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ORIGINAL ARTICLE

Invasive lobular carcinoma of the breast: mammographic and sonographic evaluation

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PURPOSE
To evaluate the efficacy of mammography and sonography together in the assessment of patients with pure invasive lobular carcinomas (ILCs) of the breast.

MATERIALS AND METHODS
We retrospectively reviewed 38 cases of pure invasive lobular carcinomas of the breast. The tumors were evaluated both mammographically and sonographically. The mammographic images were reviewed by two experienced mammographers. All patients underwent surgical management. Histopathologic assessments were made by experienced breast pathologists.

RESULTS
On physical examination, six tumors (15.7%) showed no clinical findings. The most common mammographic result was a spiculated mass or architectural distortion (42%). Eleven lesions (29%) were mammographically negative. Five cases (13%) showed pleomorphic or heterogeneous calcifications that were compatible with Breast Imaging Reporting and Data System (BI-RADS) 4 or 5. The most common sonographic result was a hypoechoic mass with or without shadowing (60.5%). Four tumors (10.5%) were sonographically invisible. Two cases (5%) were negative, and 25 cases (65.8%) were positive in both modalities. The overall sensitivity was 71.05% for mammography and 89.47% for sonography. The number of tumors detected by either of these two modalities was 36, and the overall sensitivity was 94.73%.

CONCLUSION
Mammography and ultrasonography are useful imaging methods in the evaluation of invasive lobular carcinoma. Because of the low rate of suspicious calcifications and low density of lesions, the false-negative rate tends to be high for these tumors. With the use of sonography and mammography together, invasive lobular carcinomas can be detected with a sensitivity of 94.73%. We recommend additional sonographic evaluations for all patients, especially those with dense breast tissue with or without positive mammographic findings.

Key words: • *breast cancer* • *carcinoma, lobular* • *mammography* • *breast ultrasonography*

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Invasive lobular carcinoma (ILC) is the second most common breast malignancy after invasive ductal carcinoma (IDC). In most series, ILC constitutes 5–15% of all diagnosed breast cancers, whereas IDC constitutes 70–90% (1–5). According to a recent epidemiological study, the incidence of lobular breast cancer is increasing, especially among postmenopausal women (6). The likely cause of this increase is thought to be the use of complete hormone replacement therapy (3). When compared to IDC, ILC is associated with a higher rate of multiplicity and bilaterality. However, the overall survival rate for ILC patients with a given tumor size and stage is believed to be slightly higher than for IDC patients (7–9). Because ILC is difficult to diagnose mammographically, higher false-negative results have been reported for ILC than for other invasive breast cancers (10, 11). Sonographic detection of ILC may be difficult; the sensitivity range has been reported to be between 68% and 87.7%, with a sensitivity for lesions smaller than 1 cm between 25–85.7% (12–15). ILCs are also difficult to diagnose clinically because they often present as diffuse infiltrative processes with no clinically palpable masses (8, 10).

ILCs are derived from small, uniform tumor cells with round nuclei and narrow cytoplasm that are arranged in a classic single-file pattern (8, 16). Characteristically, these cells infiltrate the stroma in single-file cell strands along ductuli (a so-called Indian-file pattern) (17, 18). ILC has a tendency to spread diffusely or between the collagen fibers of the breast and produces little desmoplastic response (16). ILC detection in mammography and sonography may be difficult because of these pathological features and the resulting low lesion density (19).

The purpose of this study was to evaluate the efficacy of mammography and sonography when used together to detect tumors in patients with pure ILC of the breast.

Materials and methods

Between 1997 and 2008, 38 patients with a mean age of 52.5 years (30–86 years) who were diagnosed with pure ILC histopathologically were retrospectively reviewed and included in this study. Cases of mixed lobular and ductal carcinoma were excluded from the study. Patients' clinical histories were reviewed, and physical examination findings at presentation were recorded.

Mammographic examination

All cases were examined with a technique using screen-film mammography (Bennett Contour Mammography System; Trex Medical Corporation, Copiague, New York, USA) and full-field digital mammography (Senographe DS; GE Medical Systems, Milwaukee, Wisconsin, USA) units. Mediolateral oblique and craniocaudal projections

were obtained, and additional views (mediolateral, spot compression and magnification views) were tailored to individual cases. The mammographic images were reviewed by two experienced mammographers. First, an assessment of breast tissue density was made, and all mammograms were interpreted using the Breast Imaging Reporting and Data System (BI-RADS) with knowledge of the clinical findings (20). When available, prior mammograms were compared with current mammograms.

