ORIGINAL ARTICLE

Mucinous Carcinoma of the Breast: Diagnostic Criteria Based on Ultrasonography

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Background: In previous studies, the benign imaging features of mucinous carcinoma (MCA) of the breast that may result in missing the diagnosis have been reported. The aim of this study was to evaluate the diagnostic criteria from ultrasonography of MCA of the breast, and to investigate the general applicability of ultrasonographic features in diagnosing this tumor.

Patients and Methods: We retrospectively reviewed the ultrasonographic findings of 41 (34 pure MCA and 7 mixed MCA) pathologically-confirmed cases of MCA of the breast. We analyzed the size, shape, margin, internal echogenicity, echotexture, intratumoral calcification, posterior acoustic enhancement, and surrounding desmoplastic reaction. The original sonogram report of each case was categorized based on the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) for ultrasound assessment categories.

Results: The median age of the patients was 52 years (range, 34–96 years). The median tumor size was 2.6 cm (range, 0.8–15 cm). Tumor size was found to significantly correlate with the duration of lesion palpability. Lobular shape (53.7%), microlobulated margin (65.9%) and mildly hypoechoic echogenicity (53.7%) were the most frequent sonographic findings. Multiple linear regression showed that tumor type was the only predictor of the presence and sonogram appearances of lymph nodes. In all cases, when the width-to-anteroposterior dimension ratio, either being less than or greater than 1.4, was taken into consideration, no significant correlation with any of the variables stated above was found. Posterior enhancement was detected in most cases, accounting for about 19.5% of the characteristics of larger tumor size, heterogeneous echotexture or evidence of mixed MCA. Most sonogram reports disclosed a suspicion of or definite malignancy in 38 cases (92.7%).

Conclusion: The sensitivity of malignant sonographic features with traditional lexicons was poor for MCA of the breast, which supports the assumption of the less invasive nature of this tumor. The deformed ovoid shape is useful for suspecting a nontypical benign lesion, and we noted a high positive reporting rate of suspicion of malignancy. Posterior enhancement occurs quite often in MCA due to its tissue characteristics.

KEY WORDS — breast, mucinous carcinoma, tumor shape, ultrasonography

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Introduction

Mucinous carcinoma (MCA) is also known as colloid carcinoma, mucoid carcinoma or gelatinous carcinoma, and accounts for about 1–7% of all invasive breast cancers [1,2]. A pure tumor must be entirely composed of MCA. Although they show histopathologic evidence of malignancy, they do have a favorable prognosis. As soon as another histopathologic pattern becomes evident as a component of the tumor mass, the lesion is classified as a mixed type MCA. The most common admixture is with regular invasive ductal carcinoma [2]. In previous studies, the benign imaging features of MCA of the breast that may result in missing the diagnosis have been reported [3]. The aim of this study was to evaluate the diagnostic criteria of MCA of the breast from ultrasonographic features, and investigate the general applicability of imaging features in diagnosing the tumor.

Patients and Methods

We retrospectively reviewed the ultrasonographic findings in 41 cases of MCA of the breast, which were pathologically confirmed between the end of 1990 and the beginning of 2005. Of these 41 cases, 34 were pure MCA and seven were mixed type MCA (with infiltrating ductal carcinoma). Patients had requested breast sonography examination under three circumstances: (1) as a result of feeling a palpable breast lump on self-examination; (2) despite feeling a palpable lesion, as a result of skin erosion of the breast tumor, nipple discharge, gynecologic complaints, hoarseness due to benign glottic tumor or survey for bone metastasis; or (3) positive mammography report.

