Magnetic resonance imaging and pathological characteristics of pure mucinous carcinoma in the breast according to echogenicity on ultrasonography

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Purpose: The aim of this study was to explore the clinical and pathological characteristics of pure mucinous breast carcinoma (PMBC) according to internal echogenicity on ultrasonography (US).
Methods: Thirty-three patients with PMBC diagnosed at surgery were included in this study. Cases of PMBC were classified according to internal echogenicity on US. The imaging features on magnetic resonance (MR) imaging and clinicohistopathological characteristics were compared between the hypoechogenic and the isoechogenic to hyperechogenic groups.
Results: Eleven cases of PMBC (33.3%) exhibited hypoechogenicity on US, while 22 cases (66.7%) exhibited isoechogenicity or hyperechogenicity. Of the isoechogenic to hyperechogenic PMBCs, 95.5% showed a high signal on T2-weighted images, which was a significantly greater percentage than was observed for the hypoechogenic group (54.5%) (P=0.010). Of the hypoechogenic PMBCs, 63.6% showed a washout pattern in the delayed phase, which was substantially more than the result of 23.8% observed for the isoechogenic to hyperechogenic PMBCs (P=0.053).
Conclusion: PMBCs with isoechogenicity or hyperechogenicity were more likely to show a high signal intensity on T2-weighted images than hypoechogenic PMBCs. However, other MR imaging and clinicohistopathological characteristics were not significantly different between the two groups.

Keywords: Breast neoplasms; Adenocarcinoma, mucinous; Magnetic resonance imaging; Ultrasonography

Introduction

Mucinous carcinoma of the breast is a rare subtype of invasive ductal carcinoma with an incidence of 1%–7%, and it usually occurs in women over 60 years of age [1,2]. Mucinous carcinoma can be classified into two types: pure mucinous carcinoma, which has a mucinous component of more

than 90%; and mixed mucinous carcinoma, which has a mucinous component greater than 50% but less than 90%, admixed with areas with distinct architectural patterns, usually of invasive carcinoma of no special type [3,4]. Pure mucinous breast carcinoma (PMBC) is less aggressive and is less likely to lead to lymph node metastasis than mixed mucinous carcinoma [1,5–7].

PMBC commonly presents as a well-circumscribed mass on mammography [2,8]. On ultrasonography (US), 64%–86% of PMBCs show isoechogenicity [2,9,10]. On magnetic resonance (MR) imaging, PMBC shows a high signal intensity on T2-weighted or short tau inversion recovery (STIR) T2-weighted images [11–14], and no restricted diffusion with high apparent diffusion coefficient (ADC) values on diffusion-weighted images [14,15].

To our knowledge, no study has evaluated the clinical and pathological characteristics of PMBC according to echogenicity on US. Therefore, the demographic, MR imaging-related, and histologic characteristics of PMBC were investigated according to internal echogenicity on US.

Materials and Methods

The Institutional Review Board of our institution approved this retrospective study and waived the requirement for informed consent.

Study Population
From March 2012 to February 2015, 57 patients at our institution were diagnosed with mucinous carcinoma in the breast, of whom 48 had PMBC. Of these patients, the following were excluded: seven patients who underwent MR imaging after excision, five who underwent MR imaging using different protocols, two who underwent MR imaging at another hospital, and one patient who was male. Ultimately, 33 female patients who underwent breast MR imaging were included. The median age of the patients was 47 years (range, 31 to 79 years). The median lesion size was 17 mm (range, 5 to 37 mm) on MR imaging.

Mammography and US
Mammography was performed using the Lorad/Hologic Selenia full-field digital mammography system (Lorad/Hologic, Danbury, CT, USA) and the General Electric Senographe digital mammography system (GE Medical Systems, Milwaukee, WI, USA). Craniocaudal and mediolateral oblique views were routinely obtained. Additional views were obtained when needed. Breast density was classified according to the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) [16,17] and was recorded in the original radiological reports. Mammographic density

was categorized as fatty (scores of A or B and 1 or 2) or dense (scores of C or D and 3 or 4).