Sonographic examination

Sonography was performed on all patients using 4–9-MHz and 5–13-MHz linear array transducers (Siemens Sonoline Antares, Isaaquah, Washington, USA) and 7.5-MHz and 13.5-MHz linear array transducers (Sonoline, Elegra, Siemens Medical Systems, Issaquah, Washington, USA) with the tissue harmonic imaging property in a dedicated breast sonography unit. The sonographic appearance was evaluated with regard to margins, echo texture, echogenecity and posterior acoustic characteristics using previously described nomenclature (21).

Pathological examination

All patients underwent surgery. Almost all of the patients underwent core needle biopsies prior to surgery. Sonographic or mammographic-guided core biopsies were performed for suspect findings that were detected by the imaging modalities. Palpable tumors with no imaging findings underwent randomized biopsies by the surgeons. Twenty-four patients underwent modified radical mastectomies, and 14 patients underwent lumpectomies. Histopathological assessments were made by experienced breast pathologists.

Results

Clinical findings

Thirty-two of the 38 tumors (84%) were positive on clinical examination. Twenty-nine tumors (76%) were detected as palpable abnormalities and discrete masses, whereas two tumors showed only skin retraction, and one tumor showed only skin induration. Three of the 29 palpable tumors were also accompanied by skin thickening, nipple retraction and skin induration (Table 1). The remaining six tumors (15%) showed no clinical findings and were detected by a screening radiological examination.

Breast density (BI-RADS category)

Breast tissue densities, determined by mammography for the 38 cases, were fatty (D1) (n=6), scattered fibroglandular (D2) (n=11), heterogeneous dense (D3) (n=13) and dense (D4) (n=8) (Table 2).

Mammographic findings

Sixteen out of 38 ILCs (42%) manifested as masses and/or architectural distortions mammographically at presentation. Eleven tumors (29%) had only asymmetric density, and the remaining 11 tumors (29%) showed no abnormality on mammographic examination, even at retrospective re-evaluation (Table 3). Seven out of 11 patients (63.6%) with negative mammographies had dense breast parenchyma. Two of these patients (18.2%) had heterogeneously dense parenchyma, and two (18.2%) had scattered fibroglandular breast parenchyma.

Breast calcifications were categorized using the American College of Radiology breast imaging reporting and data system lexicon descriptors (22). Five tumors (13%) had pleomorphic or heterogeneous calcifications that were compatible with BIRADS 4 or 5, and the remaining 33 tumors showed no suspicious calcifications.

Sonographic findings

The most common sonographic appearance was a hypoechoic, heterogeneous mass with irregular or indistinct margins and posterior acoustic shadowing. This finding was observed in 23 tumors (60.5%). Six tumors (15.8%) showed shadowing with no appearance of a mass, and five tumors (13.2%) showed well-circumscribed mass lesions. The remaining four tumors (10.5%) were sonographically invisible (Table 4).

Table 1. Clinical findings of patients

Clinical findings	Number of tumors
Negative	6
Palpable abnormality	29[a]
Skin thickening	3
Nipple retraction	2
Skin induration	1

[a]Three of these 29 palpable tumors also showed skin thickening, nipple retraction and skin induration

Table 2. Distribution of patients' breast density ratings

Breast density (BI-RADS category)	Number of patients
D1. Fatty	6 (16%)
D2. Scattered fibroglandular	11 (29%)
D3. Heterogeneous dense	13 (34%)
D4. Dense	8 (21%)

Table 3. Mammographic findings of patients

Mammographic findings	Number of patients
Negative	11 (29%)
Mass and/or architectural distortion	16 (42%)
Asymmetrical density	11 (29%)
Microcalcifications	5 (13%)

