RadioGraphics

Invasive Lobular Carcinoma of the Breast: Spectrum of Mammographic, US, and MR Imaging Findings[1]

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CME FEATURE

See accompanying test at http://www.rsna.org/education/rg_cme.html

LEARNING OBJECTIVES FOR TEST 4

After reading this article and taking the test, the reader will be able to:

- Discuss the challenges surrounding the diagnosis and management of invasive lobular carcinoma of the breast.
- Describe the histopathologic features of invasive lobular carcinoma of the breast and how they relate to its clinical and imaging features.
- List the most common mammographic, US, and MR imaging findings of this neoplasm.

TEACHING POINTS

See last page

The reported prevalence of invasive lobular carcinoma (ILC) is variable, with more recent studies indicating that ILC accounts for 10%–15% of all invasive breast carcinomas. However, the radiologic diagnosis and management of ILC can be uniquely challenging. Current imaging modalities are not very specific for differentiating ILC from other invasive breast cancers, and ILC has a tendency to have appearances at mammography that are atypical for invasive ductal carcinomas, resulting in higher false-negative rates. The clinical detection of ILC can also be difficult, since ILC frequently fails to form a palpable lesion. This tendency of ILC to have atypical imaging and clinical appearances is related to its histopathologic features and its failure to elicit a desmoplastic response. Despite these diagnostic challenges, however, imaging remains crucial in the detection and management of ILC. Mammography, ultrasonography (US), and magnetic resonance (MR) imaging all play important roles, with each modality having its own advantages and limitations. The use of US and MR imaging as adjuncts to mammography increases sensitivity in the detection of ILC and provides useful information for further management and presurgical planning. Familiarity with the spectrum of imaging appearances of ILC is essential.

Abbreviation: ILC = invasive lobular carcinoma

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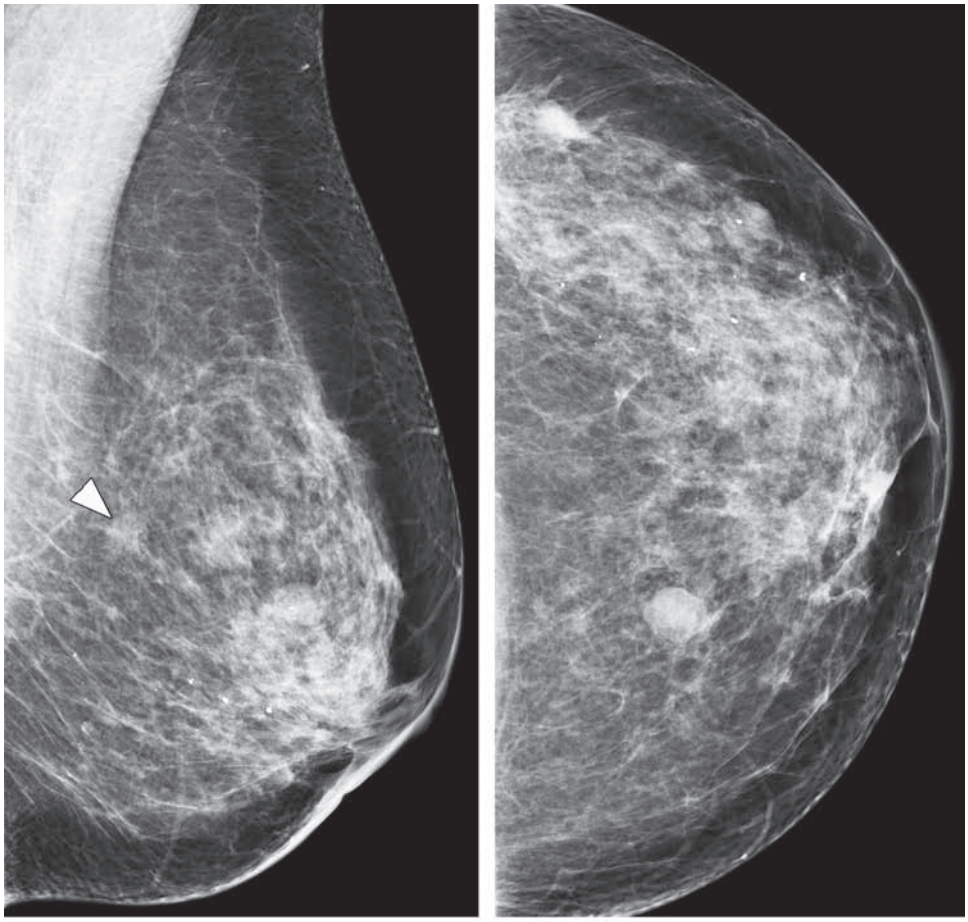
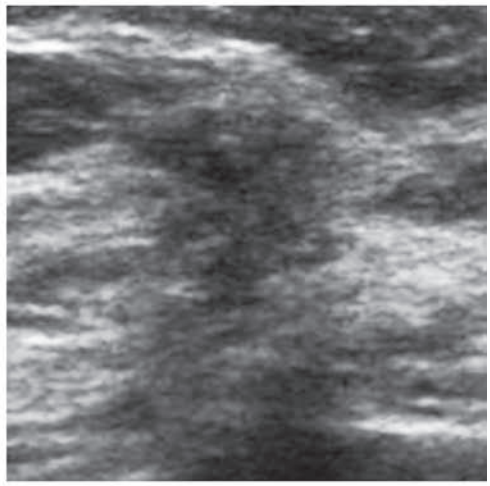


a. b.



c.

Figure 1. Low-density mass identified on a single mammographic view in a 70-year-old woman. The patient had a remote history of right breast cancer and was referred for screening mammography. **(a)** Left mediolateral oblique mammogram shows a low-density, irregular, spiculated mass (arrowhead) at a posterior depth in the left breast. **(b)** On a craniocaudal mammogram, no definite corresponding mass is identified. **(c)** Ultrasonographic (US) image of the left breast demonstrates an irregular hypoechoic mass with a thick echogenic halo at the three o'clock position. Histopathologic evaluation of a lumpectomy specimen revealed classic ILC and ductal carcinoma in situ.

