesions), atypical ductal hyperplasia (19 lesions), and atypical papillary neoplasms (20 lesions). One patient (one DCIS lesion identified on biopsy) in whom no subsequent surgical excision was performed was excluded. Of these three groups, 47 lesions were identified where post-surgical results yielded DCIS, and no microcalcifications were seen on mammography. These 47 DCIS lesions that constitute the study group were found in 35 patients of whom four patients had two lesions and four others had three lesions each. Two patients had a microinvasive component ($<$2 mm) identified after surgical excision. Medical records were reviewed to determine the following clinical features: presence of a palpable mass, nipple discharge, and Paget's disease.

Imaging and image interpretation

Two radiologists with 10 and 5 years of experience retrospectively reviewed in consensus the mammographic and sonographic features (BM) ME.

Mammographic findings

Mammography was used as the reference standard to ascertain the absence of microcalcifications. Screen film mammography was performed using the LORAD MIV mammographic unit (LORAD, Danbury, CT, USA). Mammographic characteristics were evaluated according to the American College of Radiology BI-RADS.[9]

Sonographic findings

At our institution, breast sonography is performed to evaluate specific abnormalities discovered either at clinical examination or on mammography, or as an adjunct to screening mammography in women with dense breasts (mammographic parenchymal density type 3 and 4). The entire breast is usually imaged. All studies were stored on the picture archiving and communication system (PACS). The sonographic characteristics were evaluated according to the BI-RADS classification.[9] When the echo pattern of these lesions was complex, (a solid associated with a cystic component), there were arbitrarily separated into two different subgroups (Fig. 1). A predominantly solid mass with cystic components was called type I and a predominantly cystic mass with a solid intra-cystic component was called type II. The vascularity of the lesion was also noted in cases where Doppler analysis was available (power Doppler sonography was utilized because of its higher sensitivity for detecting vessels). The colour box was enlarged to include the lesion and a margin of normal breast tissue. Colour power Doppler gain was optimized with an increase in gain until the background colour was just suppressed and a small vessel could be detected (75—85% gain).

Histological findings and analysis

Histopathologic findings in excisional biopsy or mastectomy specimens were used as the reference standard. All cases were reviewed by a pathologist with extensive experience in breast disease (KK). The following histological parameters were analysed: (1) the nuclear grade (modified Bloom and Richardson grading; 1 = low grade-, 2 = indeterminate grade, or 3 = high grade); (2) the presence and assessment of necrosis (0 = absent, 1 = mild, 2 = moderate, or 3 = extensive); (3) the architectural pattern (comedo, cribriform, papillary, micropapillary, or solid); (4) the percent of DCIS cells in cancerized lobules (COL) quantified into quartiles (0—25%, 26—50%, 51—75%, 76—100%).

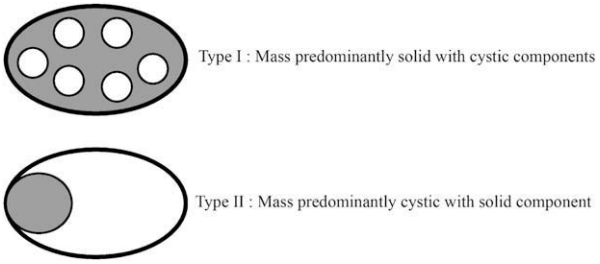


Figure 1 Diagram shows patterns of masses displaying a complex echotexture with solid and cystic components as seen at ultrasonographic examination. They were separated into two different subgroups: type I characterizing a predominantly solid mass with cystic components, and type II a predominantly cystic mass with a solid intra-cystic component.

Cancerization of the lobules was defined as partial involvement by DCIS cells of a group of lobules within a terminal ductolobular unit (TDLU).[10] This parameter was considered a surrogate of DCIS volume involving the TDLUs.