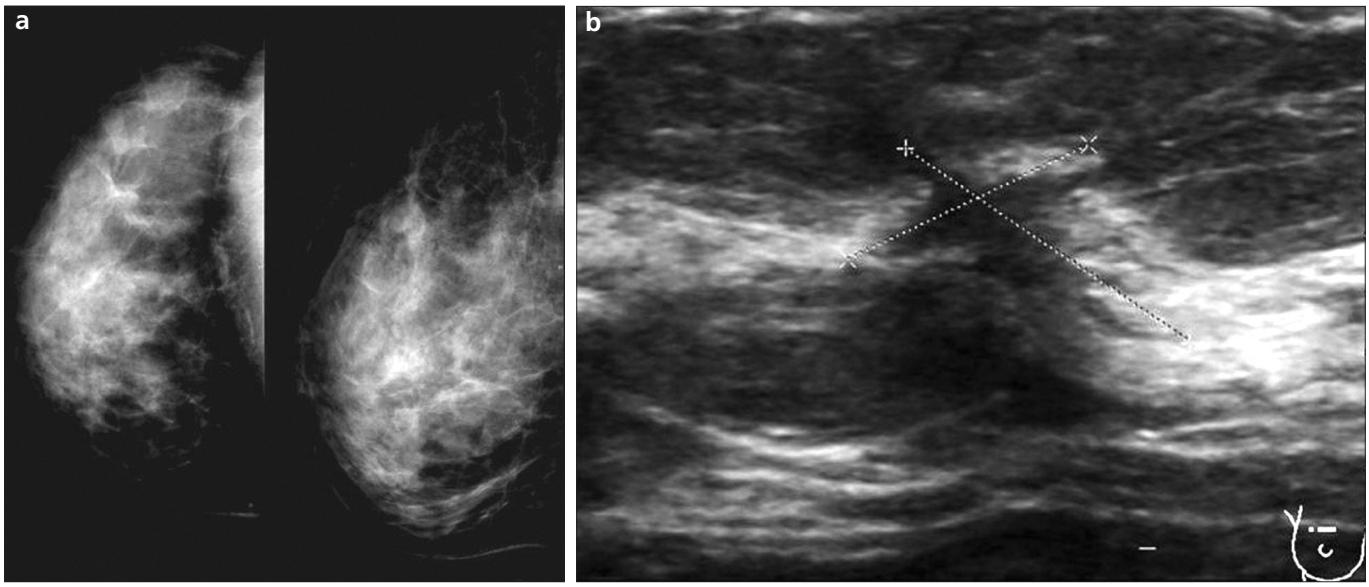

Figure 1. a, b. Thirty-eight-year-old woman with no palpation findings. Right craniocaudal and mediolateral mammograms **(a)** show a heterogeneously dense breast with no discernible abnormality. Sonographic image **(b)** shows a hypoechoic mass with posterior acoustic shadowing that lies within hyperechoic fibrous tissue at the eleven o'clock position in the right breast.

Two out of 38 ILCs were invisible in both mammographic and sonographic imaging examinations. These two patients underwent core needle biopsies at the sites of positive palpation findings. Nine out of 11 mammographically negative ILCs were sonographically positive (Fig. 1). Twenty-five out of 27 mammographically positive ILCs were also positive sonographically (Fig. 2). Two mammographically positive ILCs were sonographically negative. The overall sensitivity of mammography in ILC detection was 71.05% (27 out of 38 patients). Eleven patients had false-negative mammography scans. The sensitivity of ultrasonography in ILC detection was found to be 89.47% (34 out of 38 patients). Four patients had false-negative ultrasonography scans. In 25 out of 38 patients (65.8%), the results of both ultrasonography and mammography were positive. Consequently, the number of tumors detected by either of these two modalities was 36, and the detection sensitivity was calculated as 94.73% (Table 5). A total of 21 tumors were detected in the left breast (55%), and 17 were detected in the right breast (45%).

Table 4. Sonographic findings of patients

Sonographic findings	Number of patients
Negative	4 (10.5%)
Shadowing mass	23 (60.5%)
Shadowing only	6 (15.8%)
Well-circumscribed mass	5 (13.2%)

Table 5. Mammographic and sonographic break-up of patients

	Mammography (+)	Mammography (-)	Total
Ultrasonography (+)	25	9	34
Ultrasonography (-)	2	2	4
Total	27	11	38

In six patients, the tumor was considered multifocal with regard to the mammographic and sonographic findings (Figs. 2 and 3). Multifocality was detected histopathologically in 14 patients (36.8%), and lobular in situ components were detected in 16 patients (42%).