Introduction

The majority of invasive breast carcinomas are categorized as ductal carcinoma of the usual ("not otherwise specified") type. Invasive lobular carcinoma (ILC) is the second most common histologic type of breast carcinoma, accounting for approximately 10%–15% of all invasive breast cancers (1–5). Although ILC is associated with a higher rate of multiplicity and bilaterality than are the usual type invasive ductal carcinomas, the overall survival rate for patients with ILC of a given size and stage is believed to be slightly higher than for patients with the usual type invasive ductal carcinomas (6–8). However, higher false-negative rates (up to 19%) are reported for ILC than for other invasive cancers at mammography because ILC is often difficult to diagnose mammographically (2,9). At mammography, ILC tends to manifest as lesions with an opacity equal

Teaching Point

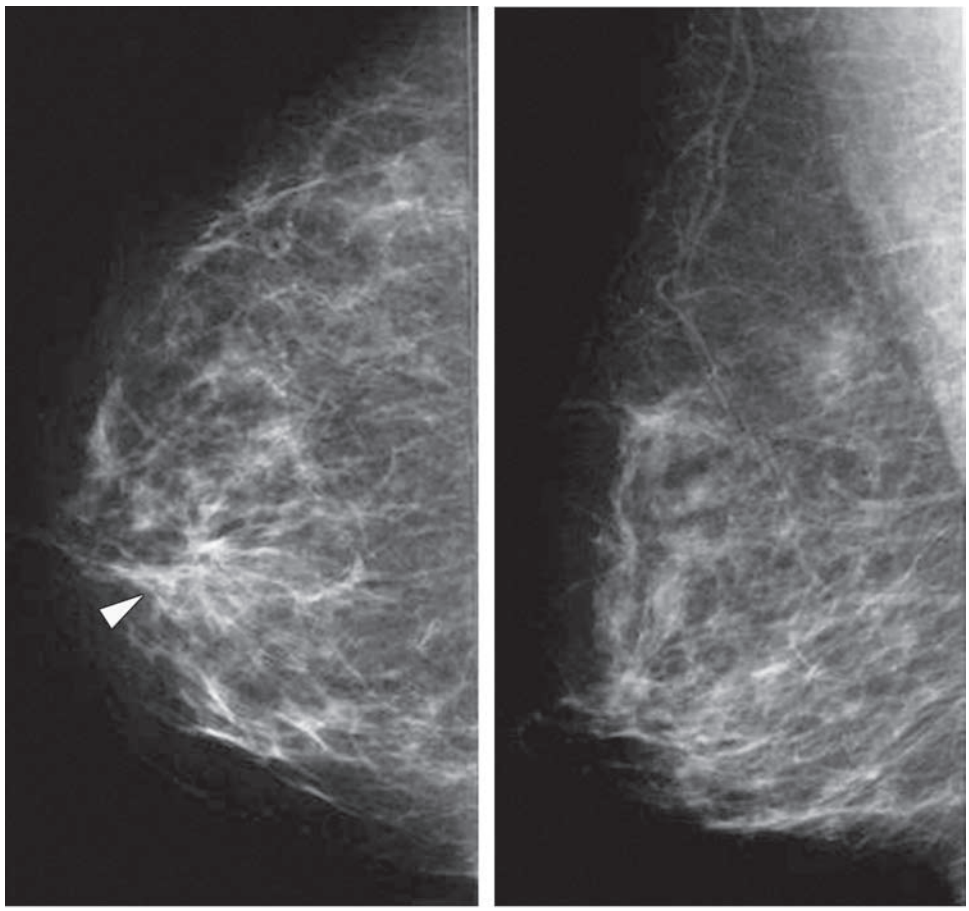


Figure 2. Architectural distortion identified on a single mammographic view. **(a)** Craniocaudal mammogram shows a subtle area of architectural distortion (arrowhead) in the inner hemisphere of the right breast. **(b)** On a mediolateral oblique mammogram, no definite matching architectural distortion is noted.

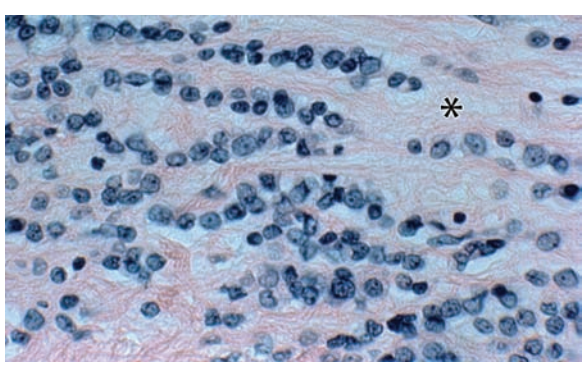


Figure 3. Photomicrograph shows ILC appearing as small irregular cells in a single-file distribution with soft collagenlike supportive tissue (*).

to or less than that of normal fibroglandular tissue. The principal mammographic abnormality is commonly not seen on either of the two standard views (craniocaudal and mediolateral oblique), although abnormalities are more frequently seen on the craniocaudal projection than on the mediolateral oblique projection (Figs 1, 2) (1,10). ILC can also be difficult to detect clinically, since lesions are often poorly circumscribed and rubbery in consistency and fail to form palpable discrete masses (2,7). The clinically and mammographically elusive nature of ILC is thought to be related to its histopathologic features and its failure to elicit a desmoplastic reaction.

At present, mammography, US, and magnetic resonance (MR) imaging are the principal imaging modalities used in the detection and evaluation of breast cancers. In this article, we review the pathologic features of ILC of the breast and discuss and illustrate its imaging features at these three modalities.

Pathologic Features of ILC

ILC has a characteristic histopathologic appearance consisting of small, uniform tumor cells with round nuclei and scanty cytoplasm arranged in a classic single-file pattern (Fig 3) (7,11). ILC has a tendency to spread diffusely or between the collagen fibers of the breast and produces little desmoplastic response (11). The diffuse spread of neoplastic cells in ILC is also reflected by its unusual metastatic pattern: Compared with invasive ductal carcinoma, ILC is far more likely to metastasize to the peritoneum-retroperitoneum, gastrointestinal tract, urogenital tract, leptomeninges, and myocardium. In most series, the metastatic rate of ILC to the liver, bone, and

