Ductal Carcinoma In Situ: Non-Mass Enhancement on MRI 10 Years Before Mammographic Microcalcifications

NANCY W. STEAD, MD, and ANDRIA P. CATON, RN, OCN[®], CHPN

From Northeast Georgia Medical Center, Gainesville, Georgia

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Correspondence to: Nancy W. Stead, MD, P.O. Box 35, Gainesville, GA 30503. E-mail: nancy.stead11@ gmail.com

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Abstract

In developed countries, the lifetime risk of developing breast cancer among women is 11%. Therefore, screening asymptomatic women for breast cancer is widely accepted as preventive health care. Mammography is the primary imaging modality for the detection of breast abnormalities. Digital breast imaging detects 90% of symptomatic or asymptomatic cancers. The sensitivity, specificity, and negative predictive values of this modality are each about 90%. As a standard of care, the Breast Imaging Reporting and Data System (BI-RADS) is used to quantify increasing degrees of positive predictive values in mammography. This can help clinicians identify abnormalities that may need additional imaging studies or biopsies. To reduce false-negative breast cancer screening results, efforts have focused on increasing the sensitivity of mammography or supplementing it with ultrasound or MRI. Advanced practitioners are strategically positioned to detect incongruities between imaging techniques and physical assessments. With increased knowledge, advanced practitioners are better prepared for shared decision-making discussions regarding follow-up imaging procedures. The case report in this article describes a 10-year discordance of imaging that proved to be high-grade ductal carcinoma in situ (DCIS) and offers a hypothesis of the physiology to explain this discordance. A better understanding of breast imaging will enable the advanced practitioner to recommend the most appropriate follow-up study for patients.

CASE STUDY

This case report describes a patient with dense breasts and a 35-year breast cancer course (Figure 1). Beginning in 1985, at the age of 41, a patient with long-standing reactive lymphoid hyperplasia, keratoconjunctivitis sicca, and Raynaud disease presented for a routine, baseline mammogram. The mammogram revealed branching microcalcifications in the left breast. Subsequently, a biopsy identified low-grade ductal carcinoma in situ (DCIS).

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Figure 1. Case study timeline. DCIS = ductal carcinoma in situ; UOQ = upper outer quadrant; ABUS = automated breast ultrasound.

Initial Treatment and Staging

The patient's first surgical intervention was a 4-cm full-thickness resection including the underlying pectoralis fascia. At that time, the breast cancer was staged as DCIS TONOMO. A 2.5-cm contralateral (right) axillary node showed reactive hyperplasia.

Ductal carcinoma in situ is the proliferation of morphologically atypical cells located within the basement membrane of the breast ducts. Risk factors for the development of DCIS are similar to those for invasive breast cancers (Bane, 2013). In clinical practice, microcalcifications are the typical presentation of DCIS (Kunitake et al., 2023).

Recurrence

Annual mammography and clinical examinations were read as normal until 2007, when, at age 63, a smooth, soft, mobile nodule at the 6 o'clock location on the left breast was self-identified by the patient. The mammography remained



Figure 2. 2017 right breast MRI upper outer quadrant.



Figure 3. 2019 mammogram with microcalcifications.

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normal. After undergoing the second resection, a T1bNOMx lobular carcinoma that was estrogen receptor (ER) > 95%, progesterone receptor (PR) > 95%, and Ki-67 60% was discovered. Additionally, a sentinel node (left axilla) showed reactive hyperplasia without metastatic carcinoma. Post-operative bilateral breast MRIs did not demonstrate residual malignancy.

After the resection of left breast lobular carcinoma, the patient received adjuvant whole breast radiation, chemotherapy, and tamoxifen. Follow-up care included annual clinical examinations and mammograms to which adjunctive MRI screening was added. For 10 years, both breasts and axilla were reported as normal, although bilateral reactive hyperplasia was described in the MRI reports intermittently.

New Imaging Findings

In 2017, at the age of 73, the patient discovered a tender area in the upper outer quadrant (UOQ) of the right breast. MRI imaging demonstrated a new 2.9 cm × 5.9 cm non-mass enhancement (NME) in the right breast (Figure 2). The patient sought a second opinion, and a repeat MRI confirmed an NME and adenopathy in the right breast.

Based on Breast Imaging Reporting and Data System (BI-RADS), an NME signifies an area of contrast enhancement without a space-occupying correlation (Lunkiewicz et al., 2021). An NME is the most frequent morphologic feature of DCIS. Ultrasound typically does not correlate with the imaging finding (Lunkiewicz et al., 2021). Unfortunately, a review of the patient's breast MRI imaging from 2013 through 2017 identified an increasing number of foci of NME deep in the UOQ of the right breast that was previously unreported. A 6-month follow-up for this new right UOQ abnormality was recommended in lieu of an image-guided biopsy.