Statistical analysis

Dichotomous and categorical outcomes were summarized by presenting counts of the numbers of outcomes in each category, together with the percentage of the total these counts represent. This was done both including all participants, and within certain patient subgroups of interest. Between groups, comparisons were reported as percentage difference with 95% confidence intervals as calculated by the normal approximation to the binomial distribution.

Results

Clinical data

This study included 35 patients (mean age 66.4 years, age range 40—86 years, four patients were younger than 50 years). Four patients had a history of previous breast carcinoma. Four patients had a palpable mass, one patient had skin dimpling without an underlying palpable mass, and none had nipple discharge or Paget's disease.

Mammographic findings (Tables 1 and 2)

Mammographic parenchymal density was class 4 (dense) in three patients (3/35, 8%), class 3 (heterogeneously dense) in eight (8/35, 23%), class 2 (scattered fibroglandular densities) in nine (9/35, 26%), and class 1 (fatty) in 15 (15/35, 43%) (Figs. 2—4). Seventeen lesions (17/47, 36%) in 11 patients (11/35, 31%) were not visible at mammography. Among 11 patients (11/35, 31%) who had 17 mammographically occult lesions (17/47, 36%), mammographic parenchymal density was class 4 (dense) in two patients (2/11, 19%), class 3 (heterogeneously dense) in four (4/11, 36%) and class 2 (scattered fibroglandular densities) in five (5/11, 45%). Except for two lesions corresponding to clinical abnormalities, six corresponded to additional foci, and nine incidental sonographic findings in patients with dense breasts (class 3 and 4). Thirty lesions (30/47, 64%) were visible at mammography in 27 patients, who presented with mammographic parenchymal density class 4 (dense) in one patient (1/27, 4%), class 3 (heterogeneously dense) in four (4/27, 15%), class 2 (scattered fibroglandular densities) in seven (7/27, 26%), and class 1 (mostly fatty) in 15 (15/27 55%). Among the 30 mammographically detected abnormalities, 26 (26/30, 87%) corresponded to masses (Figs. 2—4) and four to distortions. Mass shape was round (8/26, 31%), oval (6/26, 23%), lobular (5/26, 19%), or irregular (7/26, 27%). Mass margins were circumscribed (9/26, 34%), microlobulate (7/26, 27%), obscured (2/26, 8%), or indistinct (8/26, 31%). Mass density was high (7/26, 27%) or isodense (19/26, 73%).

Ultrasonographic findings (Table 3)

Ultrasonographic examinations were performed for clinical (two patients), clinical and mammographic (three patients), mammographic findings (25 patients), and for screening (five patients) in cases of dense breasts (type 3 or 4). Forty-seven lesions were identified, 30 being mammographically visible, and 17 mammographically invisible. With respect to the 17 mammographically occult lesions, two lesions corresponded to clinical abnormalities, six corresponded to additional foci, and nine incidental sonographic findings in patients with dense breasts (classes 3 and 4). The mean sonographic size of the masses at diagnosis was 1 cm (range 0.4—2.5 cm) in largest diameter. No difference was noted between the mean size of the 17 mammographically occult lesions (0.95 cm; range 0.3—2 cm) and the mean size of the 30 mammographically visible lesions (1.11 cm; range

Table 1 Mammographic parenchymal density of the study population

	Class 1	Class 2	Class 3	Class 4
All patients ($n = 35$)	15/35 (43%)	9/35 (26%)	8/35 (23%)	3/35 (8%)
Patients with mammographically visible lesions ($n = 27$; 30 lesions)	15/27 (55%)	7/27 (26%)	4/27 (15%)	1/27 (4%)
Patients with mammographically invisible lesions ($n = 11$; 17 lesions)	0	5/11 (45%)	4/11 (36%)	2/11 (19%)

Mammographic parenchymal density class 1: fatty; mammographic parenchymal density class 2: scattered fibroglandular densities; mammographic parenchymal density class 3: heterogeneously dense; mammographic parenchymal density class 4: dense.

