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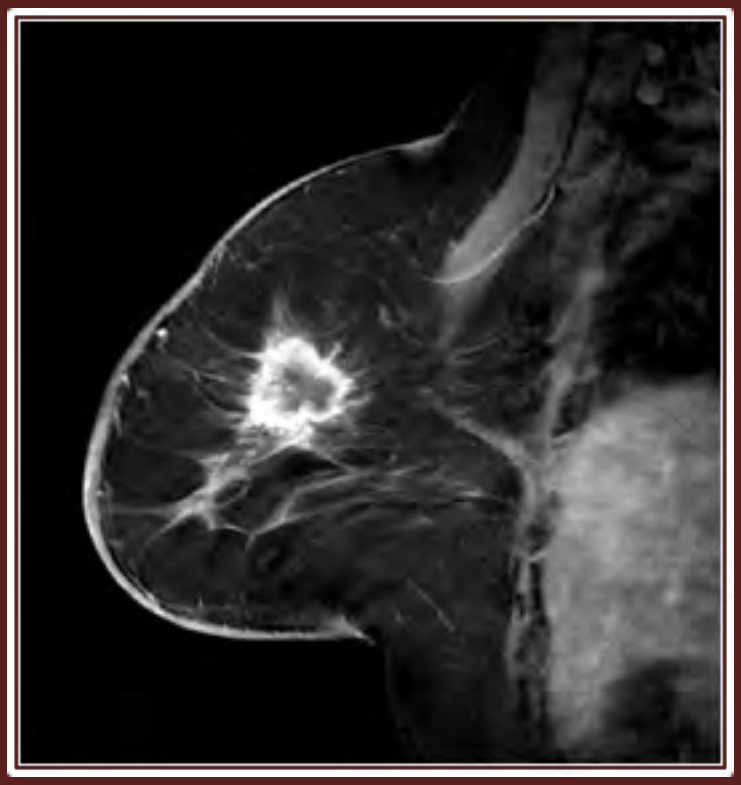
JAOCR

Official Journal of the American Osteopathic College of Radiology

BREAST IMAGING



Guest Editor: Stefanie A. Woodard, D.O.

Editor-in-Chief: Daniel J. Wale, D.O.

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JAOCR

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Aims and Scope

The Journal of the American Osteopathic College of Radiology (JAOCR) is designed to provide practical up-to-date reviews of critical topics in radiology for practicing radiologists and radiology trainees. Each quarterly issue covers a particular radiology subspecialty and is composed of high-quality review articles and case reports that highlight differential diagnoses and important teaching points.

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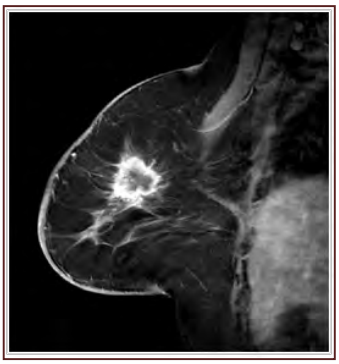

JAOCR

BREAST IMAGING

Guest Editor: Stefanie A. Woodard, D.O.

From the Editor

Review Articles

Differential-Based Case Reviews

JAOCR at the Viewbox

"Let's start this year with a reaffirmation of our choice and a renewed understanding of the privilege of our work."

—Susann Schetter, D.O.

In this Issue

Stefanie A. Woodard, D.O.

Assistant Professor, Breast Imaging
Department of Radiology, The University of Alabama at Birmingham, Birmingham, AL

I am honored to have the opportunity to serve as the guest editor for this breast-focused issue of JAOCR; however, no task is ever accomplished alone. I would like to thank my colleagues in breast imaging at The University of Alabama at Birmingham (UAB) for their camaraderie and work on several articles in this issue. My colleagues and mentors from Penn State Health Milton S. Hershey Medical Center also provided interesting and insightful contributions in addition to helping with the dedication of this issue. The brainstorming, writing, and editorial process has been at times stressful yet immensely enjoyable. I am so grateful to have accrued an energetic, enthusiastic, and articulate group of authors who have shared their wealth of knowledge. We hope that the readers find this issue thought-provoking and valuable for daily practice.