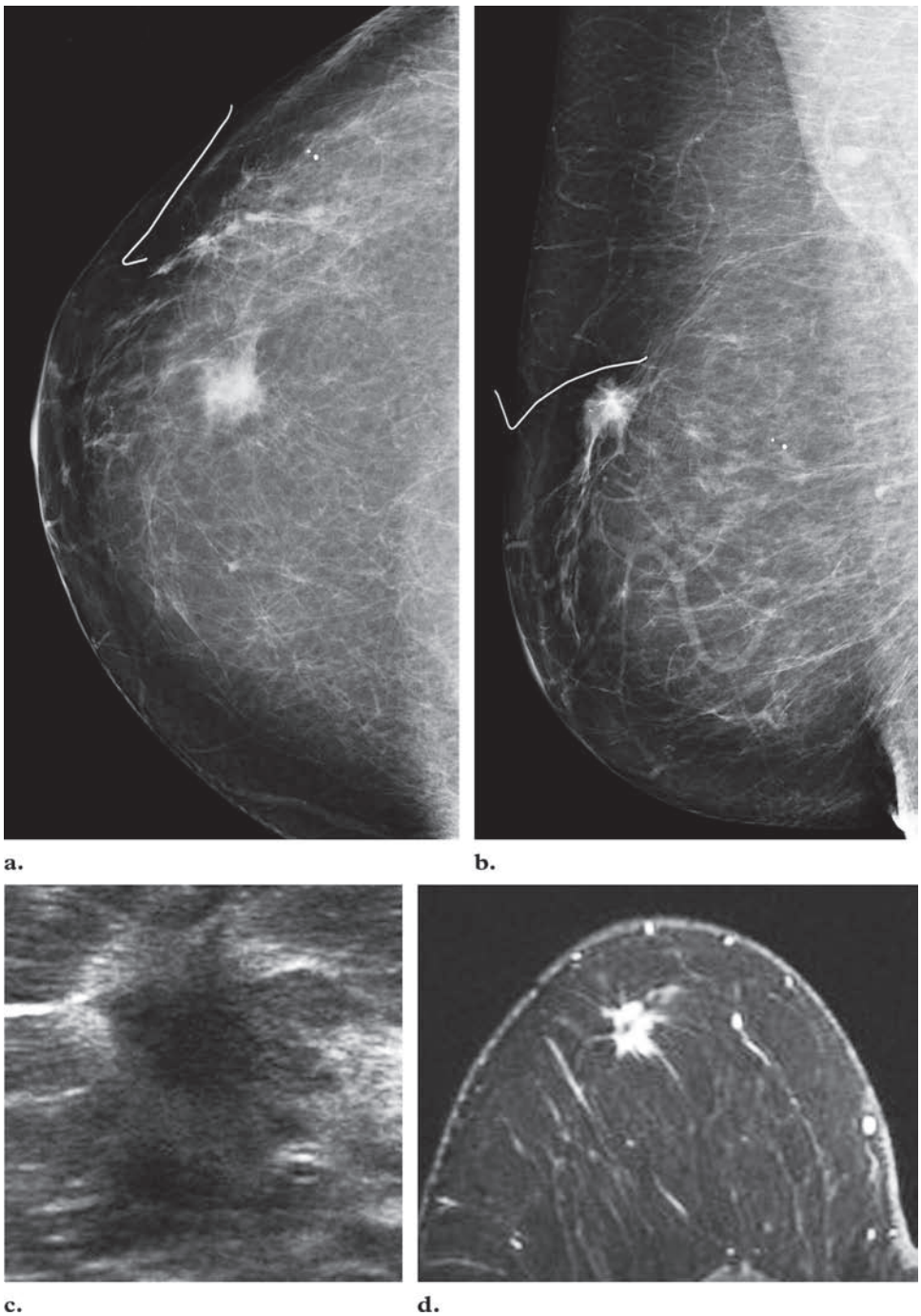


Figure 4. ILC in a 61-year-old woman who presented with focal pain in the right breast. In this case, the ILC appears similar to the typical manifestation of the usual type invasive breast carcinoma. **(a, b)** Craniocaudal **(a)** and mediolateral oblique **(b)** mammograms of the right breast show an irregular mass with spiculated and indistinct margins at the eleven thirty–twelve o'clock position. The mass was not seen at mammography performed 15 months earlier. A wire marker is seen overlying a benign scar from prior surgery in the right upper outer quadrant. **(c)** US image shows an irregular hypoechoic mass with spiculated margins and a thick echogenic halo. **(d)** Axial contrast material–enhanced fat-saturated subtraction MR image shows an enhancing, irregular, spiculated mass.

pleura is comparable to that of invasive ductal carcinoma, and parenchymal lung metastases are more common in invasive ductal carcinoma than in ILC. In addition, hydronephrosis is a commonly reported complication of metastatic ILC (5,12,13).

Tumor cells may surround cancerous or normal-appearing acini or ducts, creating a characteristic "bull's-eye" pattern (7). Not uncommonly, invasive carcinomas demonstrate histologic features of both ductal and lobular patterns, making determination of the exact prevalence of ILC difficult (7). Variants of ILC include signet ring, alveolar, solid, and pleomorphic types (11).

Imaging Findings of ILC

Mammography

The sensitivity of mammography for the detection of ILC reportedly ranges between 57% and 81% (1–3,14–16). At mammography, ILC most commonly manifests as a mass (44%–65% of cases), usually with spiculated or ill-defined margins (Figs 1a, 4, 5). Round and circumscribed masses are far less common, being seen in only 1%–3% of cases of ILC (1,3,15,17,18). These