Table 2 Analysis of 30 lesions of radiographically non-calcified ductal carcinoma *in situ* at mammography according to the Breast Imaging Reporting and Data System (BI-RADS) lexicon

BIRADS descriptors	Percentage of each term descriptor
Distortion	4/30 (13%)
Calcifications	0/30 (0%)
Masses	26/30 (87%)
Mass shape	
Round	8/26 (31%)
Oval	6/26 (23%)
Lobular	5/26 (19%)
Irregular	7/26 (27%)
Mass margins	
Circumscribed	9/26 (34%)
Microlobulated	7/26 (27%)
Obscured	2/26 (8%)
Indistinct	8/26 (31%)
Spiculated	0/26 (0%)
Mass density	
High	7/26 (27%)
Equal	19/26 (73%)
Low	0/26 (0%)
Fat	0/26 (0%)

0.5—2.5 cm; 95% confidence interval −0.503, 0.188). The most common sonographic features were masses with irregular shapes (28/47, 60%), microlobulated margins (34/47, 72%), abrupt interfaces (42/47, 90%), and complex echotextures (29/47, 62%; 24 cases of type I, which were predominantly solid with cystic components, and five cases of type II, which were predominantly cystic with a solid intra-cystic component; Figs. 2 and 3). Only 11% of the lesions (5/47) displayed posterior shadowing. Power Doppler sonography was performed in 45 out of 47 lesions; a positive signal was demonstrated in 23 (23/45 51%) lesions (Fig. 4). Duct extension was noted in 10 out of the 47 cases (21%).

Histological findings (Table 4)

The mean tumour size at pathology was 1.2 cm (range 0.5—2.3 cm). In four patients (four DCIS lesions), extensive disease was noted at pathology. The full extent of the lesion was not appreciable at ultrasonography. The dominant architectural pattern of DCIS included 14 (14/47, 30%) cribriform type, 13 (13/47, 28%) solid type, and 20 (20/47, 42%) papillary, and no micropapillary type. Most of the lesions were classified as grade II (35/47, 74%), only three were grade III (3/47, 6%). Most of the lesions showed no (27/47, 57%) or mild (13/47, 28%) necrosis. Nineteen lesions (19/47 40%) had greater than 50% of DCIS cells in the cancerized lobules (Figs. 2—4).

Specific subgroups

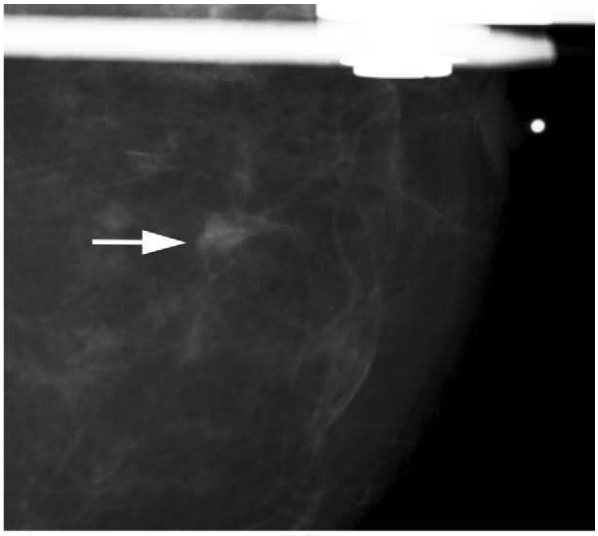
Among a subgroup of 24 lesions with a type I echotexture at sonographic examination (predominantly solid with cystic components; Figs. 2 and 3), 14 (14/24, 58%) lesions had greater than 50% DCIS cells in the cancerized lobules. Among the other 23 lesions (not displaying a type I complex echotexture), five lesions (5/23, 22%) had greater than 50% DCIS cells in the cancerized lobules (difference = 36%, 95% confidence interval 10.6%, 62.5%).