Ultrasound examination technique

All ultrasound examinations were performed using a model L500, L700, L7 (GE Yokogawa Medical Systems, Tokyo, Japan), L9 (GE Medical Systems, Milwaukee, WI, USA) or Spectra (Diasonics, Milpitas, CA, USA) with a 10-MHz linear-array transducer. The routine protocol of breast examination in our department was either radial or anti-radial scans with the patient in the supine position. Bilateral axillary lymph nodes (LNs) were searched regularly. If available, color Doppler was applied in detecting the solid mass or the LNs. Faculty radiologists specialized in breast imaging either performed the examinations themselves or supervised a specially trained sonographer. The original sonogram report of each case was categorized according to the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS). Since late 1999, the images were stored in the form of hard copies and transferred to PACS (picture archiving and communication system).

Retrospective image and report review

The three faculty radiologists (HBP, TLY, JSH) reviewed the hard-copy ultrasonographic images of 10 cases and the digital images from PACS of 31 cases. The size, shape, margin, internal echogenicity, echotexture (architecture), intratumoral calcification, presence or absence of posterior acoustic enhancement, and surrounding desmoplastic reaction were analyzed. The original sonogram report of each case was categorized based on ACR BI-RADS ultrasound assessment categories. If the original report was not found to be categorized, we endorsed the final BI-RADS assessment scripted from the original reports, which could be negative, benign, probably benign, possibly malignant, or recommendation for biopsy.

Statistical analysis

Spearman's correlation was used for univariate analysis and multiple linear regression was used for multivariate analysis for continuous and categorized variables such as size, width-to-anteroposterior (AP) dimension ratio, LNs, BI-RADS category, and duration of palpability. The Mann-Whitney test was used for univariate analysis and logistic regression was used for multivariate analysis for binary variables such as tumor type, ductal carcinoma *in situ* (DCIS), physical examination, microcalcification, and intratumoral calcification.

Table. The clinical, sonographic and pathologic findings of seven mixed type mucinous carcinomas

Age (yr)	Diameter (cm)	Width-to-AP dimension ratio	Echogenicity	Texture	Margin	Shape	LN	BI-RADS category
57	2.7	1.52	Marked hypoechoic	Heterogeneous	Angular	Irregular	1#	5
41	10.5	1.50	Mixed cystic and solid	Heterogeneous	Microlobulated	Lobulated	2#	5
56	11.0	1.40	Mildly hypoechoic	Heterogeneous	Microlobulated	Lobulated	2#	5
52	2.7	1.90	Isoechoic	Internal echo*	Microlobulated	Oval	1#	4C
53	8.3	1.25	Mildly hypoechoic	Heterogeneous	Microlobulated	Lobulated	2#	5
43	1.8	1.28	Mixed cystic and solid	Internal echo*	Circumscribed	Round	Benign	4B
56	2.0	1.11	Mildly hypoechoic	Heterogeneous	Ill-defined	Irregular	1#	4C

**Regular presentation of mixture with hyperechoic, isoechoic or hypoechoic portions. 1# = pathologic lymph node with hilum preserved at the axilla; 2# = pathologic lymph node without hilum preserved at the axilla. AP = anteroposterior; LN = lymph node; BI-RADS = Breast Imaging Reporting and Data System.*

Results

The median age of the patients was 52 years (mean, 53.3 years; range, 34–96 years). The median age of the seven patients with mixed type MCA (53 years; range, 41–57 years) was greater than that of the 34 patients with pure MCA (47.5 years), but the difference was not significant (p = 0.0852). Of the 41 patients, 31 had requested breast sonography examination as a result of feeling a palpable breast lump on self-examination; seven as a result of skin erosion of the breast tumor, nipple discharge, gynecologic complaints, hoarseness due to benign glottic tumor or survey for bone metastasis; and three because of a positive mammography report (2 cases of microcalcification, 1 case of irregular nodule). No cases were detected on ultrasound screening examination.

