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Case report

# Non-enhancing malignant lesions of the breast: A case report and review of literature

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ABSTRACT

Due to the elusive nature of invasive lobular carcinoma, mammography, ultrasound, and magnetic resonance imaging have their limitations in early detection.

A 67-year-old woman presented for mammography and found retraction of breast parenchyma of the right breast. Magnetic resonance imaging and contrast mammography showed no contrast uptake in the region in question.

Magnetic resonance imaging and ultrasound were found to be superior for the detection of invasive lobular carcinoma, with a sensitivity of more than 90%. On ultrasound examination, invasive lobular carcinoma may occur only with posterior acoustic shadowing. On breast magnetic resonance imaging, it is commonly described as an irregular mass and less commonly as non-mass enhancement. An additional advantage of magnetic resonance imaging is the higher detection rate of multifocal, multicentric, and contralateral breast lesions.

The reason for no contrast enhancement in this particular tumor before neoadjuvant chemotherapy followed by enhancement after neoadjuvant chemotherapy is most likely at the molecular and histologic level and requires further investigation in similar cases.

## 1. Introduction

Invasive lobular carcinoma (ILC) is the second most common subtype of invasive breast carcinoma and accounts for 5%–15% of all invasive breast malignancies. It is characterized by little or no desmoplastic response and is therefore difficult to detect clinically and mammographically [1,2]. ILC is a heterogeneous group of tumors and only a few variants have been described, most of which are related to loss of cellular cohesion due to E-cadherin dysfunction, which allows anoikis resistance with self-preservation. In addition, loss of E-cadherin triggers the process of epithelial to mesenchymal transition (EMT), making cells more migratory and invasive. Loss of E-cadherin is evident in the early stages of tumorigenesis and EMT in the later stages associated with invasion and spread. Histologically, classic ILC infiltrates the stroma between collagen bundles that coalesce into 'Indian files' and shows cells with small nuclei and low mitotic activity. Molecular characterization includes expression of ER and PgR and shows no HER2 overexpression [3].

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Although mammography is the gold standard for the detection of breast cancer, with an overall sensitivity of 85% (68% in denser breasts), the sensitivity for the diagnosis of ILC is reduced to 57%–81% (11% in denser breasts) [1,4,5]. The most common mammographic features of ILC include asymmetry, architectural distortion, or a mass that is isodense or of lower density than the surrounding breast parenchyma. Calcifications are rarely seen in ILC [4]. Because of the insensitivity of mammography, other imaging modalities such as ultrasound (US), magnetic resonance imaging (MRI), and contrast enhanced digital mammography (CEM) are essential. Dynamic contrast-enhanced breast MRI and ultrasonography have been shown to be superior imaging modalities for detecting ILC, with a sensitivity of more than 90% (93% and 98%, respectively) [1,5,6]. Ultrasonography of ILC shows a hypoechoic mass with or without posterior acoustic shadowing, or posterior acoustic shadowing may be the only entity present. On MRI of the breast, it is usually described as an irregular mass and less commonly as a non-mass enhancement. An additional value of MRI is a higher detection rate of multifocal, multicentric, and contralateral breast lesions [1,7].

## 2. Case report

A 67-year-old woman with a negative family history and known breast size asymmetry was bunt in the right breast. A digital synthetic mammogram with tomosynthesis (Hologic Selenia Dimensions Hologic, Bedford, Massachusetts) was performed, which revealed retraction of breast parenchyma of the right breast due to an infiltrative mass in the upper outer quadrant consuming the