Among the subgroup of 35 lesions with microlobulated margins at ultrasound examination (Figs. 2 and 3), 17 (17/35, 49%) had greater than 50% DCIS cells in the cancerized lobules, whereas among the counterpart subgroup with no microlobulated margins, only two lesions (2/12, 17%) had greater than 50% DCIS cells in the cancerized lobules (difference = 32%, 95% confidence interval 5.1%, 58.7%).

Discussion

The 47 mammographically non-calcified DCIS lesions presented most often ultrasonographically as single or multiple masses with irregular shape, microlobulated margins, complex echotexture, and without posterior shadowing (4—8). On one hand, mammographically visible lesions were detected in non-dense breasts (81% of patients had breast density type 1 or 2). This presumably relates to the fact that non-calcified DCIS is detected due to its radiodensity, which would be masked in a denser breast. On the other hand, one third of the lesions were mammographically occult. None of these mammographically occult lesions occurred in patients with class 1 breast density. Breast sonography depicted occult DCIS lesions (nine lesions in patients with dense breasts) or additional multifocal or multicentric DCIS lesions (six additional foci), altering the surgical management. This supports the role of breast ultrasonography in the evaluation of patients with dense breasts as suggested by a previous study.[11]

Interestingly, half of the non-calcified DCIS lesions displayed a type I complex echotexture (predominantly solid masses with cystic components; Fig. 1). These masses appeared markedly hypoechoic leading to a ''pseudomicrocystic'' appearance resembling clustered microcysts (Figs. 1—3). Clustered cysts are known to



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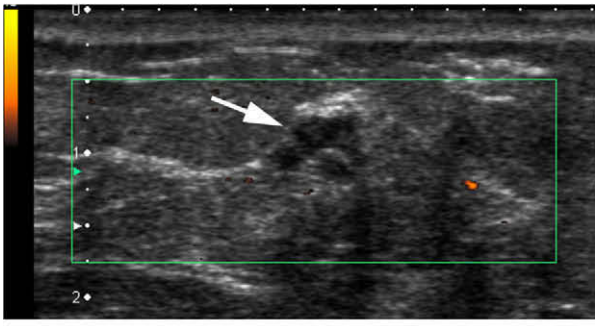

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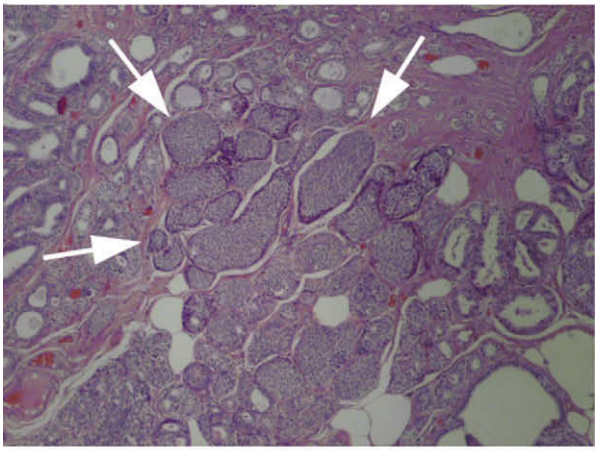

(c)

represent dilatation of individual acini of the TDLUs.[12,13] The results of this study support the hypothesis that the distension of the lobular portion of the TDLU with DCIS cells may explain the ''pseudomicrocystic'' appearance. Indeed, a majority (60%) of type I complex lesions showed a higher percentage of DCIS cells in cancerized lobules than other lesions displaying a different echotexture (complex II, isoechoic, and hypoechoic).

In practice, two factors helped in differentiating these lesions from clustered microcysts. First, the occurrence of a new mass mimicking ''clustered microcysts,'' especially in a postmenopausal patient, is an indicator to further investigate the lesion. Second, as mentioned by Berg,[13] any questionable solid component prompts the radiologist to perform sonographic-guided biopsy. This is reinforced, when vascularity is demonstrated at power Doppler interrogation, as in 51% of these lesions in the present study, thus helping identify a solid component. However, additional studies to confirm the absence of vascularity in clustered microcysts are needed prior to using vascularity as a differentiating factor between DCIS lesions and microcysts.