Breast US examinations were performed by 11 board-certified radiologists with 1 to 21 years of experience in breast imaging using US machines (iU22, Philips-Advanced Technology Laboratories, Bothell, WA, USA; Logic 9, GE Medical Systems) and 5–12- or 7–12-MHz linear array transducers. The echogenicity of the tumors on US was analyzed according to the ACR BI-RADS criteria [16,17]. The internal echo patterns of the tumors were retrospectively reanalyzed by one radiologist with 13 years of experience in breast imaging (H.J.M.). The tumors were classified into two categories according to echogenicity in comparison to the echogenicity of the premammary fat tissue, resulting in a hypoechogenic group and an isoechogenic to hyperechogenic group [17].

MR Imaging Technique
MR imaging of the breast was performed with a 3.0-T MR system (Discovery MR750w, GE Healthcare, Milwaukee, WI, USA). Commercially dedicated phased array breast coils were used in all cases with the patient in the prone position. Axial T2-weighted images were acquired using a fast spin-echo sequence (repetition time [TR]/echo time [TE], 4,187 msec/102 msec; field of view [FOV], 320×320 mm; matrix, 320×256 pixels; section thickness, 3 mm), and axial STIR T2-weighted images (TR/TE, 5,000 msec/70 msec; inversion time, 200 msec) were acquired. After obtaining diffusion-weighted MR images with a 2-dimensional spin-echo echo-planar imaging sequence, axial T1-weighted dynamic contrast-enhanced MR images of the entire breast were acquired before and 5 times after the intravenous administration of gadopentetate dimeglumine (Dotarem, Guerbet, Paris, France; Magnevist, Berlex Laboratories, Wayne, NJ, USA; Gaudiest, Bayer Schering Pharma, Berlin, Germany) using 0.2 mL/kg at a rate of 2.0 mL/sec (*VIBRAT*-Flex Din. imaging, GE Healthcare; matrix, 280×512 pixels; flip angle, 12°; FOV, 320×320 mm; section thickness, 3 mm, no intersection gap). Thus, six postcontrast images were acquired at approximately 0, 63, 126, 189, 252, and 315 seconds after the intravenous administration of contrast, and temporal samplings of the center of k-space for the post-contrast series were obtained at approximately 32, 95, 158, 221, 284, and 347 seconds. Subtraction images were generated.

The signal intensity on T2-weighted MR images and STIR T2-weighted images was visually classified as low, isointense, or high relative to the surrounding mammary parenchymal tissue. The degree of internal enhancement was classified as low, isoenhanced, or high, relative to the surrounding enhancing parenchymal tissues on the second subtraction images. Lesion size, dynamic enhancement pattern, peak enhancement, and ADC values were measured using a commercially available computer-aided evaluation

system (CADstream, Confirma, Inc., Kirkland, WA, USA). Dynamic enhancement patterns were categorized as slow, medium, or rapid for the early phase and washout, persistent, or plateau for the delayed phase. To measure ADC values, the region of interest was manually drawn on the ADC map (b value=0, 600 sec/mm²) 3 times. The mean ADC value was calculated.

Histopathologic Analysis

Pathologic characteristics such as pathologic lesion size, infiltrative or expanding tumor margins, nuclear and histologic grades, the presence or absence of lymph node metastases, and lymphovascular invasion were compared between the two groups. The groups were also compared according to the presence of estrogen receptor (ER),

progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). ER and PR assays were considered positive if at least 1% of tumor nuclei were positive. HER2 positivity was defined as HER2 immunochemistry results of 3+ or HER2 gene amplification by silver-enhanced *in situ* hybridization analysis [18,19]. Ki-67 proliferation of <14% was defined as negative and ≥14% as positive [20].

Data and Statistical Analysis

PMBCs were classified according to internal echogenicity on US, with the hypoechogenic group including PMBCs that exhibited hypoechogenicity and the isoechogenic to hyperechogenic group including PMBCs that exhibited isoechogenicity or hyperechogenicity.