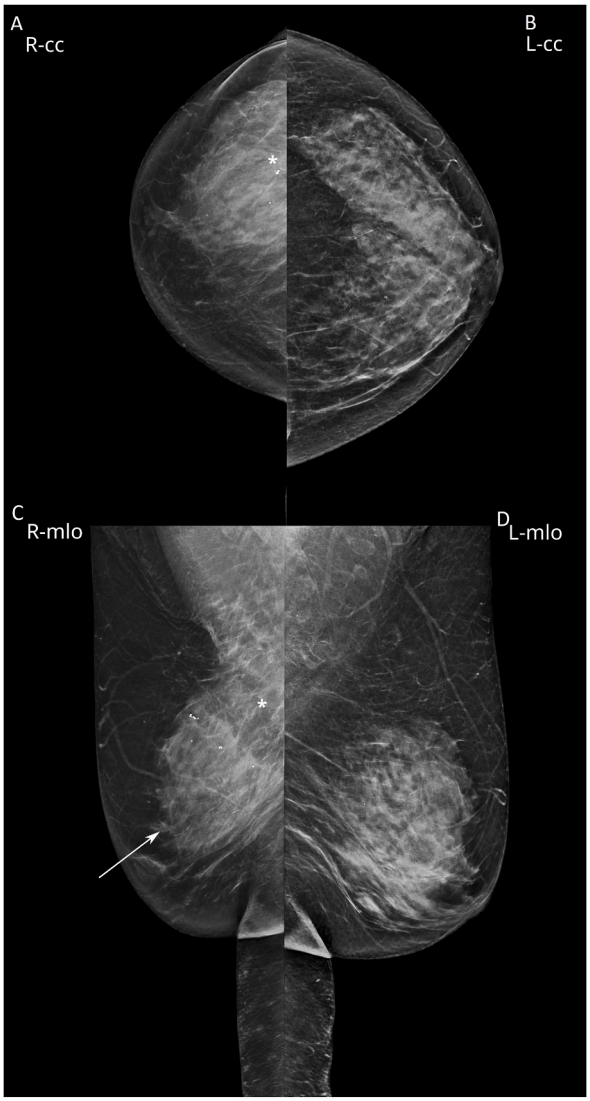


**Fig. 1.** Mammogram of the right breast shows a well-demarcated, uniformly hyperdense mass in the upper outer quadrant of the right breast (asterisk), located approximately between 9 and 12 o'clock (arrow). Upper row: craniocaudal views of the right (R-cc) (A) and left (L-cc) (B) breasts. Bottom row: mediolateral oblique views of the right (R-mlo) (C) and left (L-mlo) (D) breasts.

central portion of the breast, with nipple retraction as shown in Fig. 1. Breast ultrasound (LOGIQ S8, GE Healthcare) revealed a broad zone of poorly defined hypoechoic area with acoustic shadowing of approximately 50 mm in the right outer quadrant of the breast with normal lymph nodes in the ipsilateral axilla (Fig. 2). A core needle biopsy (CNB) was performed. Histopathologic findings revealed ILC, subtype luminal B (oestrogen receptors, ER, 75%; progesterone receptors, PgR, 1%; human epidermal growth factor receptor 2, Her-2 negative; and Ki-67 index 0.5%). Immunohistochemically, neoplastic cells lacked E-cadherin expression, nuclear grade 2 (Fig. 3a–l). MRI was indicated for further imaging diagnosis and clinical decision (MAGNETOM Aera, 1.5T, Siemens Healtheneers). The MRI scan was performed with the patient in the prone position and using a dedicated double breast coil. An intravenous injection system was inserted into a cubital vein before imaging. The MRI protocol consisted of T2-weighted images, diffusion-weighted (DWI b-value 50 and 800) and T1-weighted pre-contrast and dynamic post-contrast images after intravenous contrast administration of gadoterate meglumine (Dotarem®, Guerbet, Roissy CdG, France) at a dose of 0.2 ml/kg and a rate of 2 ml/s, followed by a 20-ml saline flush at a rate of 2 ml/s. Subtractions of precontrast and postcontrast images were also performed. The reformatted maximum intensity projection images were then created from the subtraction images. MRI findings showed a retraction of breast parenchyma of the right breast with no mass formation and no obvious contrast uptake in the region of interest, as shown in Fig. 4A–F. However, on the T2-weighted sequences, there was a pronounced architectural distortion due to a poorly defined hypo-intense mass in the outer quadrant. The DWI sequence and apparent diffusion coefficient (ADC) map showed that the mass was large and extended from areolar region with nipple retraction to the pre-pectoral region. The decision to perform CEM was made by the multidisciplinary team after a negative MRI. Since CEM had just been introduced in our hospital at the time of our patient's examination, the decision to perform CEM was made for the sake of research. Contrast agent was injected intravenously (1.5 ml/kg of body weight at an injection rate of 3 ml/s, Xenetix® 300, Guerbet) before the patient was positioned. Image acquisition began 2 min after injection and lasted for 6 min.; craniocaudal (CC) and mediolateral oblique (MLO) images of the symptomatic and asymptomatic breast. Additional delayed images of the same projections of the symptomatic breast were taken after 8 min. There was no contrast uptake on the recombined images, as shown in Fig. 5. Significant distortion and a retraction of breast parenchyma were seen on both the low-energy and recombined images. The patient was recommended neoadjuvant chemotherapy (NAC) before surgery. Preoperative MRI at the end of NAC showed areas of non-mass enhancement that were interpreted as tumor remnants, shown in Fig. 6. After NAC, a right mastectomy with lymphadenectomy was performed. The tumor bed measured 8.3 cm × 8.3 cm and there was no tumoral heterogeneity. Four out of nine sentinel lymph nodes (two with macrometastases and two with micrometastases) and two out of three intramammary lymph nodes were positive for tumor infiltration. The area of the primary tumor bed, total cancer cellularity, percentage of in situ disease, number of positive nodes, and diameter of the largest nodal metastasis were assessed to calculate the RCB (residual cancer burden) score of 3.912, RCB class III (no response to NAC). Receptor status after NAC for ER and PgR was 80% and 5%, respectively. The Ki67 proliferation index measured after treatment was 10% and was negative for human epidermal growth receptor 2 (HER2-).