Axillary sonographic examinations revealed benign sonographic features in 28 patients (73.4%) and suspicious metastatic findings in ten patients (26.3%). Histopathologically, in 14 patients (35.5%), axillary lymph node dissection showed metastatic involvement.

Radical mastectomies were performed on 24 patients (63.2%), and breast-conserving surgeries were performed on the remaining 14 patients (36.8%). Sentinel lymph node biopsies and/or axillary dissections were performed in conjunction with both surgical management procedures.

For 28 patients, the measured tumor dimensions were between 3–60 mm macroscopically. In eight of these 28 patients, the pathological sizes of the lesions were found to be more than 1 cm greater than the measured radiological sizes. Because of re-excisions, pathologically definite sizes could not be measured in ten patients.

On microscopic assessment, a classical tumor type was detected in 31 patients (81.5%), and variant subtypes were detected in seven patients (18.5%). The variant subtypes found were: pleo-

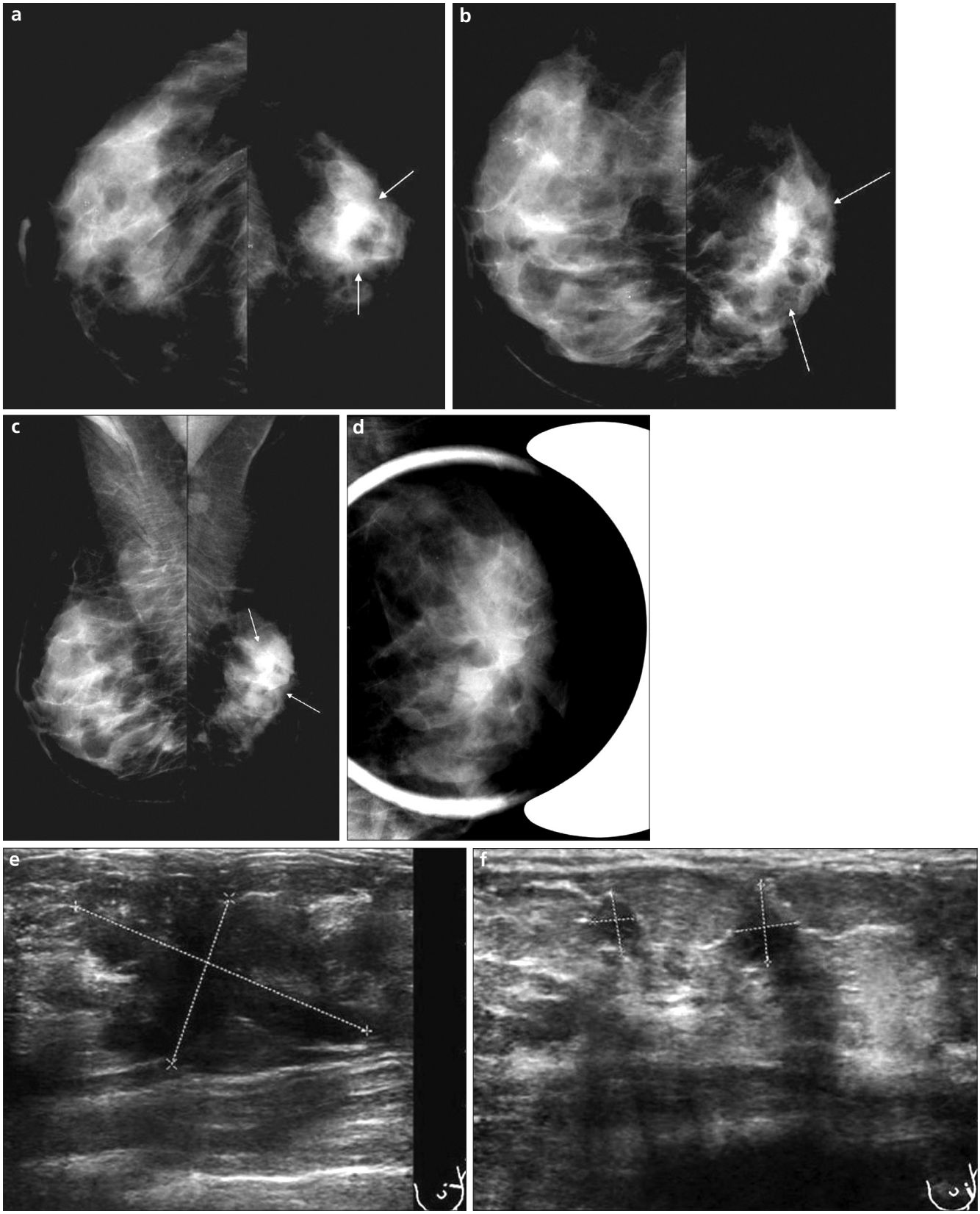