The mean tumor size was 4 cm (median, 2.6 cm; range, 0.8–15 cm). The mean size of mixed type MCA (5.36 cm; median, 2.7 cm; range, 1.8–10 cm) (Table) was larger than that of pure MCA (3.23 cm; median, 2.45 cm) (Fig. 1), but the difference was not significant. In six of the seven cases of mixed type MCA, the lesions were palpable; the duration of palpability was a few weeks in one case, a few months in two, 2–4 years in two, and about 20 years in one case. In the two patients with pure MCA who were on hormone replacement therapy, the masses were not palpable, but could be detected on mammogram by the presence of microcalcification with concurrent DCIS. In the remaining 32 patients with pure MCA, the duration of palpability was a few weeks in 13 cases (mean tumor size, 2.02 cm), a few months in 11 (mean tumor size, 3.03 cm), 1–5 years in six (mean tumor

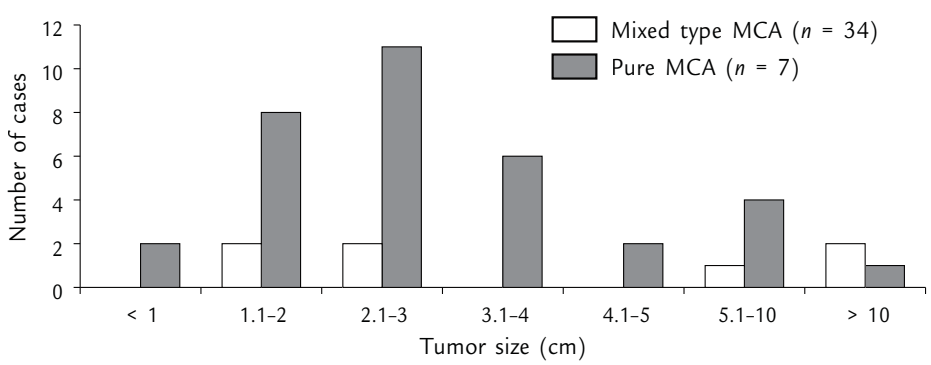

Fig. 1. *Tumor size of pure mucinous carcinoma (MCA) and mixed type MCA.*

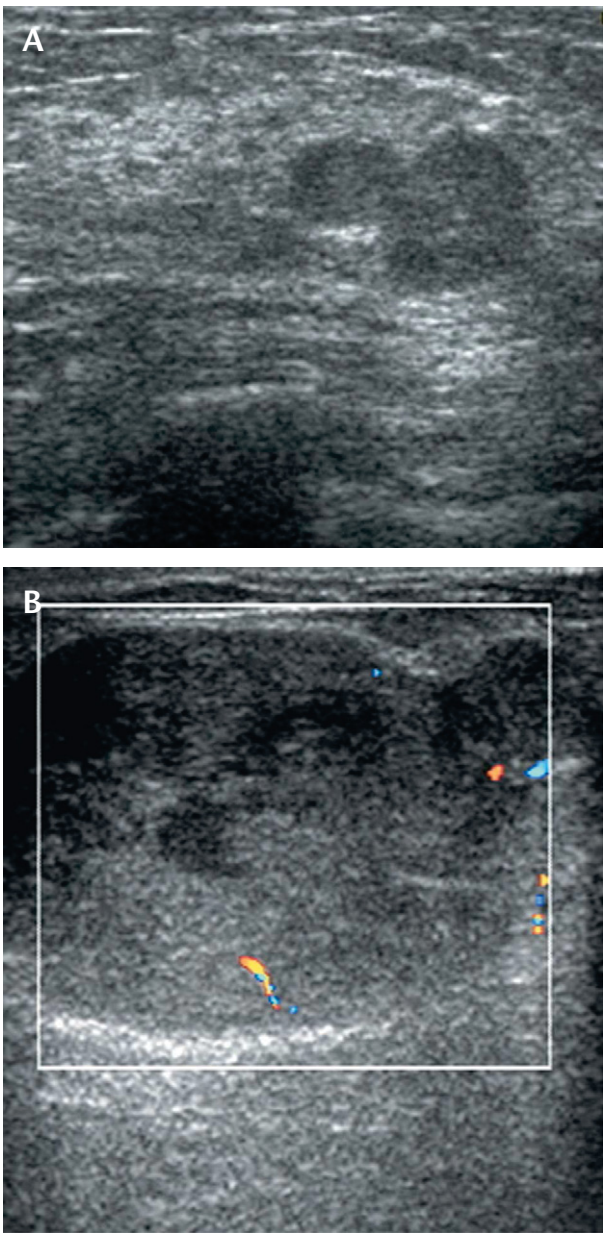

Fig. 2. *A 74-year-old woman presented with a palpable mass in the left breast, measuring about 1.6 cm. (A) Sonogram showed hypoechoic lobular tumor suggestive of regressive fibroadenoma or malignancy, categorized as BI-RADS 4A. (B) Sonogram 3 years later showed that the tumor had enlarged to about 3.2 cm, with a lobulated but well demarcated margin and moderate hypervascularity, categorized as BI-RADS 4C. Pathology showed pure mucinous carcinoma. (BI-RADS = Breast Imaging Reporting and Data System.)*

size, 3.97 cm), and > 5 years in two cases.

Tumor size was found to significantly correlate with duration of lesion palpability ($r = 0.603$, $p < 0.001$) and BI-RADS category ($r = 0.623$, $p < 0.001$). Multiple linear regression showed that duration of palpability is a predictor of tumor diameter ($R = 0.643$, $p < 0.001$). It was demonstrated that the tumor grew with the passage of time (Fig. 2). Most of