Table 1. Imaging characteristics of mucinous carcinoma according to echogenicity on ultrasonography

US echogenicity	Total	Hypoechogenic (n=11)	Isoechogenic to hyperechogenic (n=22)	P-value
Age, median (range, yr)	47 (31–79)	58 (38–79)	46 (31–69)	0.069
Symptom				>0.990
Negative	10 (30.3)	3 (27.3)	7 (31.8)	
Palpable	23 (69.7)	8 (72.7)	15 (68.2)	
Mammographic density[a]				0.121
A, B	9 (27.3)	5 (45.5)	4 (18.2)	
C, D	24 (72.7)	6 (54.5)	18 (81.8)	
MR imaging features				
Lesion size, median (range, mm)	17 (5–37)	16 (8–34)	18 (5–37)	0.849
Signal intensity on T2-weighted images				0.010
Isointense	6 (18.2)	5 (45.5)	1 (4.5)	
High	27 (81.8)	6 (54.5)	21 (95.5)	
Signal intensity on STIR T2-weighted images				0.097
Isointense	4 (12.1)	3 (27.3)	1 (4.5)	
High	29 (87.9)	8 (72.7)	21 (95.5)	
Internal enhancement				0.219
Low	3 (9.1)	0	3 (13.6)	
Isoenhancement	18 (54.5)	5 (45.5)	13 (59.1)	
High	12 (36.4)	6 (54.5)	6 (27.3)	
Early enhancement				0.593[b]
Medium	4 (12.5)	2 (18.2)	2 (9.5)	
Rapid	28 (87.5)	9 (81.8)	19 (90.5)	
Delay enhancement				0.053[b]
Persistent or plateau	20 (62.5)	4 (36.4)	16 (76.2)	
Washout	12 (37.5)	7 (63.6)	5 (23.8)	
Peak enhancement, median (range, %)	–	203 (84–376)	215 (66–549)	0.166
ADC value, mean (range)	–	1.90 (1.59–1.95)	1.92 (1.17–2.44)	0.133

Values are presented as number (%) unless otherwise indicated.

US, ultrasonography; MR, magnetic resonance; STIR, short tau inversion recovery; ADC, apparent diffusion coefficient.

[a]A, almost entirely fatty; B, scattered fibroglandular tissue; C, heterogeneously dense; D, extremely dense. [b]The analysis excluded one case without enhancement.

Patient age, the presence of symptoms, and mammographic density were compared between the two groups. Lesion size on MR imaging, signal intensity on T2-weighted images, signal intensity on STIR T2-weighted images, internal enhancement on the second contrast enhancement, early and delayed enhancement patterns, peak enhancement, and ADC values were also compared between the two groups.

The chi-square test and the Fisher exact test were used for categorical variables and the Mann-Whitney U test was used for continuous variables. All results were analyzed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA) and P-values of <0.05 were considered to indicate statistical significance.