Teaching Point

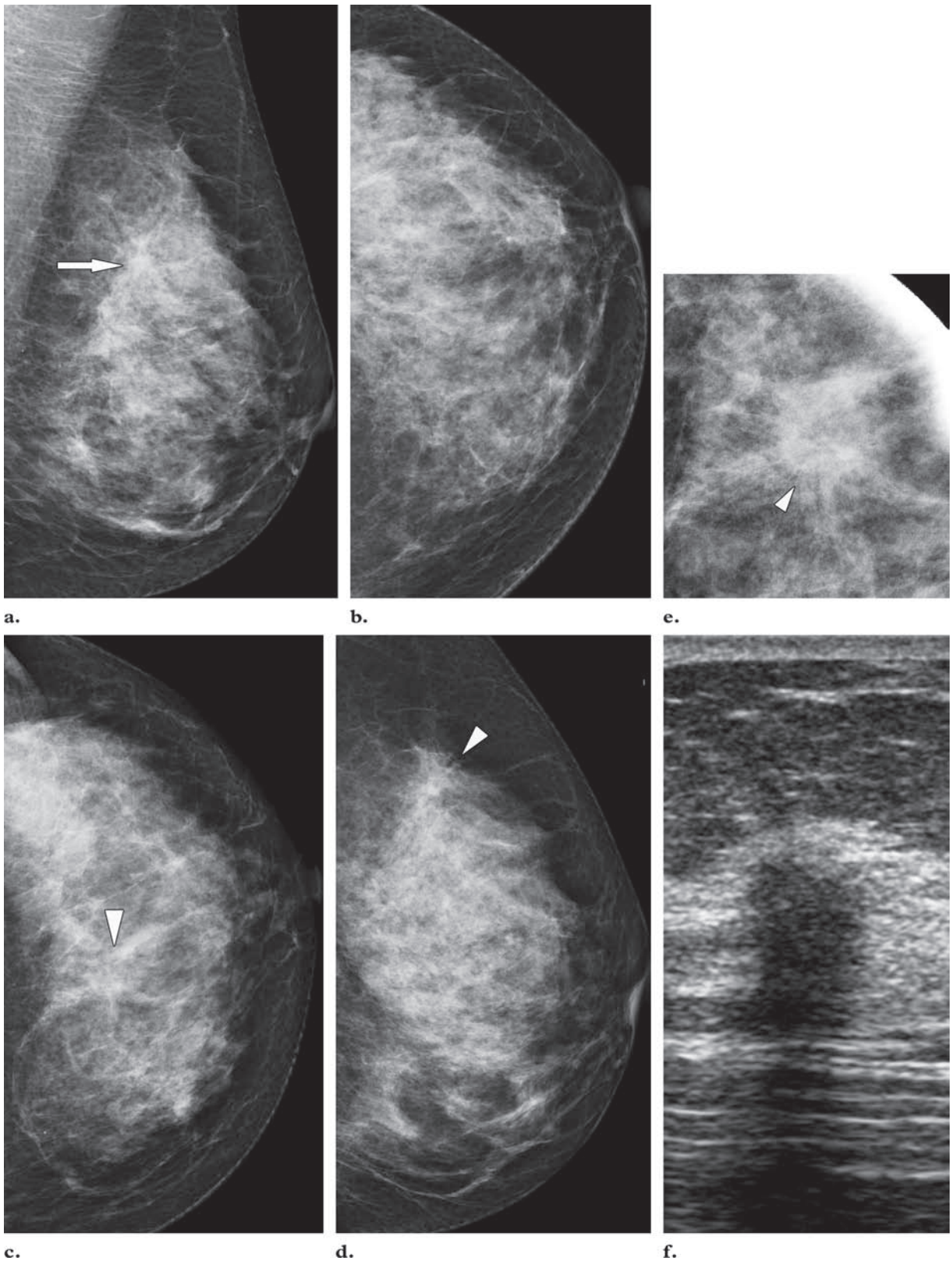


Figure 5. Spiculated mass with associated architectural distortion in a 52-year-old woman with an erythematous and painful left nipple, a finding that had resolved by the time the patient underwent screening mammography. **(a)** Mediolateral oblique mammogram shows subtle architectural distortion (arrow). **(b)** On a craniocaudal mammogram, the architectural distortion is not clearly evident. **(c–e)** Craniocaudal **(c)**, mediolateral **(d)**, and spot compression craniocaudal **(e)** mammograms obtained 9 months later as part of additional work-up show an irregular mass with spiculated margins in the left upper inner quadrant (arrowhead). The opacity of the lesion is equal to that of the surrounding fibroglandular breast tissue. No mammographic abnormality was identified in the peri- or subareolar region. **(f)** US image obtained at the same time as **c–e** shows an irregular mass, not parallel to the skin surface, with hypoechoic and heterogeneous internal echoes and posterior acoustic shadowing.

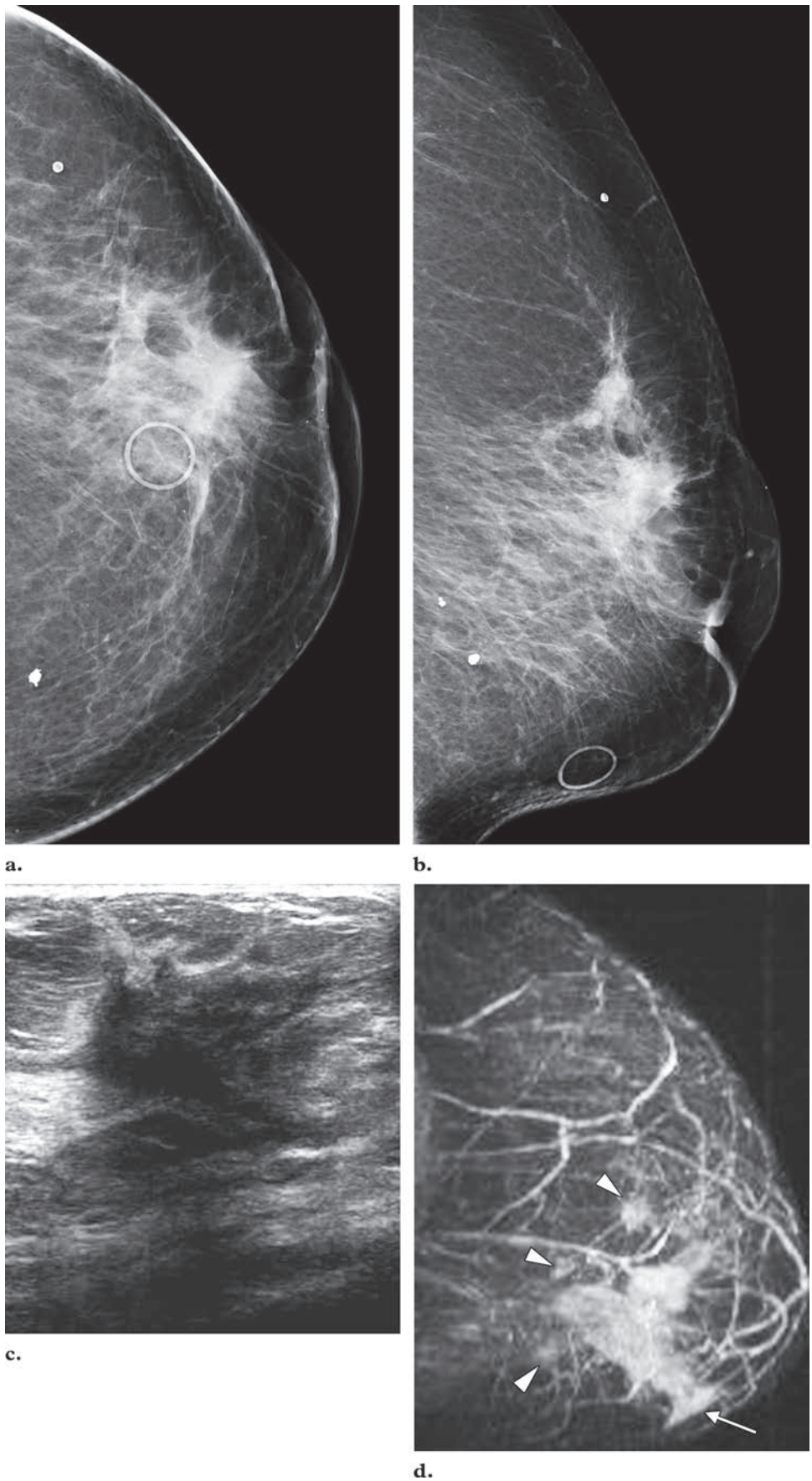


Figure 6. Nipple retraction and underlying architectural distortion in an 80-year-old woman who presented with left nipple retraction and breast hardness. **(a, b)** Craniocaudal **(a)** and mediolateral **(b)** mammograms show prominent nipple retraction with an area of architectural distortion at the twelve o'clock position in the anterior left breast. The distortion was not seen at mammography performed 16 months earlier. The radiopaque circular marker denotes a skin mole. **(c)** US image shows a large, irregular, spiculated mass with posterior shadowing. **(d)** Sagittal postcontrast maximum-intensity-projection MR image shows a spiculated, heterogeneously enhancing mass with several smaller adjacent ill-defined enhancing masses (arrowheads) extending to the nipple. Note the retraction of the skin and nipple with asymmetric enhancement of the nipple (arrow). Pathologic analysis revealed a large ILC extending to the nipple, with tumor involvement in the deep dermis.