Figure 2. a–f. Forty-three-year-old woman complaining of a palpable abnormality in the upper left breast. Craniocaudal **(a)**, mediolateral **(b)** and mediolateral oblique **(c)** mammograms of the bilateral breast show a volumetric decrease in the left breast and a prominent asymmetry with an area of architectural distortion and accompanying pleomorphic microcalcifications in the upper outer quadrant *(arrows)*. Architectural distortion and pleomorphic microcalcifications of the left upper outer quadrant are also shown by spot compression view **(d)**. Sonographic images **(e** and **f)** show multiple irregular, hypoechoic masses with posterior acoustic shadowing.

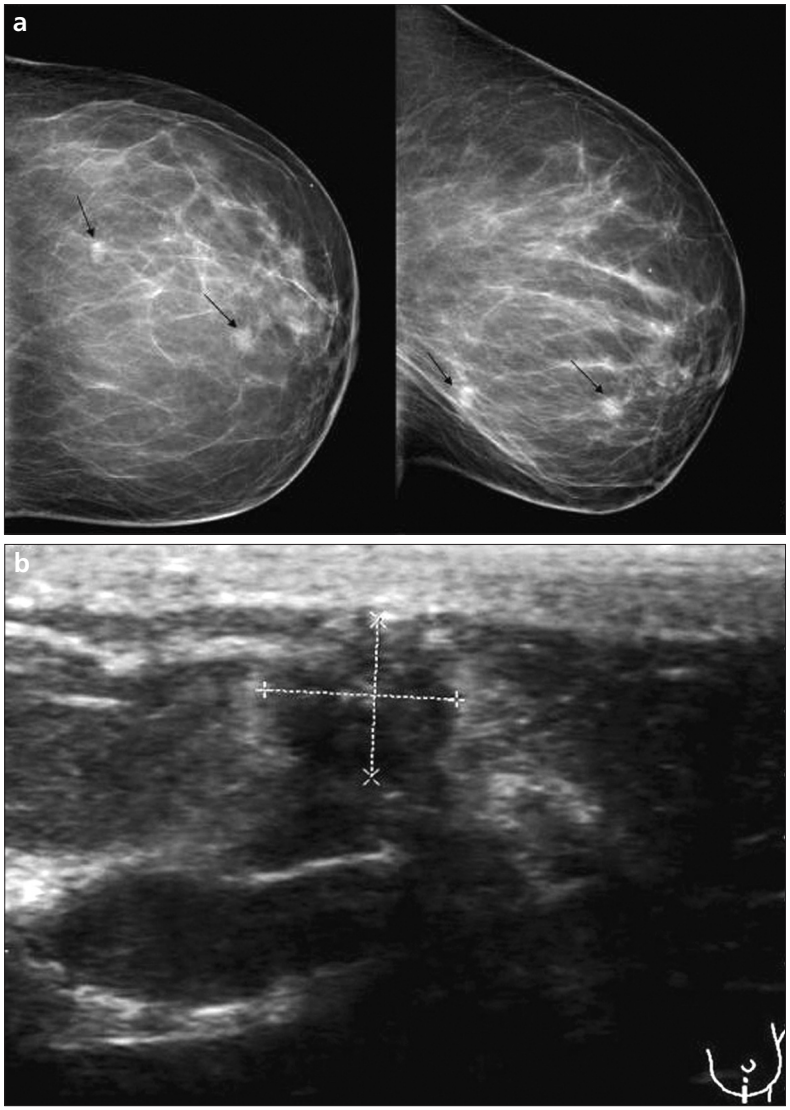

Figure 3. a, b. Sixty-seven-year-old woman. Craniocaudal and mediolateral mammograms **(a)** show ill-defined asymmetric nodular densities at the six o'clock and four o'clock positions in the left breast *(arrows).* Sonographic image **(b)** reveals irregular hypoechoic masses surrounded by an echogenic halo and posterior acoustic shadowing.