The issue begins with a review of two different but similarly complicated topics of breast radiology. These manuscripts were written through the efforts of myself, colleagues at UAB, and several trainees (UAB, Brookwood Baptist Health, and abroad). The first review article tackles the topic of high-risk breast lesions, providing a brief overview of the pathologies, corresponding images, and management goals for each. Our second review article examines the topic of nipple discharge, outlining the multiple manifestations of discharge encountered in a breast radiology clinic. A literature review was performed to create an evidence-based management algorithm. While nipple discharge is a heavily debated topic, we hope this summary helps direct some of the more complicated aspects of assessment and imaging.

Our differential case-based reviews include presentations of both benign inflammatory conditions of the breast and enhancing foci on breast MRI, interesting topics that sometimes create diagnostic dilemmas. Last but not least, the At the Viewbox cases present rare but important pathologies including breast implant-associated lymphoma, amyloid, and granular cell tumors.

Finally, this issue would never have happened had it not been for the inspiration of Dr. Susann Schetter (March 24, 1955 - December 24, 2018), who introduced me to JAOCR in 2014. I would like to thank Dr. Wale and the editorial committee for their kindness and generosity in allowing me to dedicate this issue to Dr. Schetter, my fellowship director, mentor, and friend.

Susann Schetter, D.O. (1955 – 2018)

This issue of JAOCR is dedicated to the memory of Susann Schetter, D.O., who died December 24, 2018 after courageously battling pancreatic cancer. A native of New Jersey, Susann graduated from Villanova University in 1976 and pursued graduate studies in microbiology and biochemistry at Hahnemann University in Philadelphia. In 1982, she received her doctorate of osteopathic medicine from the Philadelphia College of Osteopathic Medicine, followed by internship and radiology residency in Lancaster, Pennsylvania, and a fellowship in pediatric radiology at St. Christopher's Hospital for Children in Philadelphia. After serving two years in the Indian Health Service in Anchorage, Alaska, she undertook positions as a radiologist in Lancaster and subsequently Philadelphia, where she became section chief of mammography and medical director of the Women's Imaging Center at Pennsylvania Hospital. Ultimately, Dr. Schetter was hired by Penn State Hershey Medical Center as division chief of breast imaging and co-director of the Penn State Hershey Breast Center. While there, she served as associate chief medical officer for the Penn State Health Medical Group, and medical director of the Penn State Health Breast Center.

While she made numerous contributions to patient care that will be remembered, one of her most successful ventures was the development of a fully integrated breast center on the Penn State Hershey campus. Together with her surgical colleague, she designed and implemented a breast care center where surgeons and radiologists work side-by-side, sharing hallways as they care for mutual patients. Through specific design, the patients move seamlessly between the imaging and core-biopsy rooms to their surgical appointments, allowing surgeons, radiologists, and other clinicians to fully coordinate care. This integrated concept not only streamlined patient management, it also fostered true collegiality amongst the breast center care providers.

As a breast imager, Dr. Schetter's wealth of knowledge constantly amazed me, and her intuition was uncanny. From common presentations to the most obscure diagnoses, she always had the needed differentials on hand. While she excelled as a diagnostician, her compassion, empathy, and grace rivaled her intellect. She had the most calming demeanor and could deliver the worst news with the utmost compassion. She was the epitome of professionalism. I never heard her speak one ill word about anyone, whether a patient, colleague, or trainee.

I was a third-year radiology resident in 2013 when Dr. Schetter gave me a chance to work with her on a paper for the JAOCR. I considered it an honor and immediately agreed. As guest editor for the January 2014 issue, Dr. Schetter organized an eloquent list of breast topics, from screening to uncommon breast cases. Six years later when I heard of an opportunity to serve as JAOCR guest editor, I thought of the strong, charismatic, and humble mentor who taught me more about breast imaging, leadership, and life than she would ever know. She was not only my attending and fellowship director, but my role model and friend.

It is rare to encounter a person capable of creating within you a fervency, passion, and confidence you never knew existed. One might never have the chance to meet and learn from such an individual over the course of an entire lifetime. I am so thankful that I had such an opportunity to learn from Dr. Schetter and dedicate this issue to her memory.