the tumors were palpable by the physicians before surgery. Only one out of the 41 patients was negative on physical examination; the tumor was later shown to be DCIS with 0.5-cm pure MCA. Thirty (73.2%) cases had a width-to-AP dimension ratio greater than 1.4 (3 were mixed type MCA). In all cases, the width-to-AP dimension ratio, either less than or greater than 1.4, had no significant correlation with any of the variables stated above (also true for the threshold of 1.5 or 1.6). Tumor size was also not correlated with the width-to-AP dimension ratio ($r = –0.056$, $p = 0.729$).

The echogenicity was isoechoic in five patients, mildly hypoechoic in 22 (Fig. 3A), mixed cystic and solid components in 13 (Fig. 3B), and markedly hypoechoic in one (with mixed invasive ductal and lobular carcinoma and synchronous MCA). None had a hyperechoic pattern. There was no significant correlation with any variable against echogenicity and tumor size. Echotexture was homogeneous in two, heterogeneous in 15, and internal echo (a regular presentation of mixture with hyperechoic, isoechoic or hypoechoic portions) in 24. There was no significant correlation with any variable against echotexture and size. Posterior enhancement was found in 33 cases, but was negative in eight cases (4 of which were mixed type MCA). A circumscribed margin was found in eight cases (Fig. 4A), microlobulated margin in 27 (Fig. 4B), angular margin in three (Fig. 4C), and ill-defined margin in three (Fig. 4D). Tumor shape was oval in 12 cases, round in four, lobulated in 22, and irregular in three (Figs. 4C and 4D). Sonography showed intratumoral calcification in 12 cases (2 were mixed type MCA) (Figs. 4A and 4D), which did not correlate with the result of histologic evidence in six. In contrast, only four of 10 cases with intratumoral calcification on microscopy were detected on sonography. Probably, this might be the drawback of this retrospective study.