The majority of lesions in the present study displayed microlobulated margins. These findings concur with those of Moon et al.[4] However, the present results differ from recent studies[6,8] where DCIS lesions mainly displayed indistinct margins. This might be related to the smaller mean size of DCIS lesions in the present study (1 cm versus 2.4 cm, 3.4 cm, and 2.1 cm).[6,8] Another explanation is the low interobserver concordance recently reported in margin assessment, notably with the

Figure 2 An asymptomatic 76-year-old woman. (a) Left cranio-caudal compression view mammogram shows a new 0.6 cm mass in the medial aspect of the left breast. The mass displays irregular shape and microlobulated margins (arrow). (b) Breast sonogram demonstrates a 5 mm irregular-shaped solid mass with microlobulated margins (arrow), non-parallel orientation, abrupt interface, neutral sound transmission and complex echotexture (type I with a ''pseudomicrocystic'' appearance). Doppler interrogation does not show any tumoural vascularity. The mass was classified as indeterminate (BI-RADS category 4). Sonographically guided biopsy yielded ductal carcinoma *in situ*. (c) Final pathology result revealed a 9 mm ductal carcinoma *in situ*, cribriform type and grade 2 with mild necrosis. The percentage of ductal carcinoma *in situ* cells in cancerized lobules was greater than 75%. Photomicrograph (haematoxylin and eosin stain, $\times$100) shows expansion and distortion of the lobular architecture (arrows) due to cancerization by ductal carcinoma *in situ*.