Stefanie A. Woodard, DO

High-Risk Lesions: Review and Management Update

Kathryn Zamora, M.D.,[1] Amy Newton, M.D.,[2] S. LeeAnn Denham, M.D.,[1] Shi Wei, M.D., Ph.D.,[3] Stefanie A. Woodard, D.O.[1]

[1]Department of Radiology, The University of Alabama at Birmingham, Birmingham, AL
[2]Department of Radiology, Brookwood Baptist Health, Birmingham, AL
[3]Department of Pathology, The University of Alabama at Birmingham, Birmingham, AL

Diagnosis and appropriate management of nonmalignant pathology identified at core-needle biopsy (CNB) of the breast often requires complex management strategies and a multidisciplinary approach. Benign breast pathology is complex and several lesions, although not considered malignant at biopsy, are termed high-risk lesions (HRLs). These lesions may be associated with a significant upgrade rate at excision or may portend increased risk of breast cancer. High-risk pathology has been demonstrated in up to 9.2% of breast CNBs.[1] After biopsy, pathology results are reviewed and concordance is assessed. Even in the setting where an HRL is considered concordant with imaging characteristics, management recommendations must be made. The recommendations for managing lesions are evolving, as detection has increased with advances in imaging techniques. While excision may be recommended for many HRLs, others may only warrant surveillance. The purpose of this article is to review the common imaging findings, pathology, and current management recommendations of the following breast lesions: mucocele-like lesions (MLLs), lobular neoplasia (LN), atypical ductal hyperplasia (ADH), radial scars (RSs), complex sclerosing lesions (CSLs), flat epithelial atypia (FEA), and papillary lesions.

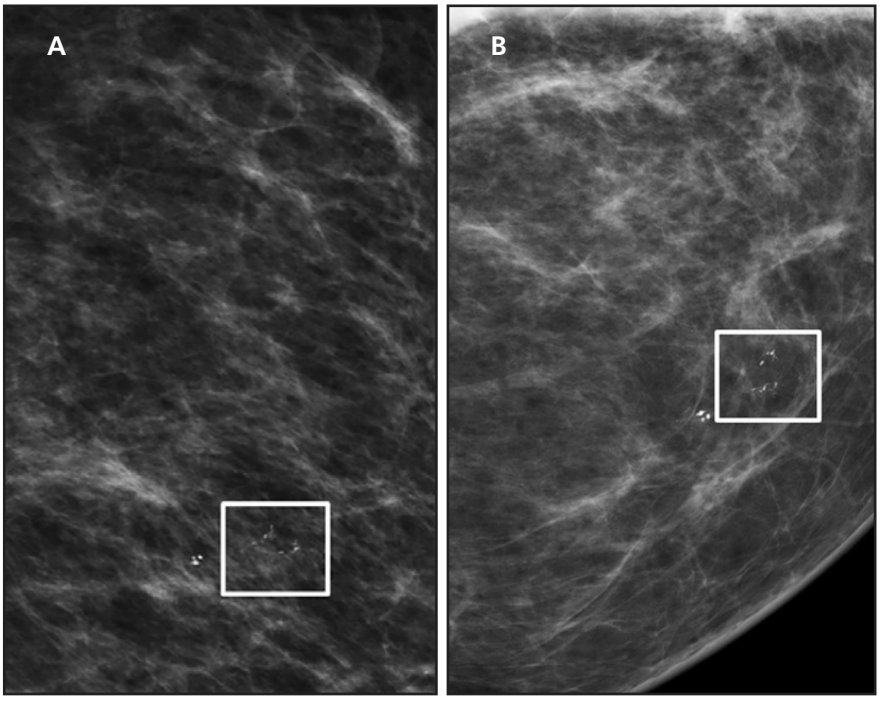

FIGURE 1. *MLL calcifications. A 58-year-old woman was called back from screening for calcifications. Diagnostic magnification CC and LM views demonstrate suspicious fine linear and coarse heterogenous calcifications demarcated by the white boxes (A, B). Stereotactic biopsy performed with a 9-gauge vacuum-assisted device demonstrated pathologic results of MLL without atypia.*

Mucocele-Like Lesions

MLLs are benign lesions described as similar to mucocele lesions of the minor salivary glands.[2] These cysts contain mucin and may rupture, expelling mucin into the surrounding tissue. MLLs, originally described as benign, have now been shown to be associated with a spectrum of atypia and malignancy.[3,4] MLLs have been identified concurrently with epithelial variations including benign columnar cell lesions, ADH, ductal carcinoma in situ (DCIS), and mucinous carcinoma.

MLLs may present as indeterminate calcifications on mammography.[5] **Figure 1** demonstrates a classic imaging presentation of an MLL as calcifications.