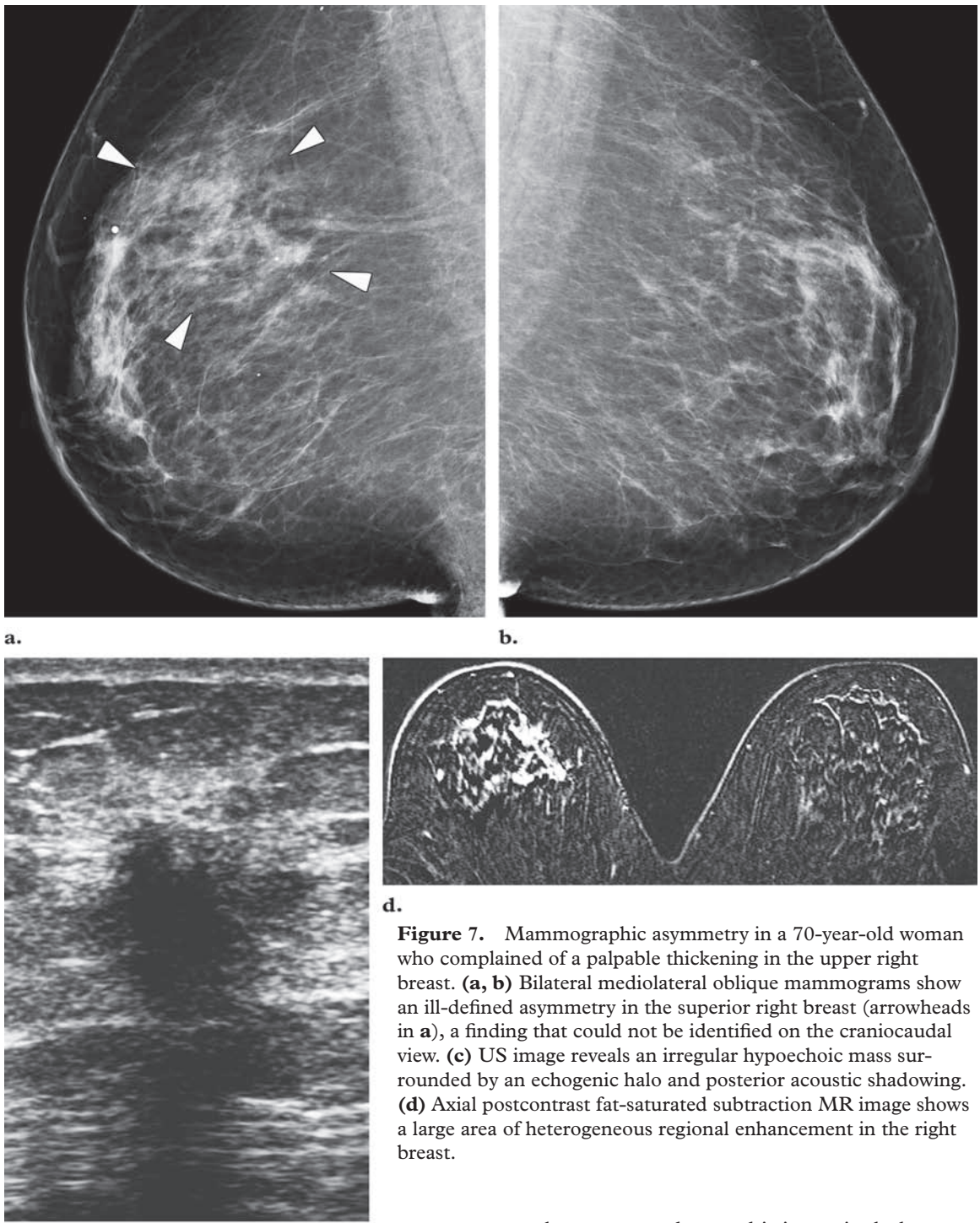


Figure 7. Mammographic asymmetry in a 70-year-old woman who complained of a palpable thickening in the upper right breast. **(a, b)** Bilateral mediolateral oblique mammograms show an ill-defined asymmetry in the superior right breast (arrowheads in **a**), a finding that could not be identified on the craniocaudal view. **(c)** US image reveals an irregular hypoechoic mass surrounded by an echogenic halo and posterior acoustic shadowing. **(d)** Axial postcontrast fat-saturated subtraction MR image shows a large area of heterogeneous regional enhancement in the right breast.

data may reflect the histologic tendency for ILC to spread diffusely through the breast stroma. As noted earlier, ILC lesions often exhibit an opacity equal to or less than that of the surrounding breast parenchyma; this is particularly true of spiculated masses (Figs 1a, 5e) (1,19).

Architectural distortion is the second most common manifestation of ILC at mammography and is seen in 10%–34% of cases (Figs 2a, 6). Asymmetries are seen in 1%–14% of cases (Figs 7, 8) (1–3,15,17–19).