morphic in two patients, alveolar in one patient and trabecular-solid, classical-solid or trabecular-alveolar-classical mixed type in four patients.

Discussion

ILC often presents diagnostic difficulties for physical examinations and conventional imaging, resulting in lower sensitivities for the detection of ILC than for IDC (12, 23). The sensitivity of physical examinations for ILC detection ranges between 65% and 98%, with generally over 50% of patients presenting with palpation findings (15, 24–26). The sensitivity of mammography for ILC detection was reported to be between 57% and 81% (15, 24–26), and the false-negative interpretation rates of ILC in mammograms were reported to be in the range of 19–43% (10, 26, 27). In our study, the sensitivity of mammography was 71.05%, and the false-negative rate of mammography was 28.9%. In the false-negative group, 75% of the patients showed D4 and 25% showed D3/D2 breast densities. None of the patients with D1 breast density produced false-negative mammographic evaluations. Similarly, Krecke and Gisvold reported false-negative mammography rates of 57% for D4, 29% for D3 and 9% for D2 breast densities (10). ILC appearing as a mass lesion mammographically may have a spiculated appearance (28, 29). In addition to an ill-defined opacity, parenchymal asymmetry and architectural distortion are the other mammographical findings of ILC (17, 28, 29). Additionally, ILC may be invisible on mammograms because the density of ILC tends to be relatively low, similar to that of normal breast parenchyma, which may be the result of the relative paucity of a desmoplastic response (30). In addition, the histological growth pattern of ILC does not have a tendency to form a mass (10). Even in mammographically positive ILCs, radiological findings can vary based on different projections. This variance can be explained by the diffuse infiltration of tumor cells and a tumoral growth pattern that is characterized by minimal connective tissue reactions. ILCs are not well defined and do not show high-density lesions mammographically; these findings can be explained by the tendency of ILC to be multifocal with spared glandular tissue areas. In a study by Evans et al. (28), 40 out of 62 pure ILC cases (64.5%) manifested as mass lesions at presentation, with 70% of the masses being spiculated, whereas 13 out of 62 lesions (21%) manifested as architectural distortions. In a study by Hilleren et al. (26), the mammographic findings were as follows: 53% spiculated opacity, 7% ill-defined opacity, 16% architectural distortion and 4% parenchymal asymmetry. A total of 16% of the cases were invisible to mammography. Le Gal et al. (24) gave results of 28% spiculated opacity, 22% ill-defined opacity, 18% architectural distortion and 19% parenchymal asymmetry, with a negative mammogram rate of 12%. In our study, 11 out of 38 cases (29%) were mammographically negative. We found that 11 cases (29%) manifested as only asymmetrical density, and 16 cases (42%) presented with mass and/or architectural distortions. Even large tumors may be undetectable by physical examination and mammography (26). Supporting this point, one of our cases with a 4-cm tumor that was found upon histopathologic assessment was undetectable by physical examination and mammography and could only be detected by sonography.

The rate of ILC lesions that are associated with suspicious calcification varies (30). In a study of Hilleren et al. (26), 2% of 137 ILCs showed suspicious calcifications, and in a study by Krecke and Gisvold, 1% of 185 pure ILCs showed suspicious calcifications

(10). The percentage of suspicious calcifications in a study of Cornford et al. (31) was 28%, and this higher rate was thought to be due to this study's inclusion of mixed invasive lobular and ductal tumors in the infiltrating lobular carcinoma category. Characteristically, tumor cells surround the ducts without obstructing them. It is postulated that the lack of ductal invasion or obstruction may explain the low rates of microcalcifications associated with ILC (26). In our study, five out of 38 ILC cases (15%) showed clusters of microcalcifications that were consistent with BIRADS category 4–5. We believe that the discrepancy between these results can be explained by the incorporation of considerably older mammograms into some of the studies. Significant technical improvements in the field of mammography have been developed since some of these older mammograms were obtained.