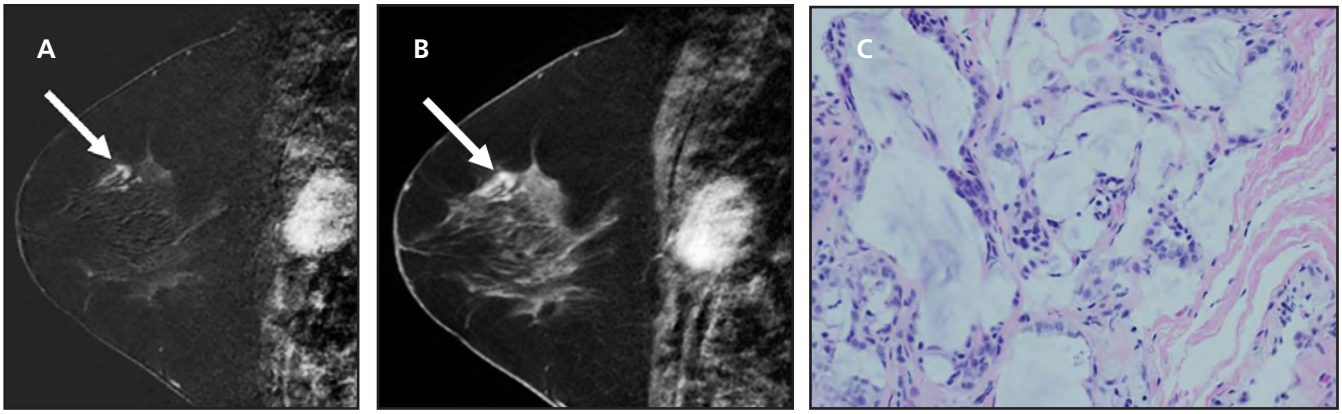

FIGURE 2. *MLL on MRI. MRI examination performed for extent of disease in a 53-year-old woman demonstrates suspicious focal NME in the upper outer quadrant of the left breast as shown on the sagittal subtraction and postcontrast T1 FS dynamic images (A, B). MR-guided biopsy was performed and showed MLL in addition to LCIS and FEA. Pathology specimen from the biopsy shows a portion of the MLL (C).*

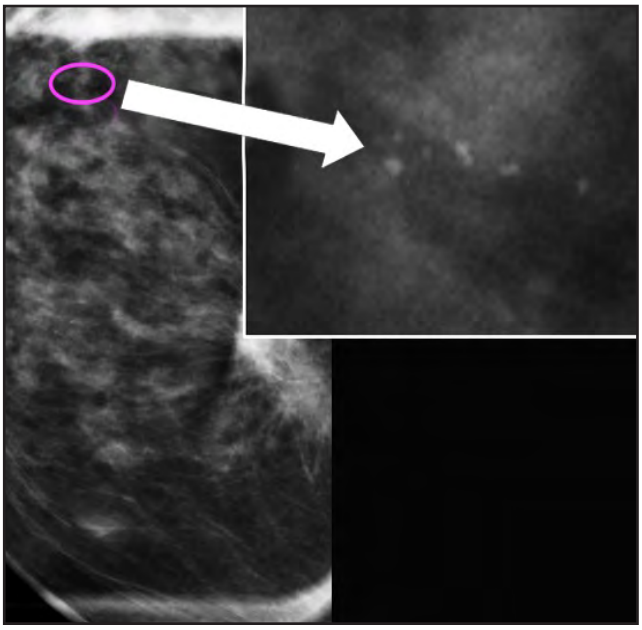

FIGURE 3. *Diagnostic magnification mammography performed to interrogate new calcifications demonstrates grouped fine pleomorphic calcifications. Biopsy was performed and pathology results demonstrated LCIS.*