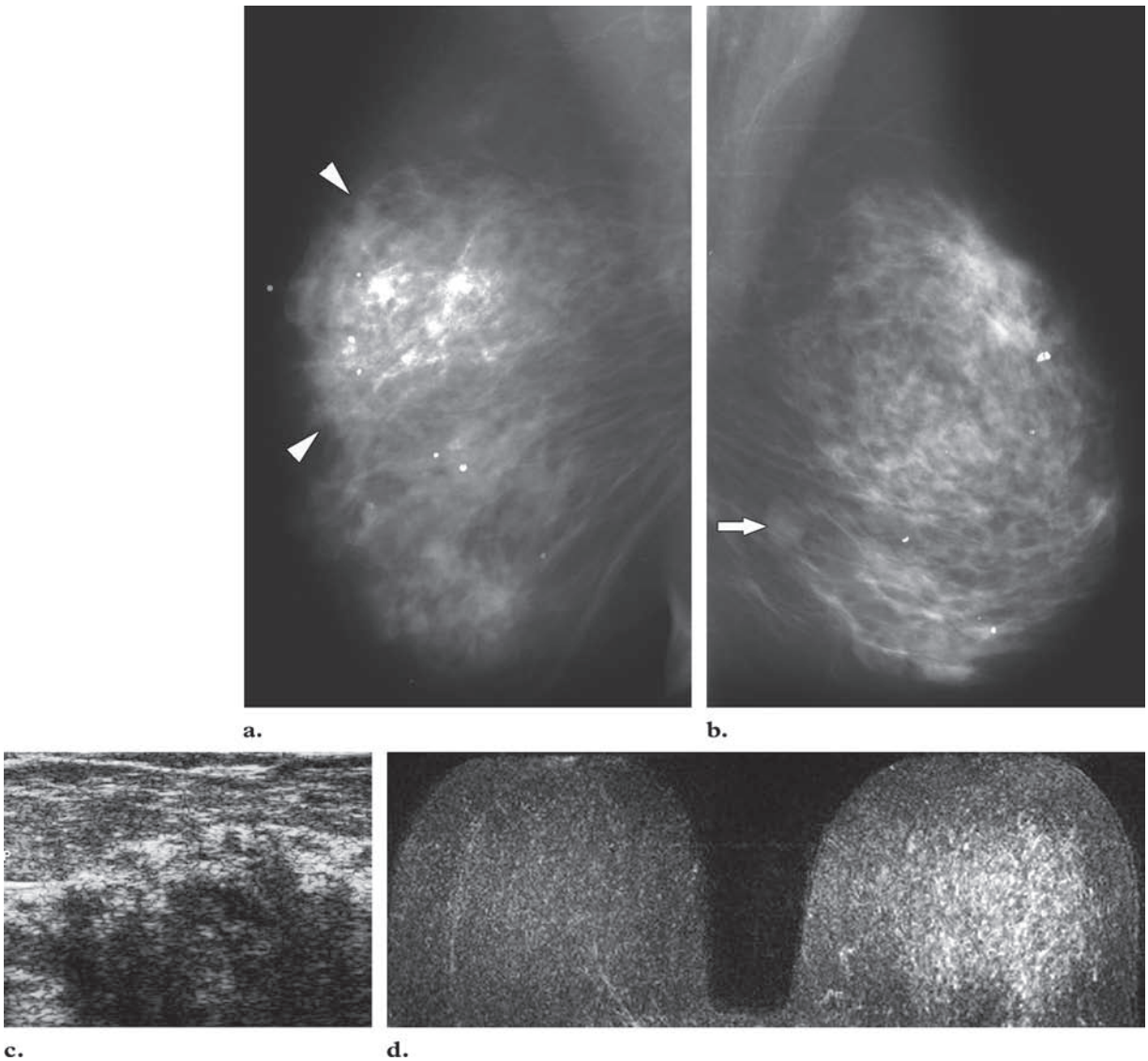
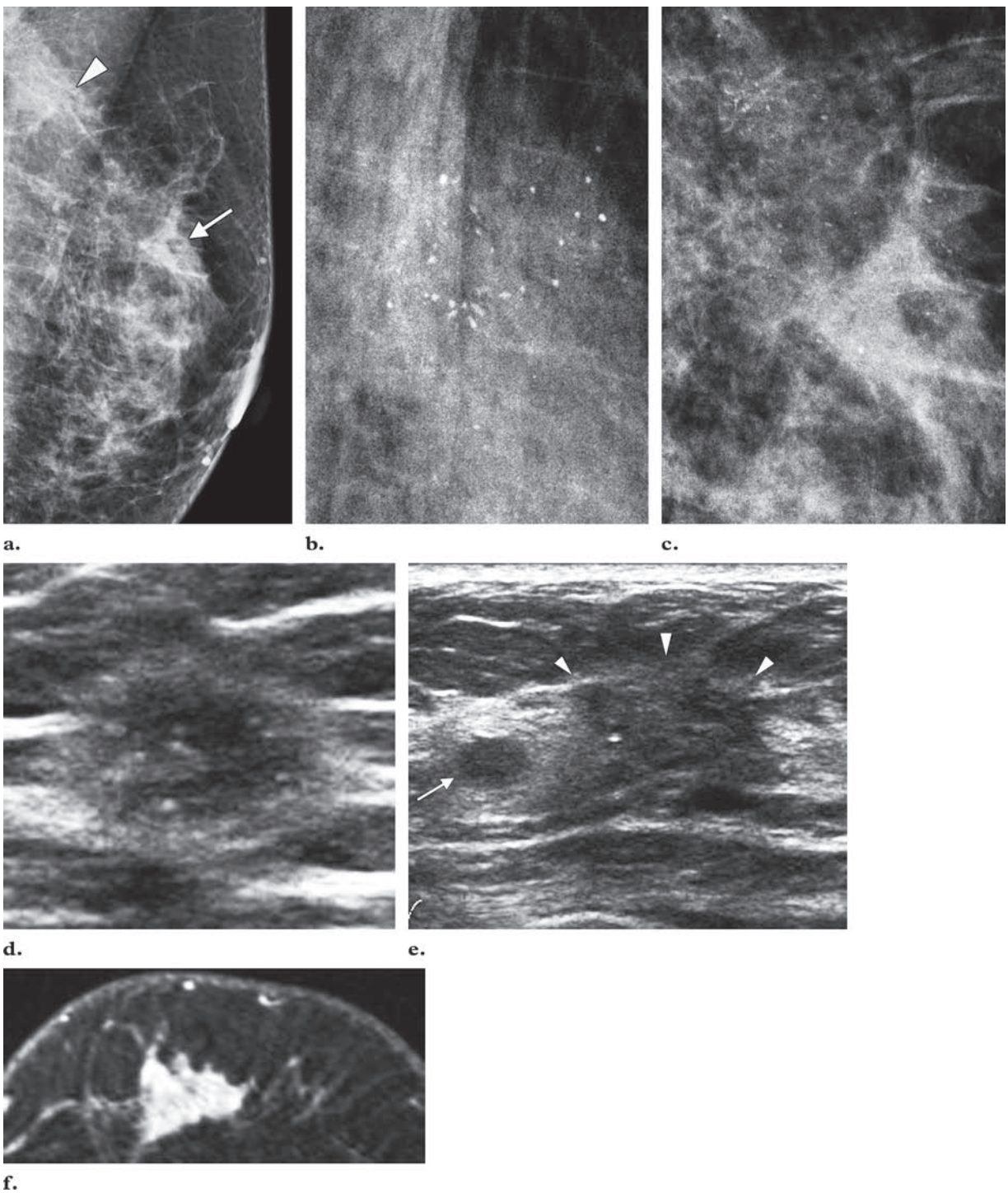


Figure 8. Subtle mammographic asymmetry in a 64-year-old woman who presented with right nipple retraction and a palpable lump in the superior right breast. **(a, b)** Right **(a)** and left **(b)** mediolateral oblique mammograms show heterogeneously dense breasts with a 5-cm area of subtle asymmetry and architectural distortion in the superior right breast (arrowheads in **a**). A new circumscribed lobular mass in the posterior left lower inner quadrant (arrow in **b**) proved to be a simple cyst at subsequent US. **(c)** US image shows a 6-cm region of ill-defined shadowing in the right breast extending from the ten thirty to the one thirty o'clock position, without a discrete mass. **(d)** Axial postcontrast maximum-intensity-projection MR image shows no significant enhancement within the right breast. Nonspecific enhancement is identified throughout the left breast. No morphologically suspicious findings were identified with the remaining MR imaging sequences, although nonspecific stranding was noted in the periareolar region. These atypical MR imaging findings could be related to neoadjuvant chemotherapy, which the patient had undergone subsequent to mammography and US but prior to MR imaging.