In 2018, the 6-month follow-up MRI was performed and demonstrated a focus of indeterminate gadolinium kinetics in the right UOQ as well as an increase in the size of the right axillary node. At the same time, the mammo-



Figure 4. 2020 pathology high-grade ductal carcinoma in situ.

gram was reported as normal. A hand-held ultrasound identified no corresponding mass to the MRI focus or physical examination.

In 2019, the mammogram revealed new microcalcifications in the right UOQ that corresponded with the focus identified on the MRI NME (Figure 3). The patient underwent a whole-breast ultrasound (automated breast ultrasound screening; ABUS) that was unable to identify a mass in the right breast, a limitation of ultrasound described in the literature (Lunkiewicz et al., 2021).

Surgical Outcome

The calcifications identified earlier in 2019 persisted at the 6-month MRI follow-up. In 2020, the MRI showed some increase in the known NME, which remained limited to the right UOQ. A repeat ABUS still did not identify a corresponding mass. Subsequently, the patient underwent a lumpectomy followed by a bilateral mastectomy with sentinel node biopsy. Pathology revealed involvement only of the right UOQ with high-grade DCIS at stage TONOMO (Figure 4).

he lifetime risk of developing breast cancer among women in developed countries is around 11%. Therefore, screening asymptomatic women for image-detected mammary lesions is widely accepted preventive health care (Kashyap et al., 2022). Advanced practitioners (APs) use imaging modalities, such as mammograms, MRI, and ultrasound in daily practice for the diagnosis of malignancy. There have been efforts to reduce the number of women with false-negative screening results by making mammography more sensitive or to supplement it with ultrasound or MRI (Durand et al., 2021). Advanced practitioners are well prepared to identify inconsistencies with imaging results and the physical assessment of the breast.

SCREENING MAMMOGRAPHY

Digital breast imaging detects 90% of symptomatic or asymptomatic cancers (Park et al., 2013). Additionally, the sensitivity, specificity, and negative predictive values of digital breast imaging are each about 90% (Park et al., 2013). As a standard of care, the Breast Imaging Reporting and Data System (BI-RADS) is used to quantify increasing degrees of positive predictive values in mammography that help clinicians identify abnormalities that may need additional imaging studies or biopsies (Rahman & Helvie, 2022).

Challenges for APs who manage the results of abnormal breast mammography have not changed much over time. Advanced practitioners can have complex clinical practice settings, variability of reading radiologists, and differences in screening guidelines (Institute of Medicine, 2011; Rahman & Helvie, 2022). Overall, the cost, time, validity of comparison of serial studies, and the non-invasive nature make mammography acceptable to the patient, the radiologist, the clinician, and the payor (Rahman & Helvie, 2022).

Microcalcifications without an associated mass presenting on screening mammography have become the textbook presentation of DCIS. They account for approximately 20% of new breast cancer diagnoses in the United States (Bragg et al., 2021). In an additional 30% of new breast cancer diagnoses, the pathologist finds DCIS coexistent with invasive ductal cancer (Bragg et al., 2021). When coexisting with invasive breast cancer, microcalcifications are not obligate for identification by mammography (Kim et al., 2022).

Mammography has a negative predictive value of only 90% (Zeeshan et al., 2018). Radiologists have searched for a screening modality and protocol that identifies early mammographically occult breast lesions, including lobular carcinoma, non-calcified DCIS, or sub-centimeter invasive ductal cancers occurring in women with a prior mammographically occult cancer or women with dense breast tissue or at a high lifetime risk for breast cancer. The latter group includes women carrying recognized gene mutations or prior mediastinal radiation as a young adult (Vourtsis & Berg, 2019; Kim & Haffty, 2023; Wong, 2023). No form of mammography can increase the negative predictive value, hence the evaluation of supplemental breast screening using automated breast ultrasound screening (ABUS) or MRI for women at increased lifetime risk of breast cancer (Kerlikowaske et al., 2022).

The validity of comparison of sequential studies is a requirement of any screening protocol (Aggarwal et al., 2022). An apparent change from one study to the next is easier for the radiologist to detect than a de novo finding. The use of mammography meets this standard (Aggarwal et al., 2022). It is imperative for APs to consider the impact of breast density when comparing serial screening mammograms (Mann et al., 2022). The sensitivity of mammography is less in dense breasts than in those with more fat. As many as 40% of random women screened for breast cancer have dense breasts (Nazari & Mukherjee, 2018). Fatty tissue does not block X-rays as well as benign or malignant glands, and neither blocks as well as calcium (Mann et al., 2022). The less the blocking of X-rays, the darker or black-appearing the tissue is viewed on a mammogram. Subsequently, dense breast tissue with increased volume of normal glands can obscure the detection of small abnormalities or cancers (Vourtsis & Berg, 2019).