## 3. Discussion

Cases of nonenhancing ILC have been reported. Ghai et al. reported a 15 mm ILC based on US and mammography findings, but without any MRI correlation [8]. In the study by Wurdinger et al. (total of 424 patients), 27 malignant lesions were not detected on MRI, including five invasive carcinomas (four ILC) with a grading of G2 to G3 and tumor sizes ranging from 4 to 35 mm [9]. An important morphologic feature of ILC is diffuse infiltrative growth, which poses a major challenge for early diagnosis due to its similarity to normal fibro-glandular tissue [10]. According to the literature, contrast accumulation in MR is primarily due to angiogenesis and neovascularization of malignant tumors [11,12]. In addition to tumor size and location, histologic type may also influence contrast accumulation in MR [13]. DCIS with multifocal or diffuse growth that fills the excretory ducts without forming a tumor mass

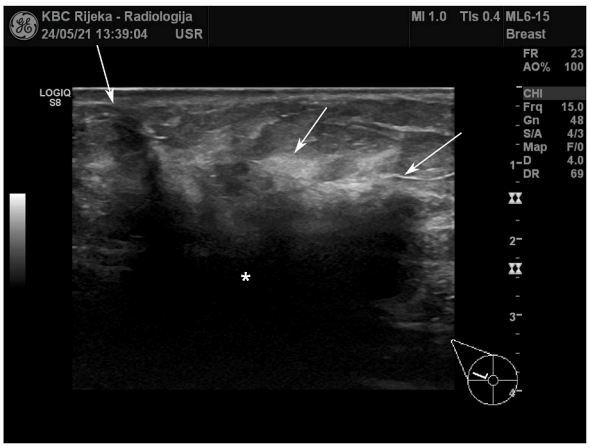


**Fig. 2.** Ultrasonography of the right breast shows a large, homogeneous, hypoechoic mass with multiple lobulations and spiculations and indistinct posterior margins (asterisks), measuring approximately 5 cm. Multiple protrusions into the overlying subcutaneous tissue are seen at the edges of the mass (arrows). The mass causes severe acoustic shadowing in the posterior region.