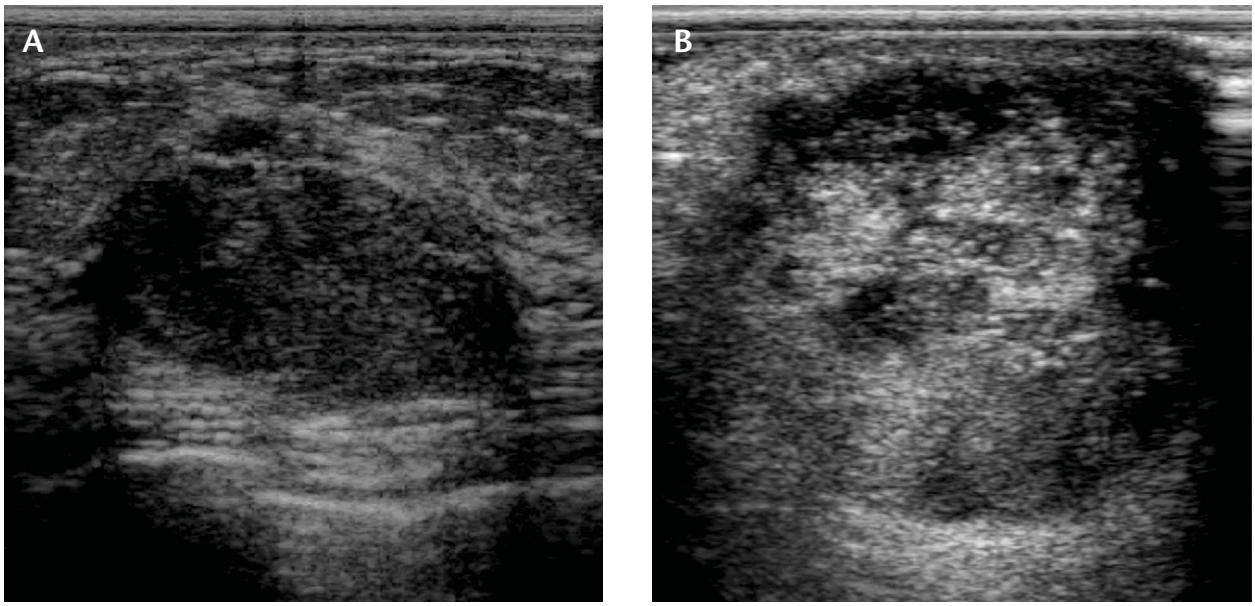

Fig. 3. *(A) A deformed ovoid mass shown on ultrasonography, measuring 3 cm in size, with a width-to-anteroposterior dimension ratio of about 2, microlobulated margin, mildly hypoechoic echogenicity against a background of fat, and positive posterior enhancement, categorized as BI-RADS 4B. Pathology showed pure mucinous carcinoma. (B) A 96-year-old woman presented with erythematous skin change and ulcerating mass for a few months. An irregular tumor mass with a partially ill-defined margin and central necrosis (hyperechoic areas) in the right breast, 4.5 cm in size, was indicative of inflammatory breast cancer. Pathology showed pure mucinous carcinoma. There was no metastasis to lymph nodes. (BI-RADS = Breast Imaging Reporting and Data System.)*

Twelve cases had positive desmoplastic reaction in the areas surrounding the tumor. In most cases (10 cases), the color Doppler images recorded as hard copies were not clear. Eight cases had a very strong Doppler shift at the central and peripheral regions of the tumor (mixed type MCA in 3); four cases had a very weak Doppler shift at the central or peripheral region of the tumor; and the others displayed borderline intense color encoding. There was no significant correlation with any variable against frequency shift and size or other factors.

According to the pathologic report, eight cases (19.5%) of MCA had LN metastases (5.9% in pure MCA, 85.7% in mixed type MCA). According to the appearances on sonography, pathologic LNs of three cases had hila preserved (all were mixed type MCA, including 1 case of obvious bone metastasis), and five cases had no hila preserved (mixed type MCA in 3). One of the seven cases of mixed type MCA had no metastatic axillary lymphadenopathy (Table). The presence and morphology of LNs were significantly correlated with tumor type ($r = 0.618$, $p < 0.001$) and BI-RADS category ($r = 0.348$, $p = 0.026$). Multiple linear regression showed that tumor type was the only predictor of the presence and sonogram appearance of LNs ($R = 0.725$, $p < 0.001$). The size of all mixed type MCAs was < 3 cm. In four of the five cases of pure MCA with duration of palpability > 2 years, the lesions were > 7 cm in size. However, multiple linear regression showed no significant correlation between tumor size and duration of palpability.