Results

Of the 33 patients with PMBC, 11 (33.3%) were classified into the hypoechogenic group and 22 (66.7%) into the isoechogenic to hyperechogenic group. The median age of the patients in the hypoechogenic group was 58 years; this value was notably higher than the corresponding figure of 46 years in the isoechogenic to hyperechogenic group, although this difference was not statistically significant (P=0.069) (Table 1). The presence of symptoms and
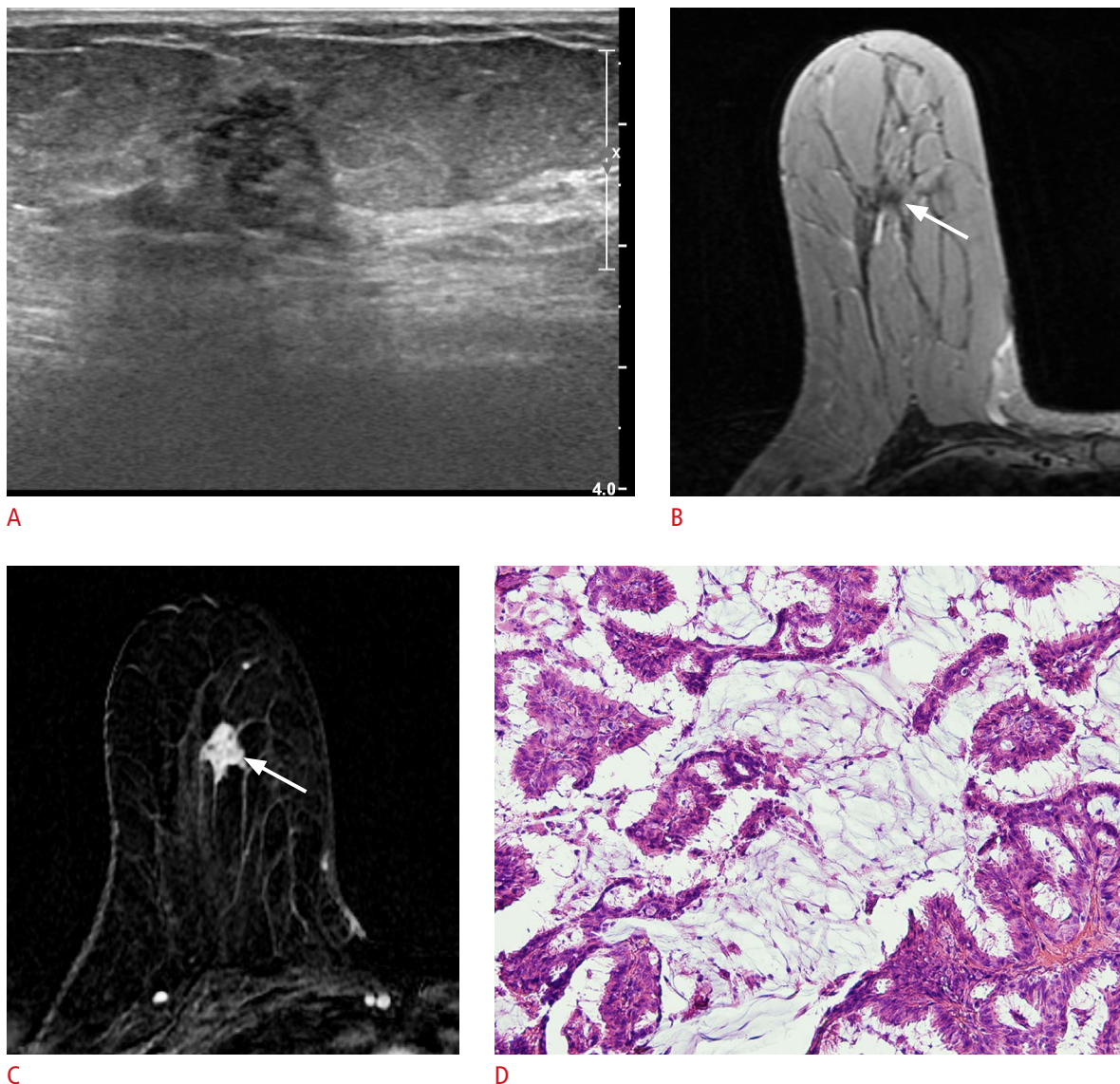

Fig. 1. A 75-year-old woman confirmed to have pure mucinous carcinoma of the right breast.
A. Ultrasonography of the area with a palpable lump in the right breast shows a 13-mm hypoechoic mass. B, C. The mass shows isointensity on T2-weighted images (arrow, B) and high internal enhancement on the second subtraction images (arrow, C). D. A low-power view visualizes the large lakes of extracellular mucin and clusters of tumor cells (H&E, ×10).

mammographic density were not significantly different between the two groups (P>0.990 and P=0.121, respectively). Of 33 PMBCs, 27 (81.8%) and 29 (87.9%) showed high signal intensity on T2-weighted images and on STIR T2-weighted images, respectively. The PMBCs in the isoechogenic to hyperechogenic group were significantly more likely to show high signal intensity on T2-weighted images (21 of 22, 95.5%) than the hypoechogenic group (six of 11, 54.5%) (P=0.010) (Figs. 1, 2). On STIR T2-weighted images, 95.5% of the PMBCs in the isoechogenic to hyperechogenic group (21 of 22) showed a high signal intensity, in contrast to 72.7% in the hypoechogenic group (eight of 11), but this trend did not show statistical significance (P=0.097). Internal enhancement, early and delayed enhancement patterns, peak enhancement, and mean ADC values did not exhibit significant differences between the two groups (P=0.219, P=0.593, P=0.053, P=0.166, and P=0.133, respectively).