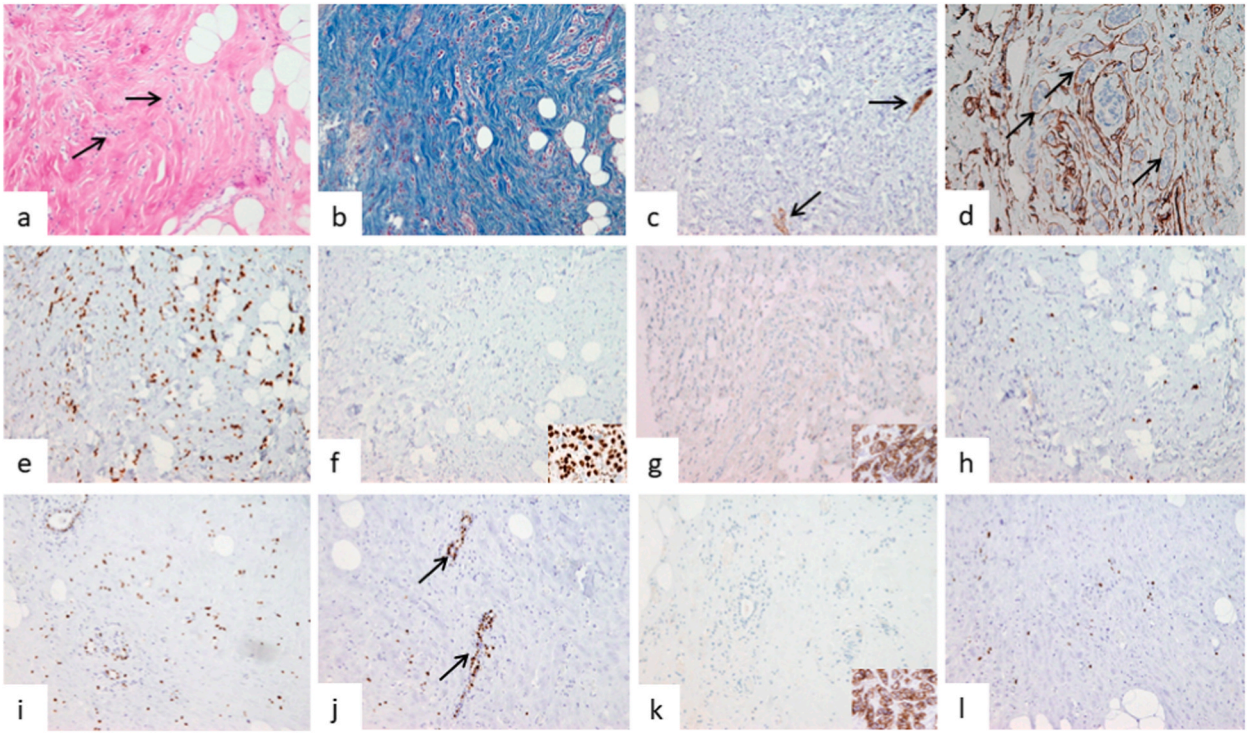


**Fig. 3.** Tumor tissue stained with hematoxylin and eosin from a core needle biopsy showing invasive lobular carcinoma with infiltrative diffuse growth with a single-celled file pattern (arrows) in the abundant collagenous connective stroma (a), stained with Masson trichrome histochemical stain (b). Immunohistochemical staining with anti-E-cadherin shows the absence of membranous immunoreactivity around the invasive neoplastic cells, whereas staining is preserved in the remaining involuted lobules (arrows) (c). Angioinvasion is shown by anti-CD34 staining (arrows) (d). Immunohistochemical staining of molecular surrogate markers before neoadjuvant therapy shows high (75%) expression of estrogen receptors in dispersed tumor cells (e), low (1%) expression of progesterone receptors (f) with the positive external control (insert), low (0.5%) proliferation index (g), and negative (0) HER2 receptor staining (h) with the positive external control (insert). Immunohistochemical staining of molecular surrogate markers after neoadjuvant therapy shows similar high (80%) expression of estrogen receptors (i), low (5%) expression of progesterone receptors (j) with positive internal control (arrows), negative (0) HER2 receptor staining (k) with positive external control (insert) and low (10%) proliferation index (l). (Magnification ×100).

and inflammatory breast carcinomas pathologically defined by an angioinvasive appearance with obstruction of skin vessels are both described with weaker contrast enhancement on MR [14,15].