From the original sonogram reports, two cases of pure MCA were classified as category 2; one as category 3; 10 as category 4A; eight as category 4B (mixed type MCA in 1); 10 as category 4C (mixed type MCA in 2); eight as category 5 (mixed type MCA in 4); and two as category 6. By the Mann-Whitney test, it was found that tumor type was significantly correlated with LN ($p < 0.01$) and BI-RADS category ($p = 0.021$).

In our study, mammography was positive in 17 cases (mixed type MCA in 4), negative in two,

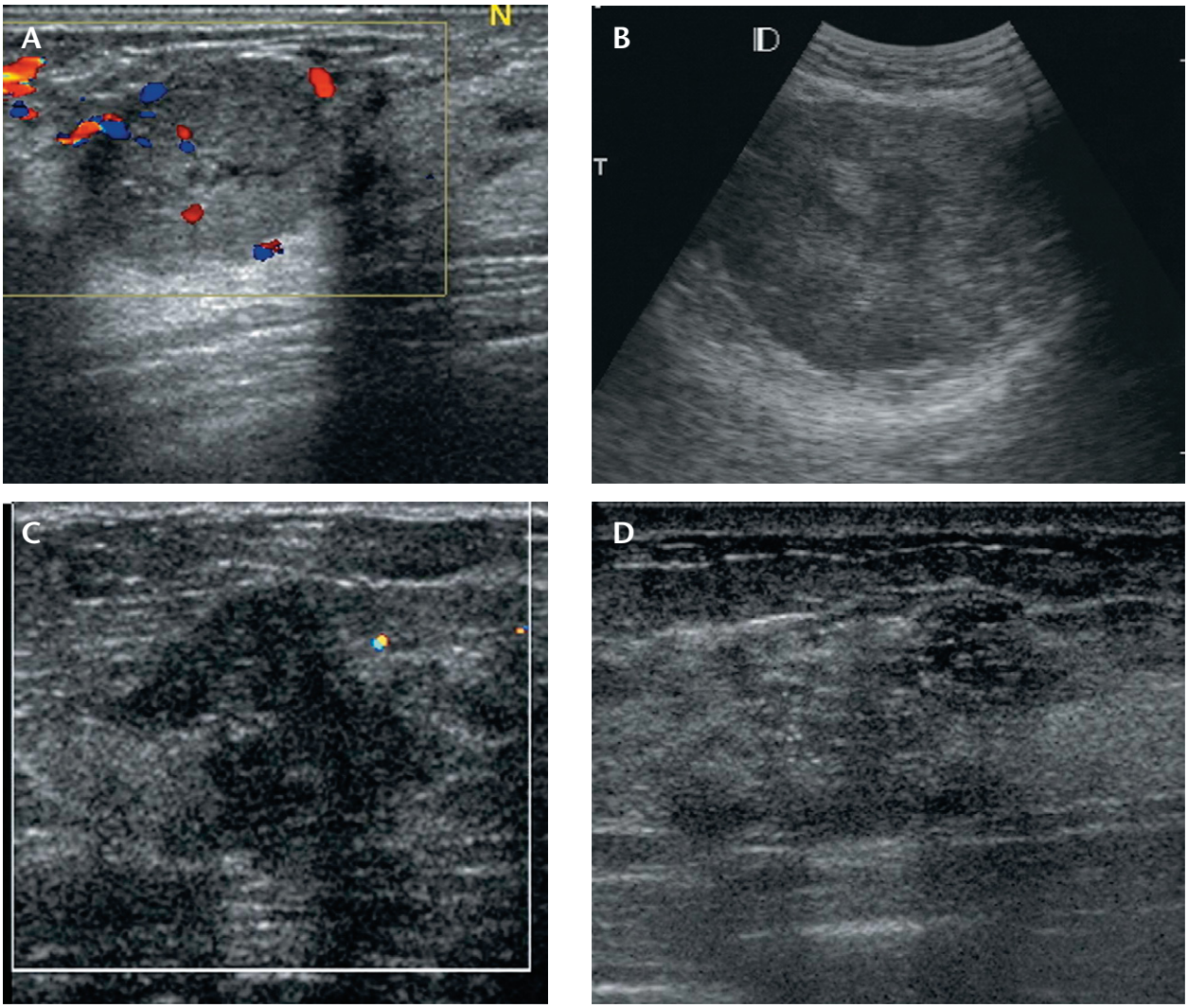

Fig. 4. *(A) Ultrasonography showed a well circumscribed round nodule with feeding arteries in the surrounding areas (not shown here) and inside the tumor, and hyperechoic spots in the lesion center, indicating calcifications that were confirmed by excisional biopsy. Pathology showed mucinous carcinoma (MCA) of hypercellular type, with calcifications and focal necrosis. But after modified radical mastectomy, focal invasive ductal carcinoma was found, and was classified as mixed MCA. (B) A 53-year-old woman had a palpable mass in the left breast for 20 years and growth in recent months. The size of the tumor could only be measured by 3.5 MHz (8.3 cm), and the tumor was shown to have a microlobulated margin; hypervascularity was demonstrated by color Doppler (not shown). Pathology on excisional biopsy showed MCA, but focal invasive ductal carcinoma was found in the mastectomy specimen, and axillary and neck lymph nodes were positive. Chest wall recurrence was noted 6 months later. (C) A 56-year-old woman had a palpable 2-cm mass in the left breast for 1 week. Irregular shape, ill-defined margin and desmoplastic reaction in the surrounding area were suggestive of malignancy (category 4C). The