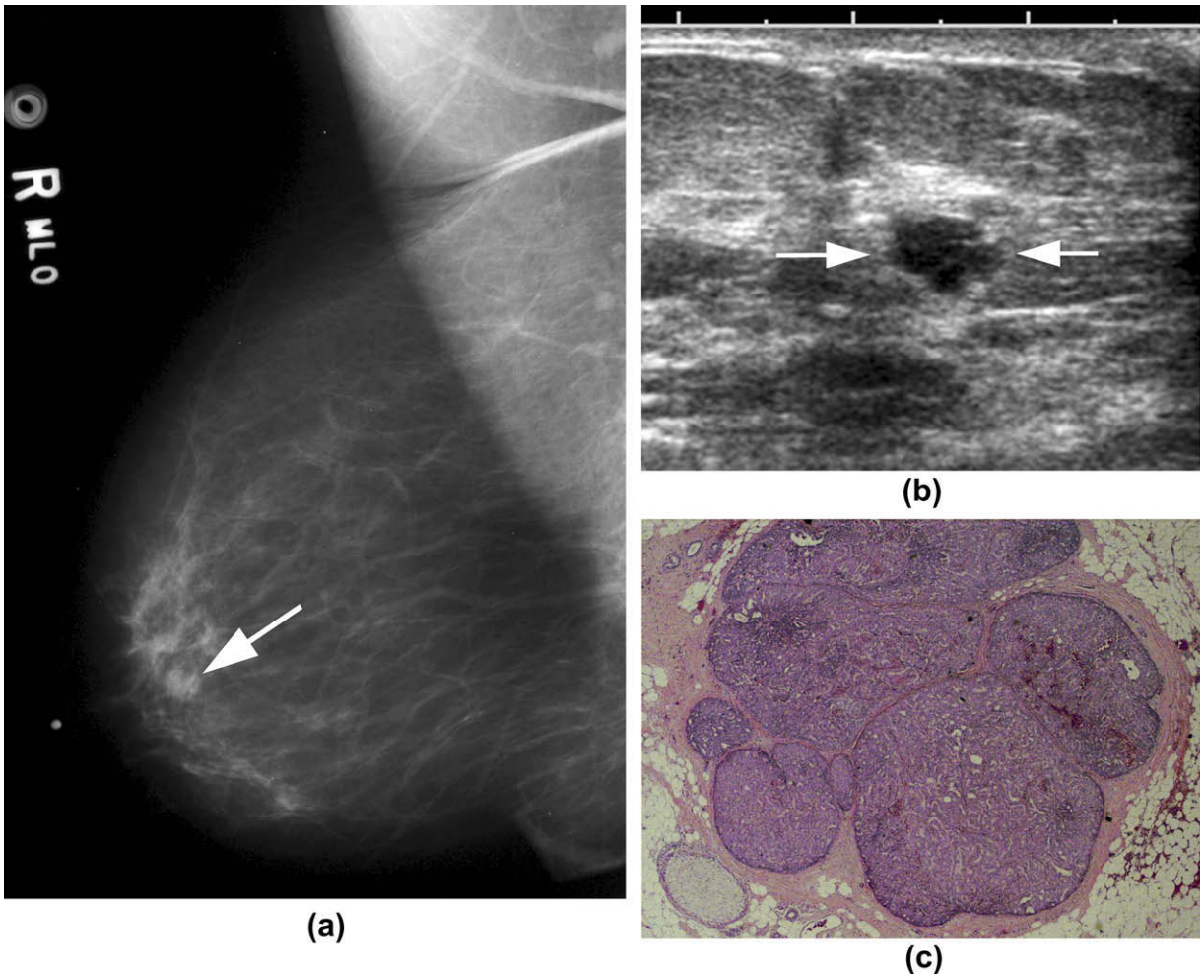

Figure 3 An asymptomatic 71-year-old woman. (a) Right medial—lateral oblique view shows a 6 mm irregular-shaped mass in the retro-areolar region (arrow). (b) Breast sonogram demonstrates a 5 mm irregular-shaped solid mass (arrows) with microlobulated margins, complex echotexture (type I with a ''pseudomicrocystic'' appearance), non-parallel orientation, abrupt interface, and mild posterior acoustic enhancement. The mass was classified as indeterminate (BI-RADS category 4). Sonographically guided core biopsy yielded ductal carcinoma *in situ*. (c) The final pathology result demonstrated 5 mm of ductal carcinoma *in situ* papillary type, grade 1, without associated necrosis. The percentage of ductal carcinoma *in situ* cells in cancerized lobules was greater than 75%. Photomicrograph (haematoxylin and eosin stain, $\times$40) shows an expanded lobule due to cancerization by predominently papillary ductal carcinoma *in situ*. Despite marked expansion, the outline of the lobular unit is preserved.

''indistinct'' descriptor.[14,15] A further factor may be that readers were limited to selecting a single term representing the most appropriate descriptor from each of the category of the BI-RADS lexicon, some lesions exhibiting probably more than one type of margin.

Regarding the histological correlation, it has been hypothesized that microlobulations might correspond to tumour-distended ducts or cancerized lobules.[4,5] The latter hypothesis was supported by the present results, as lesions displaying microlobulated margins showed a tendency to have a greater percentage of DCIS cells than other lesions displaying different margin types.

Although duct extension was previously described as one of the most common features of DCIS, ranking next to irregular masses,[6] it was only encountered in 21% of the DCIS lesions. One would be tempted to explain these findings by the predominance of non-high nuclear grade lesions in the present series. Indeed, unlike high-grade lesions, those of low or intermediate grade are less likely to distend the involved ducts enough for them to be detected by sonography.[5] Nevertheless, none of the three high nuclear grade DCIS