None of the 33 patients with PMBC had lymph node metastasis. Lesion size on pathology, tumor margin, nuclear and histologic grades, and lymphovascular invasion were not significantly different between the two groups (P=0.778, P>0.990, P=0.538, P=0.121, and P>0.990) (Table 2). All mucinous carcinomas showed ER positivity. PR positivity was not significantly different between the
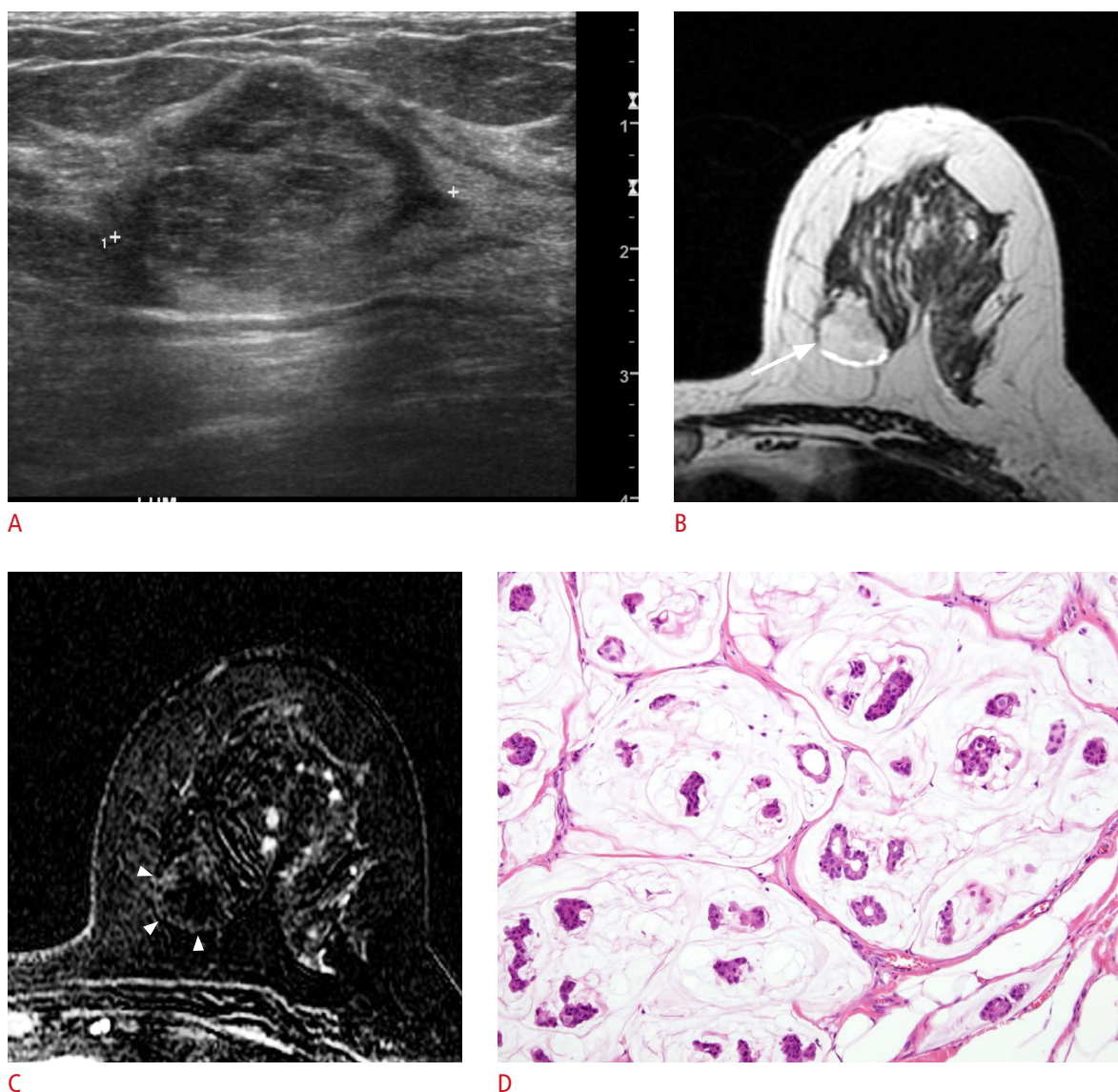
Fig. 2. A 44-year-old woman confirmed to have pure mucinous carcinoma of the left breast.
A. Ultrasonography of the area with a palpable lump in the left breast shows a 27-mm hyperechoic mass. B, C. The mass shows high signal intensity on T2-weighted images (arrow, B) and no internal enhancement on the second subtraction images (arrowheads, C). D. A low-power view visualizes small islands of tumor cells within lakes of extracellular mucin (H&E, ×100).