Lobular invasive carcinoma is also characterized by poorly circumscribed margins and diffuse infiltrative growth with scattered cellular infiltration, which may be accompanied by a specific type of vascularization [7,15]. Infiltration by single cell clusters that have lost the cell adhesion molecule E-cadherin around preserved anatomic structures and a weak desmoplastic response are described as the main reasons for the poor radiologic appearance [16]. Loss of E-cadherin protein in ILC cancer cells is caused by alterations in the CDH1 gene on chromosome 16q22.1 and is found in 90% of these tumors [12,17]. Some authors have associated slower enhancement in lobular carcinomas to lower levels of vascular endothelial growth factor, leading to more mature and thus less leaky capillaries, which in turn leads to reduced or absent contrast enhancement in these tumors [5,7]. The authors noted that the slower growth of lobular carcinoma may be the reason for the less pronounced need for neovascularization, which in turn may be the result of difficult tumor visualization [7].

Various observations related to molecular immunophenotype and radiological features are described in the literature. While some authors have noted a difference between PgR expression and lesion appearance at MR, with PgR negative tumors occurring more frequently with larger lesions and without mass enhancement, other authors have found no association between molecular phenotype and MR appearance [13,18]. Some cancers, including DCIS, some invasive lobular carcinomas, and some other low-grade invasive tumors, may not show enhancement on MRI. Therefore, the radiologist should be extremely cautious when performing an MRI instead of a biopsy to clarify suspicious mammography or US findings, as false-negative cancers may occur.

In the case report by Jafri et al., ILC presented as a marked decrease in breast tissue volume compared with patients' previous mammograms and showed retraction of the breast parenchyma on screening mammography with findings on ultrasound and diffuse enhancement on breast MRI [1]. They referred to these findings as "shrinking" breast corresponding to diffuse tumor infiltration. Retraction of the breast parenchyma is a specific mammographic sign that is more pronounced in our case compared with previous studies. We had no previous images for comparison and assessment of progression or stability was impossible. At the beginning of the diagnostic examination, we were not aware of any information about previous (congenital) breast asymmetry in the patient, but even

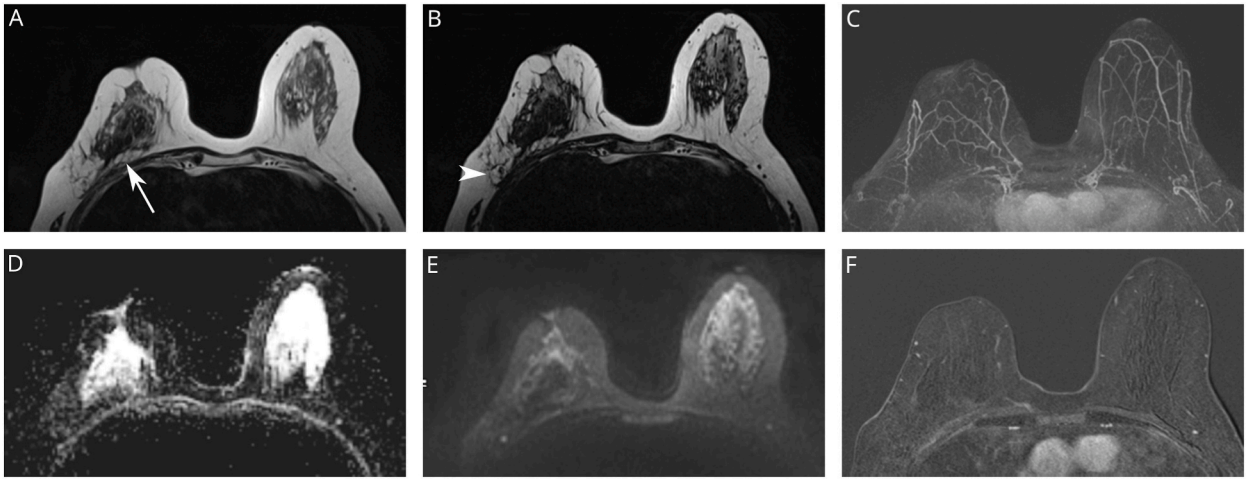


**Fig. 4.** (A) T2-weighted sequences show asymmetric density and infiltration of the prepectoral fat pad (arrow). (B) T2-weighted sequences show marked architectural distortion due to a poorly defined hypo-intense mass (arrowhead) in the outer quadrant, which also causes nipple retraction. (C) On maximum intensity projection, asymmetry of breast size with a shrunken right breast is the main MRI sign of lobular carcinoma. No pathologic post-contrast enhancement is noted. (D) Diffusion-weighted image of *b-800* and (E) Apparent diffusion coefficient show that the mass is large and extends from the retro-areolar region to the pre-pectoral region, with infiltration along the areolar region and nipple. (F) Axial subtracted T1-weighted dynamic contrast-enhanced images show no contrast enhancement.