tumor showed hypovascularity on color Doppler. Pathology showed mixed type MCA with positive axillary lymph node (1 in 7 nodes). (D) Carcinoma with an ill-defined margin. An irregular hypoechoic mass about 2.2 cm in size with obvious microcalcification was found in the right breast, in the 12 o'clock position, categorized as BI-RADS 5. Pathology showed mixed type MCA. (BI-RADS = Breast Imaging Reporting and Data System.)*

and not available in 22. According to the pathology report, DCIS was found in 58.5% (24/41) of patients in this series; 55.9% (19/34) in pure MCA and 71.4% (5/7) in mixed type MCA.

Discussion

MCA of the breast is classified into two groups: pure MCA that consists solely of tumor tissue with extra-

cellular mucin production, and mixed type MCA that also contains infiltrating carcinoma without producing extracellular mucin. Mixed type MCA is generally more aggressive, with a higher rate of metastatic nodal involvement, which corresponds with more aggressive imaging characteristics. This situation may also be true for pure MCAs that have a small percentage of mucin component [4], probably depending on the percentage of the infiltrating component of mixed type MCA. In some patients in whom a lump was noticed clinically, they hesitated to seek treatment until symptoms of tumor ulceration, discharge or adverse symptoms appeared. The size of most tumors was related to the duration of palpable lumps. The longer a tumor exists, the larger its size. MCA is generally slow growing, but some patients complained that their breast lesions enlarged in a short period of time, which prompted them to visit their physician. However, there is not enough evidence to prove this phenomenon, although it has been previously reported [5].