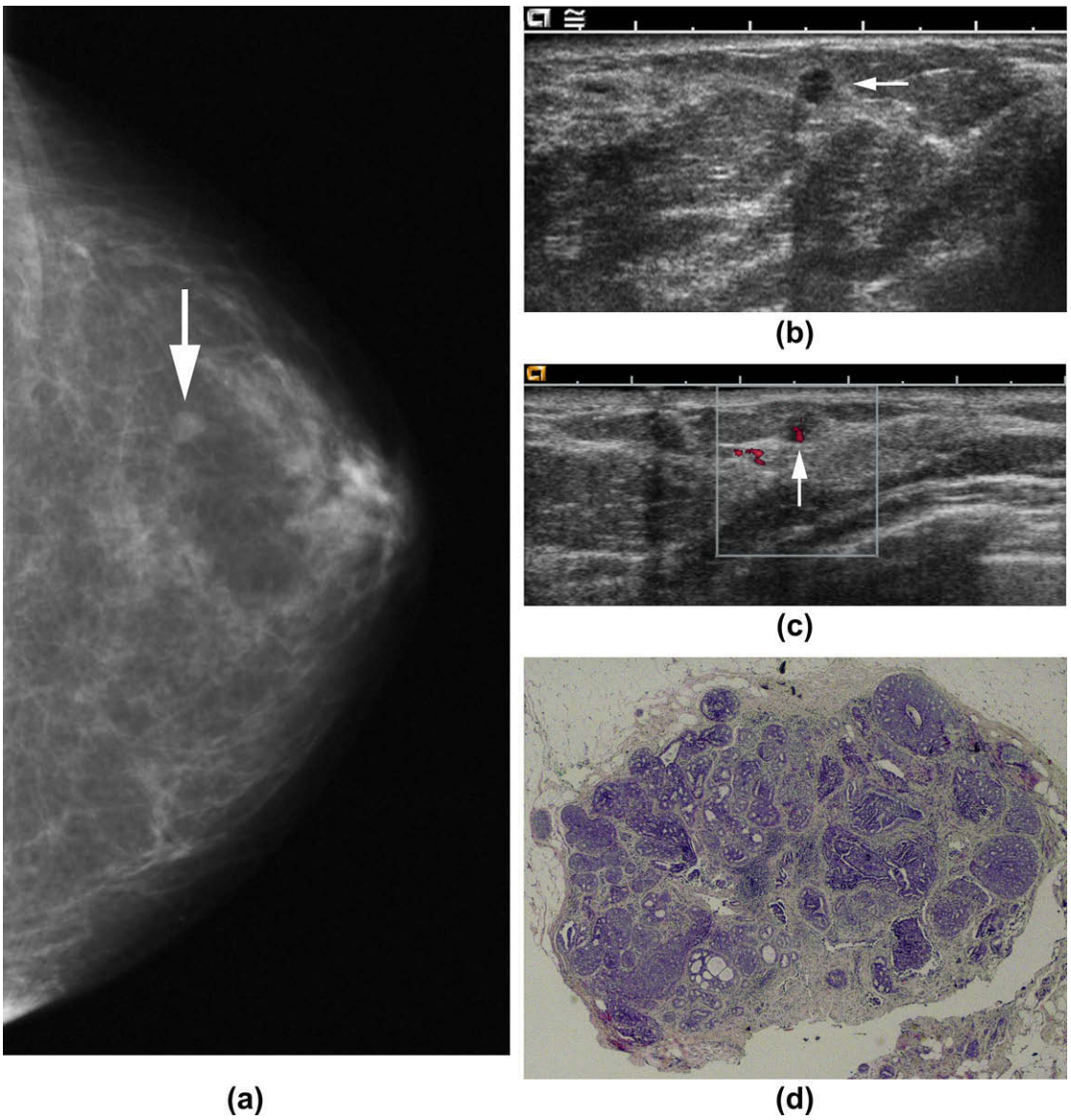

Figure 4 An asymptomatic 47-year-old woman. (a) Left cranio-caudal view shows a 5 mm round mass with well-circumscribed margins in the lateral aspect of the breast (arrow). (b) Left breast sonogram demonstrates a round hypoechoic 5 mm mass, with well-circumscribed margins, abrupt interface, and neutral sound transmission (arrow). (c) Doppler interrogation shows tumoural vascularity (arrow). The mass was classified as indeterminate (BI-RADS category 4). Ultrasonographically guided core biopsy yielded ductal carcinoma *in situ*. (d) The final pathology result demonstrated 5 mm of ductal carcinoma *in situ* cribriform type, grade 1, without associated necrosis. The percentage of ductal carcinoma *in situ* cells in cancerized lobules was greater than 75%. Photomicrograph of a focus of predominantly cribriform ductal carcinoma *in situ* (low magnification, ×100; haematoxylin and eosin stain). Normal lobular histology is almost entirely replaced by variably expanded lobules due to cancerization.

lesions in the present study showed duct extension.