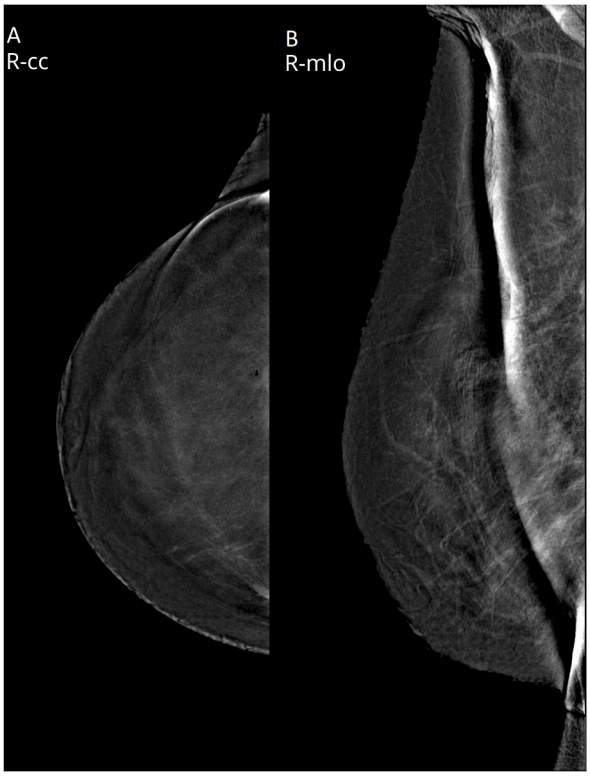


**Fig. 5.** Contrast enhanced digital mammography of the right breast. Craniocaudal (R-cc) (A) and mediolateral oblique views (R-mlo) (B) show no contrast enhancement on recombined images.

without this information, we were confident about the finding of retraction of breast parenchyma with associated signs of architectural change in breast structure and nipple retraction.

The retraction of the breast parenchyma was also the only positive MRI sign of an infiltrating lesion. Discrepancies between imaging findings have been reported in other studies. While Selinko et al. reported higher US sensitivity in detecting ILC, they also

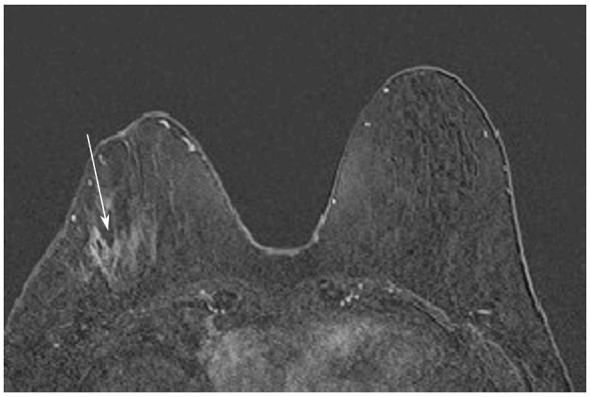

**Fig. 6.** Axial subtraction image of bilateral breast MRI acquired at the end of neoadjuvant chemotherapy shows non-mass enhancement in the same region as in Fig. 4, indicating residual disease (arrow).

reported a 28% increase in detecting smaller lesions on mammography (1 cm), especially when they appeared as spiculated masses [6]. In the case report by Vlastarakos, the tumor measured 23 mm on breast MRI but was not detected on mammography [19]. There are few studies addressing non-enhancing ILC on MRI, which are summarized in Table 1 [8,9,20–22].

In our case, there were also discrepancies between imaging modalities. Although US breast examination has the highest sensitivity for detecting ILC, we had more relevant findings on mammography, including signs of retraction of the parenchyma of the breast, mass formation, and nipple retraction with enhancement in the BI-RADS report.