The reported prevalence of cases of ILC manifesting with microcalcifications (Figs 9, 10) varies widely, ranging from 0% to 24% (1–3,15,17–19). It is clear that microcalcifications are far less frequently associated with ILC than with the usual type invasive ductal carcinoma. However, older reported numbers for ILC patients presenting with calcifications may be underestimated in today's era of digital mammography and computer-aided detection.

Teaching Point

Figure 9. Microcalcifications in a 56-year-old woman who presented with two palpable masses in the left breast. **(a)** Mediolateral oblique mammogram shows two irregular masses with spiculated and indistinct margins and associated pleomorphic microcalcifications in the left breast, one at the eleven o'clock position posterosuperiorly against the pectoralis muscle (arrowhead), and the other at the ten–eleven o'clock position at a medium depth (arrow). **(b, c)** Magnified mediolateral mammographic images more clearly depict the posterosuperior **(b)** and medium-depth **(c)** lesions. **(d)** US image shows a hypoechoic mass with spiculated margins and an echogenic halo at the eleven o'clock position, findings that correspond to the posterosuperior lesion seen at mammography (cf **a** and **b**). Associated microcalcifications are seen within the mass. **(e)** US image shows a hypoechoic mass (arrowheads) with spiculated margins, posterior acoustic shadowing, and a lateral nodular extension at the ten o'clock position (arrow). The mass corresponds to the medium-depth lesion (cf **a** and **c**). Associated microcalcifications are seen within this mass as well. **(f)** Axial postcontrast fat-saturated subtraction MR image shows an irregular spiculated mass with heterogeneous enhancement, which extended from the left upper inner quadrant to the left lower outer quadrant. Histopathologic evaluation of a lumpectomy specimen revealed ILC that spanned more than 9 cm, as well as ductal carcinoma in situ. Microcalcifications were found in association with ductal carcinoma in situ and benign ducts.



Normal or benign mammographic findings are more frequently reported with ILC (8%–16% of cases) than with other invasive breast cancers (Fig 11) (1,3,18,19).

In a retrospective review of 405 patients with invasive breast carcinoma who were seen from January 1, 2003, through August 31, 2007, at two women's imaging centers affiliated with the authors' institution, a total of 49 patients (12%) were found to have biopsy-proved ILC (mixed or pure). Among these 49 patients, the following mammographic manifestations of ILC were noted: masses (43% of cases [*n* = 21]), architectural distortions (20% [*n* = 10]), asymmetries (18% [*n* = 9]), calcifications (16% [*n* = 8]), and normal or benign findings (10% [*n* = 5]).

Ultrasonography

US is a valuable adjunct to mammography, with reported sensitivities for the detection of ILC ranging from 68% to 98% (14,16,18). US is superior to mammography in identifying multicentricity and multifocality (Fig 9) and more accurately reflects the size of a mass than does mammography or clinical examination (18). US also plays a valuable role in biopsy and localization procedures, especially when ILC lesions are identified on only one mammographic view.

Teaching Point

The most common US manifestation of ILC is an irregular or angular mass with hypoechoic and heterogeneous internal echoes, ill-defined or spiculated margins, and posterior acoustic shadowing, findings that are seen in 54%–61% of cases (Figs 1, 4–7, 9, 11) (14,16,18). Additional manifestations include circumscribed masses, focal shadowing without a discrete mass (Fig 8c), and sonographically invisible lesions (Fig 10). Although the US appearances of various subtypes of ILC overlap considerably, classic ILC tends to manifest as focal shadowing without a discrete mass, whereas pleomorphic type ILC is more typically seen as a shadowing mass. Signet ring, alveolar, and solid subtypes of ILC are more likely to manifest as a lobulated, well-circumscribed mass (14).

Breast MR Imaging

In recent years, MR imaging has proved to be a useful adjunct to mammography and US in the detection and management of ILC, with a reported sensitivity of approximately 95% (20,21). MR imaging has been shown to be superior to mammography and US in detecting multifocality and multicentricity, as well as in estimating tumor size, which tends to be underestimated with conventional imaging (20–24). A meta-analysis by Mann et al (21) found that MR imaging was able to help detect additional ipsilateral malignant findings not evident at mammography or US in 32% of ILC patients. In addition, unexpected cancer in the contralateral breast was seen exclusively at MR imaging in 7% of cases (21). Most important, MR imaging has been shown to affect clinical management in 50% of patients with ILC, leading to changes in surgical management in 28% of cases (21,25). MR imaging may also provide valuable information (eg, the presence of residual tumor or of extensive or multifocal disease) in women who have already undergone excisional biopsy (25).

Teaching Point

Although breast MR imaging should not be used as a first-line screening tool for the general population, the 2007 American Cancer Society guidelines recommend screening breast MR imaging for women with a lifetime risk of breast cancer of approximately 20%–25% or greater, including women with a strong family history of breast or ovarian cancer and women who have been treated for Hodgkin disease (26). Because of insufficient data, no recommendation was made regarding high-risk women with a personal history of breast cancer, carcinoma in situ, atypical hyperplasia, or extremely dense breasts at mammography (26). At present, MR imag-

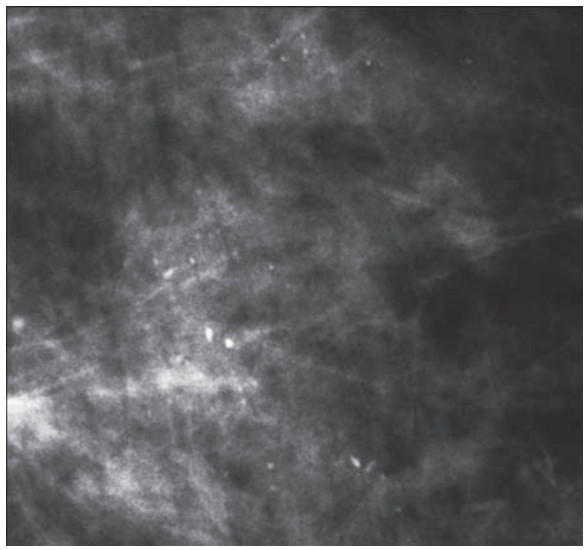


Figure 10. Microcalcifications in a 72-year-old woman who was referred for screening mammography. Magnified mammographic image shows clustered pleomorphic calcifications. No sonographic abnormalities were detected at real-time US. Histopathologic evaluation of an excisional biopsy specimen revealed classic ILC and pleomorphic type lobular carcinoma in situ with signet ring cell features. Microcalcifications were present in association with lobular carcinoma in situ and benign ducts.