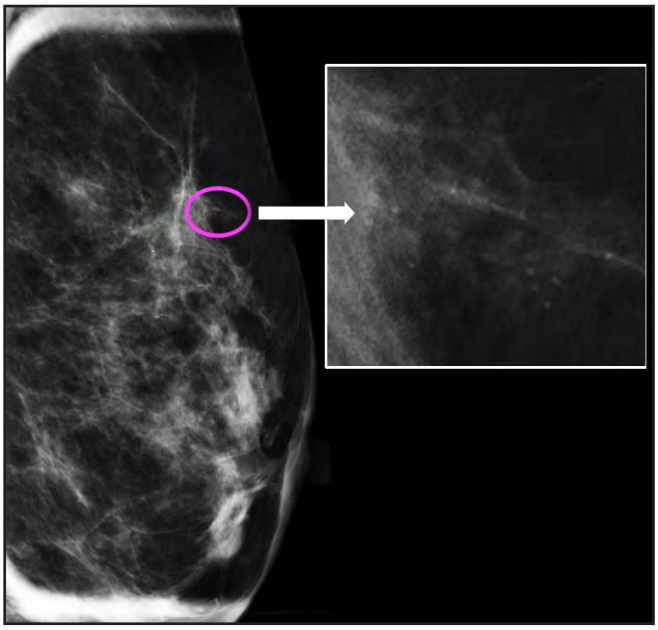

FIGURE 4. *ALH calcifications. Diagnostic left breast magnification view of new calcifications demonstrates grouped amorphous calcifications. Pathology results following biopsy showed ALH.*

Less commonly, it may present as a focal asymmetry or asymmetry. Although infrequently identified on ultrasound, MLLs may be seen as a cluster of microcysts or complex cystic/solid masses.[6] MLL on MRI examination may be associated with nonmass enhancement as demonstrated in **Figure 2**.

Management of MLLs is variable. MLLs without atypia at core biopsy demonstrate 0% to 4% upgrade to malignancy.[7-9] However, Ha et al found that while MLLs without atypia at core biopsy do not demonstrate significant upgrade to malignancy, they do demonstrate upgrade to atypia at surgical excision.[8] On the contrary, MLLs with atypia at core biopsy demonstrate a variable upgrade rate to DCIS of 3% to 31%.[7,9] Limitations of the literature include small sample sizes of studies. As with all biopsies, radiologic-pathologic concordance, adequate sampling, and type of biopsy device should be reviewed prior to management decisions. Given the current knowledge of these lesions, if the lesion is concordant and sufficiently sampled, imaging follow-up in lieu of surgical excision may be considered for MLLs without atypia. However, given the high upgrade rate for MLLs with atypia, surgical excision remains the recommendation.

Lobular Neoplasia

LN is a spectrum of disease that originates in the terminal duct lobular unit (TDLU).[10] LN has multiple subtypes including atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS), and pleomorphic lobular carcinoma in situ (PLCIS). All LN demonstrates reduced or absent expression of E-cadherin, the cell-cell junction protein.[11] ALH appears as discohesive small,

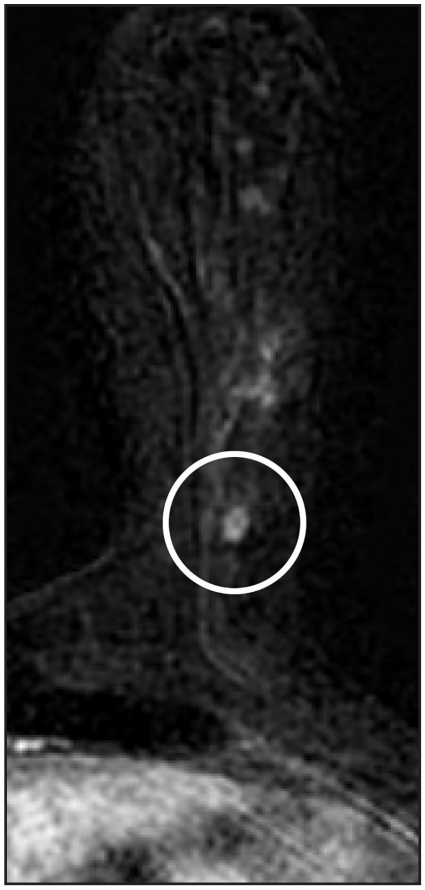

FIGURE 5. *LCIS on MRI. Breast MRI examination demonstrates NME in the lower outer quadrant left breast. Biopsy performed under MR guidance yielded LCIS.*