The sensitivity of physical examination for ILC ranges between 65 and 98%, with usually over 50% of patients presenting with palpable abnormalities [23]. Up to 50% of ILC have opacity less than or equal to that of normal breast tissue on mammography [24]. Measuring the extent of ILC can be difficult because conventional screening methods have low sensitivity for detecting ILC compared with other invasive breast tumors.

Regarding the size of the tumor in our case, it is possible that it was radiologically underestimated, considering the diffuse growth of single-cell files in the dense collagenized stroma, but it is also possible that the tumor did not respond well to neoadjuvant chemotherapy because of the low value of the proliferation index and other molecular features. Increased stromal collagenization corresponds to a hypo-intense appearance on MRI before NAC. There is a hypothetical possibility that the dense, hypocellular, collagenized connective tissue and angioinvasion shown in Fig. 3 show slow contrast flow and contribute to the lack of enhancement before NAC. Increased angiogenesis after neoadjuvant therapy has been described in more than 30% of cases and may explain the mild contrast enhancement in our case after NAC [25].

MRI has been reported to have higher sensitivity in detecting and characterising ILC than the “gold standard” mammography. Breast lesions that show abnormal features on mammography or sonography should be considered suspicious for malignancy, even if there is no evidence of malignancy on MRI. Because DBT significantly improves the accuracy of mammographic interpretation of ILC, it should be recommended for follow-up of unusual initial findings of ILC along with US, MRI, or CEM [26]. US and elastography may be useful to assess breast tenderness, a feature that cannot be detected by mammography or MRI. In our case, the effect of NAC was monitored with US and MRI after a 4 cycle of anthracycline and tamoxifen therapy. After completion of NAC (12 weeks of paclitaxel) and before surgery, DBT and MRI were repeated to assess residual disease, and ultrasound was performed for axillary restaging.

**Table 1**
Studies involving non-enhancing ILC on MRI.

| First author name, year, journal | Study name | Findings | Suspected reasons of non-enhancement |
|---|---|---|---|
| Boetes et al. (2004), Breast Cancer Res Treat | False-negative MR imaging of malignant breast tumors. | ILC measuring 40 mm, non-enhancement on MRI, occult on sonography, detected only on mammography | Histologic growth pattern; tumor cells were diffusely spread through thin fibrous threads between normal fatty areas. |
| Weinstein et al. (2001), AJR | MR imaging of the breast in patients with invasive lobular carcinoma. | Failed MRI detection of residual tumor or underestimated tumor extent in four of 32 cases. | Not clear. |
| Wurdinger et al. (2001), Breast | False-negative findings of malignant breast lesions on preoperative magnetic resonance mammography. | Four lobular carcinomas detected on US not detected on preoperative MRI. | Slow contrast enhancement. |
| Ghai et al. (2005), AJR | Nonenhancing Breast Malignancies on MRI: Sonographic and Pathologic Correlation. | Two non-enhancing ILC on MRI. | Selected MRI protocol, physiologic basis, pattern of cellular growth. |
| Song et al. (2022), Diagnostics | The Frequency and Causes of Not-Detected Breast Malignancy in Dynamic Contrast-Enhanced MRI. | Three ILC measuring 55 mm, 12 mm and 20 mm, all visible on mammography, US but not on DCE MRI. | Unique growth pattern, less dependance in neovascularization. |

At our institution, the MRI protocol is tailored to the latest guidelines for lesions with delayed enhancement [27]. However, false-negative results occur even with multiparametric and state-of-the-art diagnostic procedures. The causes of false-negative results can be divided into technical and reading difficulties and lesion characteristics. Technical and examiner difficulties include: late or non-existent application of contrast agent, removal of pre-existing signal from T1 pre-contrast images, poor positioning of the patient, motion artefacts, and an undersized field resulting in a para-coil lesion, hidden small lesion or pseudo-enhancement, dense breast tissue, and moderate to marked extent of normal background parenchymal enhancement, as well as the investigator's perception to distinguish false-positive and false-negative findings on breast MRI [28]. Tumor features include the following: small tumors up to 3 mm in size without angiogenesis, tumor location near normal enhancement tissue (nipple and vessels), prior biopsies with hematoma formation and placement of metal clips that may lead to hidden tumors, and tumor shrinkage with change in vascularity due to pro-angiogenic growth factors after chemotherapy [29].