The majority of the lesions displayed neutral or enhanced sound transmission. As previously described, mammographically non-calcified DCIS rarely presents posterior attenuation,[4,6,8] because of the absence of desmoplastic reaction. Although posterior enhancement has been attributed to the high nuclear grade,[6] none of the lesions demonstrating posterior acoustic enhancement demonstrated high nuclear grade.

There were limitations to the present study. The size of the population, especially the total number of patients, is relatively small in relation to the various parameters evaluated. The retrospective nature of the study probably limited and possibly underestimated the value of some sonographic criteria, such as duct extension or the presence

Table 3 Ultrasonographic findings according to the Breast Imaging Reporting and Data System (BI-RADS) lexicon, in 47 lesions of radiographically non-calcified ductal carcinoma *in situ*

BIRADS descriptors	Percentage of each term descriptor
Shape	
Irregular	28/47 (60%)
Round	8/47 (17%)
Oval	11/47 (23%)
Margins	
Circumscribed	5/47 (11%)
Microlobulated	35/47 (75%)
Angular	1/47 (2%)
Spiculate	2/47 (4%)
Indistinct	4/47 (8%)
Orientation	
Parallel (long axis of lesion parallels the skin line)	23/47 (49%)
Not parallel (long axis, not oriented along the skin)	24/47 (51%)
Posterior acoustic phenomena	
Enhancement	15/47 (32%)
Neutral	22/47 (46%)
Shadowing	5/47 (11%)
Combined	5/47 (11%)
Lesion boundary	
Abrupt interface	42/47 (90%)
Echogenic halo	5/47 (10%)
Echo pattern	
Hypoechoic	16/47 (34%)
Isoechoic	2/47 (4%)
Hyperechoic	0/47 (0%)
Complex type I	24/47 (51%)
Complex type II	5/47 (11%)
Duct extension	10/47 (21%)
Power Doppler sonography	
Not performed	2/47 (4%)
Negative	22/45 (49%)
Positive	23/45 (51%)

Complex echotexture can be of type I (complex type I) in case of predominantly cystic component, or of type II (complex type II) in case of solid intra-cystic component.

Table 4 Histological findings of 47 lesions of radiographically non-calcified ductal carcinoma *in situ*

Histological findings	Percentage of each histological feature
Architecture	
Comedo	0/47 (0%)
Solid	13/47 (28%)
Papillary	20/47 (42%)
Cribriform	14/47 (30%)
Micropapillary	0/47 (0%)
Nuclear grade	
I	9/47 (19%)
II	35/47 (74%)
III	3/47 (6%)
Necrosis	
Absent	27/47 (57%)
Mild	13/47 (28%)
Moderate	6/47 (13%)
Extensive	1/47 (2%)
Percent of DCIS cells in lobules	
1—25	20/47 (43%)
26—50	8/47 (17%)
51—75	10/47 (21%)
76—100	9/47 (19%)

DCIS, ductal carcinoma *in situ*.

of Doppler signal. Nevertheless, the strength of the present study is the description of the large spectrum of sonographic features of mammographically non-calcified DCIS lesions with pathological correlation, which was not previously established.[4,5]

In conclusion, a sonographically irregularly shaped mass with microlobulated margins and complex echotexture (conferring a ''pseudomicrocystic'' appearance) should alert the radiologist to a possible diagnosis of non-calcified DCIS. The results of the present study support the hypothesis that a ''pseudomicrocystic'' appearance and microlobulated margins might be related to cancerization of the lobules.

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