Table 2. Histopathologic characteristics of mucinous carcinoma according to echogenicity on US

US echogenicity	Total	Hypoechogenic (n=11)	Isoechogenic to hyperechogenic (n=22)	P-value
Lesion size (mm)	20 (3–40)	20 (3–38)	19 (8–40)	0.778
Margin				>0.990
Expanding	22 (66.7)	7 (63.6)	15 (68.2)	
Infiltrative	11 (33.3)	4 (36.4)	7 (31.8)	
Nuclear grade				0.538
1	16 (48.5)	4 (36.4)	12 (54.5)	
2	17 (51.5)	7 (63.6)	10 (45.5)	
Histologic grade				0.121
1	24 (72.7)	6 (54.5)	18 (81.8)	
2	9 (27.3)	5 (45.5)	4 (18.2)	
Lymph node metastasis				
Absence	33 (100)	11 (100)	22 (100)	
Lymphovascular invasion				>0.990
Absence	31 (93.9)	10 (90.9)	21 (95.5)	
Presence	2 (6.1)	1 (9.1)	1 (4.5)	
ER				
Positive	33 (100)	11 (100)	22 (100)	
PR				0.304
Positive	28 (84.8)	8 (72.7)	20 (90.9)	
Negative	5 (15.2)	3 (27.3)	2 (9.1)	
HER2[a]				0.312
Positive	1 (3.1)	1 (10)	0	
Negative	31 (96.9)	9 (90)	22 (100)	
Ki-67[b]				
Median (range)	5 (1–20)	7 (2–20)	5 (1–20)	0.606
Positive (≥14%)	5 (15.6)	3 (27.3)	2 (9.5)	0.310
Negative (<14%)	27 (84.4)	8 (72.7)	19 (90.5)	

Values are presented as median (range) or number (%).

US, ultrasonography; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

[a]The analysis excluded one case with hypoechogenicity that had a 2+ HER2 immunohistochemistry result, but for which an additional silver-enhanced *in situ* hybridization analysis was not performed. [b]The analysis excluded one case with hyperechogenicity for which a Ki-67 assay was not performed.

two groups (P=0.304). Only one tumor was positive for HER2 in the hypoechogenic group and none were positive in the isoechogenic to hyperechogenic group (P=0.312). No significant differences were observed between the two groups when the cut-off value of ≥14% was adopted for Ki-67 proliferation.

Discussion

PMBCs with isoechogenicity or hyperechogenicity were significantly more likely to show high signal intensity on T2-weighted images than PMBCs that exhibited hypoechogenicity. The histopathologic characteristics of PMBCs did not significantly differ according to their internal echogenicity on US.