Several studies have reported false-negative cases owing to non-enhancement of invasive cancers [9,30,31]. Dietzel et al. performed a systematic comparative study in 811 patients comparing IDC and ILC over a 12-year period. The dynamic and morphologic profiles of ILC and IDC overlapped, and only minor differences were found between the two subgroups [32]. Features of ILC described by Schelfout et al. on MRI are spiculated, irregular inhomogeneous mass or a dominant lesion surrounded by multiple small foci of enhancement; multiple small foci of enhancement with interconnected strands of enhancement. Architectural distortions were described in three cases; in one case, there was a focal area of inhomogeneous enhancement and normal MRI examination. They concluded that MRI can play an important role in the evaluation of patients with ILC, which is often difficult to diagnose on clinical examination and conventional imaging and is more likely to occur at multiple sites and in both breasts, adding that false-negative MR findings occur in a small percentage of ILC [33]. The systematic review by Alaref et al. found that the most typical morphologic feature in most invasive breast cancers is irregular margins in ILC and IDC, with ILC being slightly more likely to be positive for this feature than IDC. Overall, the morphologic profile of ILC was not significantly different from that of IDC [34].

In situ breast cancer usually presents as microcalcifications on mammography or non-mass enhancement on MRI [35]. Less commonly, it may also manifest as a mass on MR, in which case it is most likely irregular. The kinetics of DCIS are variable, with rapid uptake and a plateau curve described as the most common kinetic pattern [36]. This is consistent with the clinical observation that the accumulation kinetics of DCIS are different from those of invasive cancers and that a time course of the washout signal is rare in DCIS [37]. For pathophysiological reasons, breast MRI is more likely to detect high-grade DCIS because the vascular density (strong VEGF expression) than the low-grade DCIS [38] and high-grade DCIS is more likely to show up as an enhancing mass. DCIS may be invisible or hypointense on pre-contrast T1-weighted images and non-fat-saturated or fat-saturated T2-weighted images because it may be masked by normal breast parenchyma, although it may sometimes appear bright on T2-weighted images due to ductal secretions or necrosis [39]. DCIS may also remain hidden on MRI images, especially if there is a large enhancement of background tissue [40]. In addition, DCIS lesions that do not show enhancement on MR images may be lesions that are not preparing invasive growth because their basement membrane is intact and they are not actively recruiting periductal blood vessels [41].

## 4. Conclusion

MRI is the most sensitive imaging modality for breast cancer detection, but some invasive carcinomas, particularly small invasive carcinomas and diffuse infiltrating carcinomas, may not show washout kinetics on MRI, resulting in false-negative cases. DCIS and inflammatory breast carcinomas may also show poor contrast accumulation on MRI. Clear clinical information, medical history, and risk factors should be considered, and use of all available previous studies for comparison and viewing images at all planes and sequences to better assess abnormalities are essential for appropriate MRI interpretation and avoidance of errors. Because no single imaging feature alone can confirm a benign cause, radiologists should carefully consider all features when characterizing lesions.

## Statement of ethics

This case report complies with the guidelines for human studies and includes evidence that the research was conducted ethically in accordance with the Declaration of Helsinki of the World Medical Association was conducted. The patient has given written consent for publication of her case (including publication of images). Information revealing the patient's identity will be avoided, and her real name will not be mentioned. Study Approval Statement: This study protocol was reviewed and approved by the Ethics Committee of the Clinical Hospital Centre Rijeka, N°2170-29-02/1-22-2Informed consent for publication: written consent was obtained from the patient (K.R., b. 1955) for publication of the details of her medical case and all accompanying images. The signed consent is available.

## Declarations

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Data included in article/supplementary material/referenced in article.

## Abbreviations

| | |
|---|---|
| ILC | invasive lobular carcinoma |
| NAC | neoadjuvant chemotherapy |
| EMT | epithelial to mesenchymal transition |
| CEM | contrast enhanced mammography |
| ADC | apparent diffusion coefficient |
| CC | craniocaudal |
| MLO | mediolateral oblique |
| DBT | tomosynthesis |
| RCB | residual cancer burden |

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