In this series, the tumor characteristics that occurred at the highest frequency were: lobular shape, microlobulated margin, regular internal echotexture (regular presentation of mixture with hyperechoic, isoechoic or hypoechoic portions), and mildly hypoechoic echogenicity (followed by mixed cystic and solid components). In mixed type MCA, the sonographic pictures had a wide and varied presentation on shape, margin, echogenicity and texture (Table; Fig. 2). The sonographic BI-RADS descriptors that showed high predictive value for malignancy include irregular shape, ill-defined, spiculated or angular margin, heterogeneous echotexture, and marked hypoechoic echogenicity. Although MCA is an invasive cancer, only 2.4% (1/41) had all of the descriptors stated above; 4.9% (2/41) had 2–3 malignant parameters. For a single factor to predict MCA, ill-defined or angular lesion margin had a sensitivity of 14.6% (6/41), while irregular shape had a sensitivity of 7.3% (3/41). The width-to-AP dimension ratio of solid breast tumors is one of the factors that can be used to distinguish benign from malignant tumors [6]; a higher ratio indicates a higher probability of malignancy [7]. However, in our study, the ratio was ≥ 1.4 in 73.2% of MCA; thus, basing the diagnosis on width-to-AP dimension ratio alone is not reliable, and other factors are needed for accurate diagnosis. However, this result can represent the characteristic of benign MCA appearance.

The sonographic BI-RADS descriptors highly predictive of benign lesions include circumscribed margin and round or ovoid shape, or even lobular shape in some cases [8]. If we consider that a circumscribed margin is characteristic of a benign lesion, then we would have a 19.5% false negative rate (8/41) in this series, but only 4.9% (2/41) is accounted for. According to Stavros et al, benign nodules had no malignant characteristics and had either intense homogeneous hyperechogenicity or a thin echogenic pseudocapsule with an ellipsoid shape or fewer than four gentle lobulations [9]. Probably, our sonologist considered not only the margin as the sole evidence for diagnosing malignancy but also other factors such as shape, size, clinical palpability, and even the patient's age. Nonetheless, the statistical results explored were not exactly representing the high positive report rate (95.1%, 39/41). The BI-RADS lexicons can be useful for sonographic reports; however, they did not reflect the facts. In many cases, tumor shape was not exactly round or ovoid (Figs. 1A and 2A). Furthermore, the tumors may not have developed to lobulation to be categorized. In practice, a more precise term such as *deformed ovoid shape* should be used. Posterior enhancement was noted in most cases, except in 19.5% (8/41) of cases with either one or two of the conditions of larger tumor size, heterogeneous echotexture or evidence of mixed type MCA. The phenomenon of obvious posterior enhancement probably results from the transmission of the ultrasound beam through the high mucin content [1]. Microcalcification within the tumor may represent malignancy but is not specific for MCA. Microcalcification was also the dominant radiologic abnormality for diagnosing mucocele-like lesions [10]. In our study, the incidence of intratumoral calcification detected by sonography was 31.7%; the decay of some of the hard-copy films may be

a possible reason for this assumed low detection rate.

The admixture of a DCIS component occurred more often in mixed type MCA (71.4%) than in pure MCA (55.9%). Mammography had no definite contribution in our study as only the mammograms of 19 cases were available for analysis. However, 21.2% of MCA could not be detected by mammography [11]; two cases of negative mammogram reports in our series were false negative for diagnosing MCA. In the study of Matsuda et al, the calcification frequency was 50–75% [12]; the contribution of mammography in our series mainly comes from a cluster of microcalcification, which is DCIS of a part of MCA [11]. The incidence of axillary nodal metastases was 5.9% in pure MCA and 85.7% in mixed type MCA. Axillary nodal involvement in MCA patients should strongly indicate the presence of mixed type MCA [13]. The accuracy of sonographic examination for axillary LN metastasis was 79.2% [1]. In this series, the pathologic LNs presented as enlarged LNs with or without hila preservation.

In conclusion, the malignant sonographic features with traditional lexicons have poor sensitivity for MCA, which supports the assumption of the less invasive characteristics of this tumor. The high rate of positive reporting noted here revealed suspected or definite malignancy in 38 cases (92.7%). Deformed ovoid shape, rather than the width-to-AP dimension ratio, is useful for suspecting a nontypical benign lesion. Posterior enhancement occurs quite often in MCA, which is due to its tissue characteristics.

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