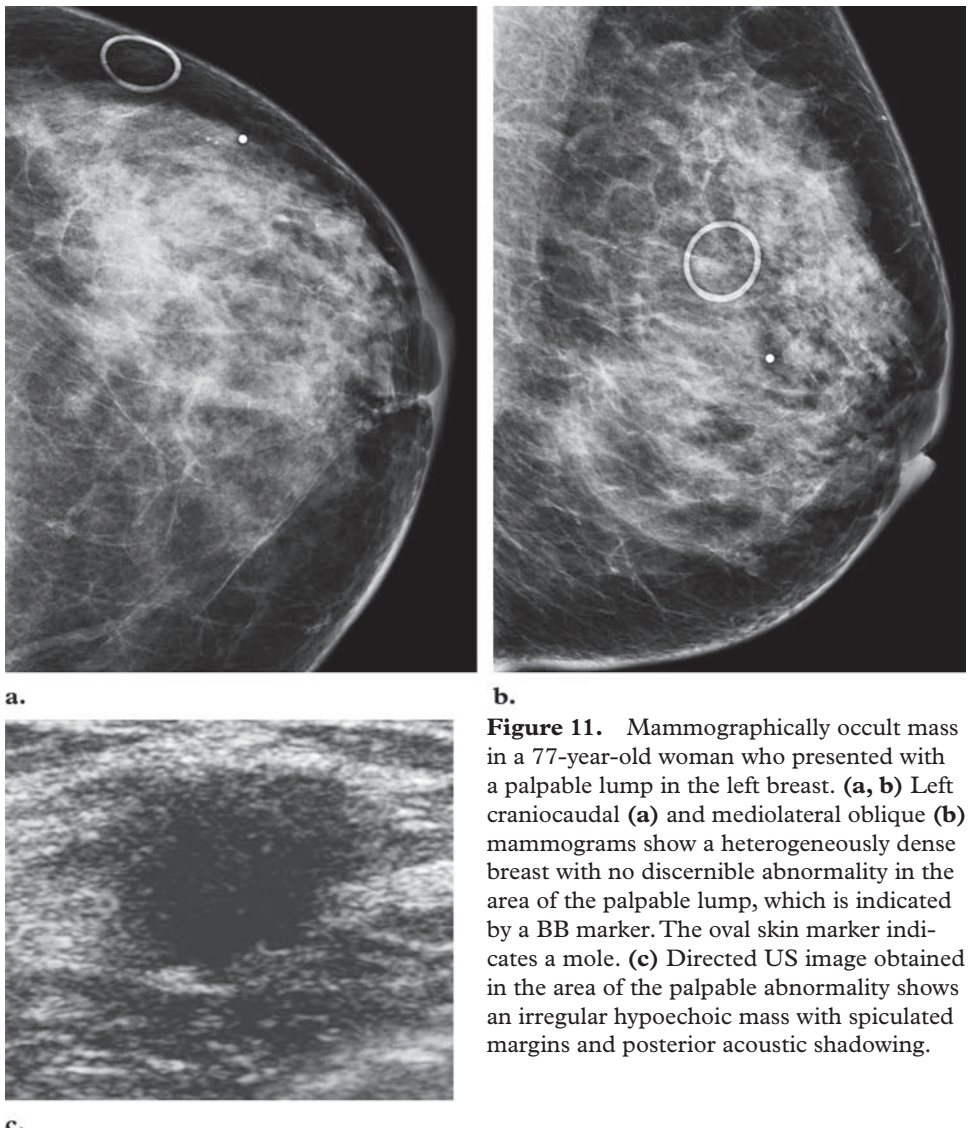


Figure 11. Mammographically occult mass in a 77-year-old woman who presented with a palpable lump in the left breast. **(a, b)** Left craniocaudal **(a)** and mediolateral oblique **(b)** mammograms show a heterogeneously dense breast with no discernible abnormality in the area of the palpable lump, which is indicated by a BB marker. The oval skin marker indicates a mole. **(c)** Directed US image obtained in the area of the palpable abnormality shows an irregular hypoechoic mass with spiculated margins and posterior acoustic shadowing.

ing is not widely used due to its cost and limited availability.

At MR imaging, the most common manifestation of ILC is a solitary irregular or angular mass with spiculated or ill-defined margins (31%–43% of cases) (Figs 4d, 9f) (21,22,25,27). Additional manifestations include a dominant lesion surrounded by multiple small enhancing foci (Fig 6d), multiple small enhancing foci with interconnecting enhancing strands, architectural distortions, regional or focal heterogeneous enhancement (Fig 7d), enhancing septa, and normal findings (22,25,27). Interestingly, histopathologic findings suggest that the enhancing strands and septa correlate with tumor cells streaming within the breast stroma (27).

Limited data on the findings of ILC at dynamic contrast-enhanced breast MR imaging suggest that, unlike most invasive breast carcinomas, which demonstrate a classic pattern of rapid enhancement and washout, ILC has a tendency to demonstrate delayed maximum enhancement, with washout exhibited by only a minority of lesions (21).

Conclusions

The sometimes clinically and mammographically elusive nature of ILC makes the diagnosis and management of this neoplasm uniquely challenging compared with that of other invasive breast cancers. As illustrated in this article, ILC can have a variety of imaging appearances and can even be mammographically occult, especially in dense breasts. Despite these challenges, however, imaging remains a fundamental tool in the detection and management of ILC. Despite its cost and limited availability, breast MR imaging will likely play an expanding role in the management of ILC, having been shown to be superior to mammography and US in detecting multifocality and multicentricity and in evaluating tumor extent in this disease entity.

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Higher false-negative rates (up to 19%) are reported for ILC than for other invasive cancers at mammography because ILC is often difficult to diagnose mammographically (2,9).

Pages 168, 171
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Page 172
It is clear that microcalcifications are far less frequently associated with ILC than with the usual type invasive ductal carcinoma.

Page 174
The most common US manifestation of ILC is an irregular or angular mass with hypoechoic and heterogeneous internal echoes, ill-defined or spiculated margins, and posterior acoustic shadowing, findings that are seen in 54%-61% of cases (Figs 1, 4-7, 9, 11) (14,16,18).

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Most important, MR imaging has been shown to affect clinical management in 50% of patients with ILC, leading to changes in surgical management in 28% of cases (21,25).