BREAST ULTRASOUND

Breast ultrasound is another screening modality tool to improve assessment of dense breast tissue (Boca Bena et al., 2021). Automated breast ultrasound, which is different from hand-held ultrasound, has been available since 2012 (Boca Bena et al., 2021). Like mammography, ABUS meets the standard for comparison of sequential studies. Ultrasound detects malignancy by identifying masses or distortion of normal breast architecture that alter sound wave patterns (Berg et al., 2012). Physician-performed ultrasound added to mammography yielded 4.2 cancers per 1,000 women with BRCA mutations, personal history of mediastinal radiation, or prior biopsy of atypical hyperplasia (Berg et al., 2008). Adding ABUS screening to mammography in women with very dense breasts detected an additional 2.2 cancers per 1,000 women (Wilczek et al., 2008). In summary, when employed as screening supplemental to mammography, the additional cancer yield ranges from 3 to 4 cases per 1,000 women (Wilczek et al., 2008).

BREAST MRI

Breast dynamic-contrast MRI protocols measure patterns of breast vascularity (Comstock, 2020). One of the hallmarks of the physiology of malignant vasculature of breast carcinomas is both rapid uptake and rapid elution of gadolinium (Bakker et al., 2019). Differences in vascular patterns of benign or malignant tissue are visible in dense breast tissue imaged by MRI using a single-sequence, 10-minute protocol called abbreviated breast MRI (AB-MRI; Millet et al., 2012).

Among MRI protocol considerations are magnet power, axial or sagittal view of breast, 2D or 3D images, scanning one or both breasts at once, degree of resolution, and dynamic contrast recording (Lehman, 2010). If these parameters are constant, comparisons of serial MRI studies are valid, as mentioned previously on mammography and ultrasound. As with other MRI studies, APs should consider costs to the patient, ability of the patient to complete the MRI, and other medical contraindications of MRI prior to ordering the examination (Millet et al., 2012).

Trials of women with dense breasts completing screening mammography randomized to supplemental screening with MRI were completed in Europe and the United States. Endpoints of the studies were additional cancers detected at initial, screening or new cancers detected at shortinterval (1–2 years) follow-up screening (Kuhl et al., 2014). Supplemental screening of women with slightly increased to intermediate risk of breast cancer yielded 18 cases of breast cancer per 1,000 women (Kuhl et al., 2014). In the DENSE trial, 8,061 women were offered supplemental MRI screening, and 4,783 were enrolled to the trial (Mann et al., 2022). Investigators reported additional cancers detected by MRI were 16.5 cases per 1,000 women (Mann et al., 2022). Interval breast cancers were 0.8 cases per 1,000 women who accepted supplemental screening, down from 4.9 breast cancers per 1,000 women in the 3,278 who did not receive supplemental MRI screening (Mann et al., 2022).

In an Eastern Cooperative Oncology Group (ECOG) multi-institutional study, 1,444 women with dense breasts were screened with both AB-MRI and digital breast tomosynthesis (Comstock et al., 2020). In this study, invasive or non-invasive cancers were detected at a rate of 6.2 cases per 1,000 women by digital breast tomography alone (Comstock et al., 2020). AB-MRI yielded an additional nine invasive or non-invasive ductal cancers cases per 1,000 women, and there were no interval cancers reported (Comstock et al., 2020).

DISCUSSION

In the case study, multiple foci of high-grade DCIS were imaged intermittently by MRI for more than a decade before the DCIS was proven pathologically. An additional 2 years elapsed before the development of mammographically-identified microcalcifications that could be surgically removed.

The patient described in this case report was one of the 10% of women for whom mammography has been inaccurate (Lotter et al., 2021). In 2007, a palpable mass was occult. The DCIS, visible by MRI since 2009, developed microcalcifications only in 2019 (Figures 3 and 5). Pathologically, calcium apatite deposits in soft tissue usually occur in foci of necrosis occurring in sites of infection or ischemia (Vidavsxy et al., 2021). The calcifications suggestive of DCIS are usually less than 0.5 cm, clustered, and variable in shape (Bane, 2013). Abnormal cells proliferating unchecked inside ducts ultimately become foci for calcium apatite deposition (Bane, 2013). Analysis of microcalcifications harvested from breast cancers yields not only inorganic apatite associated with calcium, zinc, or magnesium but also lipids and proteins (Kunitake

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Figure 5. 2009 right breast MRI upper outer quadrant.

et al., 2023). The composition depends not only on the benign or malignant epithelial cells, viable or necrotic, but also on the microenvironment (Kunitake, et al., 2023). A hyper-vascularized lesion in the breast identified as an NME by MRI might be expected to have delayed calcification (Lunkiewicz et al., 2021). Such is the situation for the woman described in this case report.