With the additional use of ultrasonography, the overall sensitivity for ILC detection increases; as mentioned previously, mammographically, the ILC density is not higher than that of the normal parenchyma, and an ILC lesion may be hidden inside dense breast tissue. The sensitivity of ultrasound is stated to range from 68% to 98% (15, 32–35). Mann et al. (17) have given this rate as 83%, and they concluded that with the use of newer, high-frequency transducers, the sensitivity of ultrasound may improve further. However, initial series using 7.5-MHz transducers showed sensitivities of 68% (15) and 78% (33), whereas series that used 10–13-MHz transducers reported sensitivities up to 98% (34, 36). In our study, which used 4–9-MHz and 5–13-MHz linear array transducers, the sensitivity of ultrasonography was found to be 89.47%.

The most common sonographic finding for ILC is a heterogeneous hypoechoic mass with irregular borders and posterior acoustic shadowing (12, 26, 37). In a study of Butler et al. (12), ten out of 81 ILC cases (12%) were sonographically occult, and 12 out of 81 patients (15%) showed focal shadowing without a discrete mass. In our study, four out of 38 ILC cases (10.5%) were invisible sonographically. Five out of 38 cases (15.8%) showed focal shadowing with no mass appearance, and 23 out of 38 cases (60.5%) appeared sonographically as shadowing mass lesions.

At the time of diagnosis, the tumor diameters observed in ILC are reported to be larger compared to those of IDC (1, 2, 38). In our study, the mean tumor size was measured as 17.8 mm sonographically and mammographically. Some studies have stated that mammography and ultrasonography tend to underestimate tumor size in ILC (17). In Yeatman et al.'s study (5), the underestimation of mammography was calculated to be 12 mm. Le Gal et al. (24) and Uchiyama et al. (38) also confirmed that mammography underestimates true tumor sizes. Rodenko et al. (39) studied the correlation between mammographic and histopathologic tumor sizes in 20 cases and reached a correlation value of 32%. Tressera et al. (40) and Watermann et al. (41) showed an underestimation of tumor size with ultrasonographic examinations. In our study, using mammographic and sonographic examinations, eight out of 28 ILCs (28.5%) were found to be smaller than their histopathological sizes by 1 cm or more. In the remaining ten ILCs, the histopathologic sizes could not be measured due to re-excisions. In one case in our series, the estimated tumor dimension was approximately 2 cm mammosonographically, whereas the histopathologic size was given as 6 cm.

Another clinical feature of ILC is the multifocal development of the ipsilateral or bilateral breast. In the literature, multifocality and bilaterality rates were given as approximately 30% and 10%, respectively (42). In another study, ILC bilaterality was reported as 20–29% (43). In our study, the number of patients with multifocal ILC detected sonographically and mammographically was six (15.7%), and on histopathological examination it was 14 (36.8%); this higher rate was thought to occur because of the small number of cases and/or ILCs reported to be microscopically multifocal.

One of our study limitations was the small number of patients analyzed. Although this study was designed as a retrospective analysis, all patients' imaging findings could be correlated with their histopathologic findings. Another limitation was that the interpreters were not blinded during the image review process. They were aware of the ILC diagnosis in all cases, which may have affected their interpretations of mammographic and sonographic examinations.

One of the striking points of this study is that three out of 38 ILC patients (7.8%) with absent physical and mammographic findings were diagnosed earlier with only sonographic assessments. In five out of eight mammographically negative patients (62.5%), the ILC diagnosis was again made sonographically.

In conclusion, ILC has several distinct sonographic and mammographic findings. Mammography or sonography alone plays limited roles in ILC diagnosis. With the combination of these two imaging modalities, however, the possibility of early ILC detection increases. The physician and radiologist must always be extremely careful in their early diagnoses of ILC, as it is a confusing breast cancer type with properties that make diagnosis difficult by physical examination and radiological imaging methods. Especially for dense breast tissues with suspicious clinical findings, ultrasonography should be performed and may even be repeated by another radiologist.

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