In the hypoechogenic group and the isoechogenic to hyperechogenic group, 82% and 88% of PMBCs showed high signal intensity on T2- and STIR T2-weighted images in our study, respectively, which is comparable to previously reported findings of 82% to 100% for T2-weighted images [12,13,21] and 67% to 100% for STIR T2-weighted images [11,14]. The large amount of extracellular mucus, which is rich in free water, in PMBCs is thought to contribute to their high signal intensity on T2-weighted and STIR T2-weighted MR images [11,12,21]. PMBCs with isoechogenicity or hyperechogenicity showed high signal intensity on T2-weighted images more frequently than those with hypoechogenicity. This

is most likely because PMBCs with hypoechogenicity have more hypercellularity and less extracellular mucin. On STIR T2-weighted images, 72.7% of PMBCs in the hypoechogenic group showed a high signal intensity, in contrast to 54.5% of hypoechogenic PMBCs on T2-weighted images. STIR sequences increase the relative signal intensity of water content as a result of the additive T1 and T2 contrast effect, and this results in a notable contrast between water content and other tissues [22]. The increased contrast between mucin and the background parenchymal tissue might be the reason for this difference.

The mean ADC values were not significantly different between the two groups (1.90×10^{-3} mm²/sec vs. 1.92×10^{-3} mm²/sec, P=0.133), similar to the ADC value of 1.99×10^{-3} mm²/sec in a previous study [14]. This might be because the number of PMBCs included in our study was small, and the relative hypercellularity of PMBC with hypoechogenicity might not have been a strong enough trend to cause a significant difference in ADC values.

Our results showed that 62.5% of our sample of PMBCs exhibited persistent or plateau enhancement pattern in the delayed phase, while 37.5% showed a washout pattern. Delayed enhancement patterns were substantially different between the two groups. Of the PMBCs with hypoechogenicity, 63.6% showed a washout pattern on the delayed phase, substantially more than the corresponding value of 23.8% of PMBCs with isoechogenicity or hyperechogenicity. This difference in the delayed enhancement pattern probably occurred because the abundant mucin delays the diffusion of contrast medium throughout the stroma and around the epithelial component [1,12]. Internal enhancement was not significantly different between the two groups. Of the PMBCs, 54.5% and 9.1% showed isoenhancement and low internal enhancement, respectively, which is consistent with previous studies that found 58.8% of PMBCs to show mild enhancement and 5.9% to be without enhancement [13].

The pathological characteristics were not significantly different between the 2 groups. All PMBCs had nuclear and histologic grades of 1 or 2, corresponding to previous results showing 89% and 100% of PMBCs to be grade 1 or 2 [1,23]. None of the PMBCs exhibited lymph node metastasis, in contrast to previous studies that reported 0%–16.7% of PMBCs to have lymph node metastasis [1,5,6,8,23–25]. Our study found lymphovascular invasion in 6.1% of PMBCs, similar to the values of 5.7%–10.3% that have been reported in other studies [23,24]. PMBCs are slow-growing and are known to have a favorable prognosis due to the presence of mucin lakes, which are not vascularized and can slow tumor growth [1]. Although, hypocellular breast tumors have a more favorable prognosis [26], the relative hypercellularity of PMBCs in the hypoechogenic group did not lead to significant differences in the pathologic characteristics.

No statistically significant differences in immunohistochemical staining were found between the two groups. All PMBCs were positive for ER, and 84.8% were positive for PR, comparable with previously reported rates of 91%–100% for ER-positivity and 79%–85.7% for PR-positivity [23,24,27]. Only 3.1% of PMBCs showed HER2-positivity in the hypoechogenic group, which is comparable to previous reports of 2.9%–7.7% for HER2 expression [23,24]. Of the PMBCs, 84.4% were negative for Ki-67 expression when <14% was chosen as the cut-off value, which is comparable to the results of a previous study in which most PMBCs showed low Ki-67 proliferation [24].

Our study had several limitations. First, this study had a retrospective design and a small number of cases were included. Selection bias may have been present. Second, we did not consider menstrual status, which can influence the signal intensity of the background breast parenchyma.

In conclusion, PMBCs with isoechogenicity or hyperechogenicity were more likely to have a high signal intensity on T2-weighted images than PMBCs that exhibited hypoechogenicity. However, the pathological characteristics were not significantly different between PMBCs exhibiting isoechogenicity or hyperechogenicity and those that displayed hypoechogenicity.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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