Valid comparison of serial images from this patient's serial MRI studies required stability of both patient position and image acquisition protocol (Lehman, 2010). Those parameters varied in this patient's series of images. The patient's long-standing axillary lymphadenopathy was a fiducial for variation in image acquisition between sequential MRI studies. Bilateral lymphadenopathy was described in 2009, but not in 2007, 2008, or 2010. In 2010, the resolution of the lymphadenopathy was an artifact of imaging that became visible in 2014 when the adenopathy, unchanged from 2009, again became apparent. The optics of these variations resemble those between CT images of the chest viewed on mediastinal windows or on lung windows. For example, the imaging variations occur without any change in anatomy because chest structures can appear larger and whiter on lung windows.

The 2018 MRI examination that identified a possible mass visualized as indeterminate gadolinium flow also described an apparent 50% increase in length of a lymph node present since 1985 and first imaged in 2009. No breast mass was identified at mastectomy. Both findings were attributed to an artifact of patient positioning during the MRI.

Imaged with a high spatial protocol, that is, more slices per centimeter, the DCIS exhibited NME as described in the case report in 2009 and 2014 through 2020 (Lunkiewicz et al., 2021). Conversely, the NME appearance is not seen with a high temporal protocol, that is, more slices per minute (Lehman, 2010). For continuity, the presence of these types of variations in image acquisition should be communicated by the reading radiologist to the requesting physician or AP.

In the case study, the first prospective recognition of multiple foci of NME in the UOQ of the right breast occurred in 2017. A review of prior studies identified small foci to have been present in 2009 and multiple larger foci in 2014 through 2016. In clinical practice, the discovery of inconsistent studies along with noncongruent clinical breast examination findings should signal to the AP to evaluate the patient for a differential diagnosis. For example, when reviewing the aforementioned case report, the duration of the finding of multiple enhancements without development of a mass, no gadolinium kinetics suggestive of malignant vasculature on MRI, and the absence of microcalcifications on mammogram all made the possibility of chronic mastitis or sclerosing adenosis more probable etiologies of the MRI findings than malignancy (Guirguis et al., 2021).

As mentioned before, multiple whole breast ultrasounds (ABUS) did not identify a mass to target for biopsy (Lunkiewicz et al., 2021). In 2019, 10 years after development of multiple foci of NME on the MRI and 2 years after their recognition, a circular cluster of calcifications was identified by mammography and its persistence confirmed at 6-month follow-up (Figure 3). The distribution was that of a focus of MRI-visualized NME, unlike the branching morphology of DCIS first identified in this patient's left breast in 1985. The newly recognized focus in the right breast could now be wire-localized for surgical resection. In retrospect, the NME right breast lesions would probably have been biopsied years earlier if the patient had been in the study groups of Kuhl et al. (2014) or Comstock et al. (2020; Figure 4).

CONCLUSION

Screening women for breast cancer is accepted preventive health care. Advanced practitioners can help navigate shared decision-making and follow-up imaging discussions with patients with dense breasts by taking additional steps to understand the possible limitations of mammography, ultrasound, and MRI.

First, it is essential for APs to consider the ability of mammography to detect subtle abnormalities in dense breasts and the impact of breast density when comparing serial screening mammograms (Mann et al., 2022). Second, the AP should be alert to imaging results incongruent with clinical examination findings. In the past, efforts to reduce false-negative results have stimulated evaluation and utilization of other methods of breast cancer screening like MRI and ABUS (Comstock et al., 2020). Collaboration with reading radiologists can help the AP better understand the potential differences in imaging protocols and incongruent clinical examinations. A differential diagnosis should also be considered should incongruencies between imaging and clinical examinations persist (Guirguis et al., 2021).

Thirdly, APs should be aware that NMEs identified on MRI are not commonly identified as abnormalities with ABUS (Lunkiewicz et al., 2021). With increased knowledge of ultrasound limitations, there is an opportunity to reduce additional imaging examinations, costs, and time for the patient.

Lastly, when considering MRI screening, the AP needs to weigh the increased detection rates in dense breasts with MRI access, costs, and the ability of the patient to perform the MRI study (Comstock et al., 2020). For the patient in the case study, there was a benefit of serial MRI examinations when compared to mammography and ultrasound.

In the future, breast imaging researchers like Comstock, Kuhl, and Mann suggest if single sequence AB-MRI replaces the original 4-sequence protocol and if a screening interval of 2 to 4 years can be shown to reduce death from breast cancer, the goals of improved screening of women with dense breasts will have been achieved with a financial cost to society and time investment of the individual patient acceptable to both (Comstock et al., 2020; Kuhl et al., 2014; Mann et al., 2022).

Disclosure

The authors have no conflicts of interest to disclose.

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