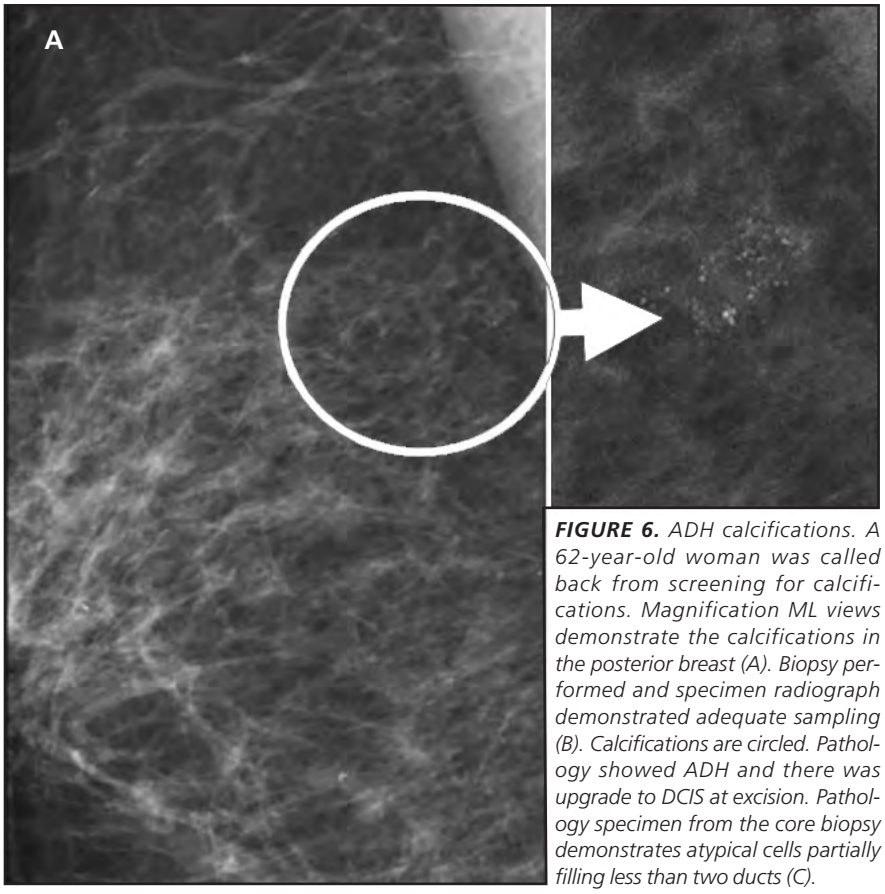

FIGURE 6. *ADH calcifications. A 62-year-old woman was called back from screening for calcifications. Magnification ML views demonstrate the calcifications in the posterior breast (A). Biopsy performed and specimen radiograph demonstrated adequate sampling (B). Calcifications are circled. Pathology showed ADH and there was upgrade to DCIS at excision. Pathology specimen from the core biopsy demonstrates atypical cells partially filling less than two ducts (C).*

monotonous, polygonal and round epithelial cells that fill and expand the acini of the lobular unit.[11,12] LCIS appears similar to the ALH but is more extensive. It involves the expansion of more than half of the acini in a lobular unit.[11,12] PLCIS has the appearance of LCIS with the addition of nuclear membrane irregularity, easily identifiable mitotic forms, significant nuclear pleomorphism, and variable prominent nucleoli.[13] Despite these definitions, pathologist interobserver agreement between the WHO classification of ALH, LCIS, and PLCIS is poor.[14]

LN is often an incidental finding on CNB. Mammographically, it may present as fine pleomorphic calcifications (**Figure 3**). Less frequently, it may also present as grouped amorphous or grouped coarse heterogeneous calcifications (**Figure 4**). Unfortunately, calcification appearance on mammography does not assist in differentiating among the pathologic spectrum. LN is histologically associated with calcifications in about 20% to 40% of biopsies. LN may present as foci of enhancement or nonmass enhancement (NME) on MRI. **Figure 5** shows an example of LCIS presenting on MRI as focal NME. On MRI examination, there is no evidence that LN forms a mass lesion. If MRI biopsy of a targeted mass demonstrates lobular neoplasia, the biopsy could be considered discordant.[10]

Management of LN is variable. According to Sen et al, published upgrade rates for ALH range from 0% to 46% with an accepted rate of 2.4%. For LCIS, they found the upgrade rate is 0% to 60% with an accepted rate of 9.3%.[15] PLCIS demonstrates a variable upgrade rate of 18% to 100%.[16] Pleomorphic LCIS also recurs locally in 4% to 19% of cases.[13] Currently the National Comprehensive Cancer Network (NCCN) recommends excision for all LN found at CNB.[17] Management of ALH remains controversial, however, as the upgrade rate is

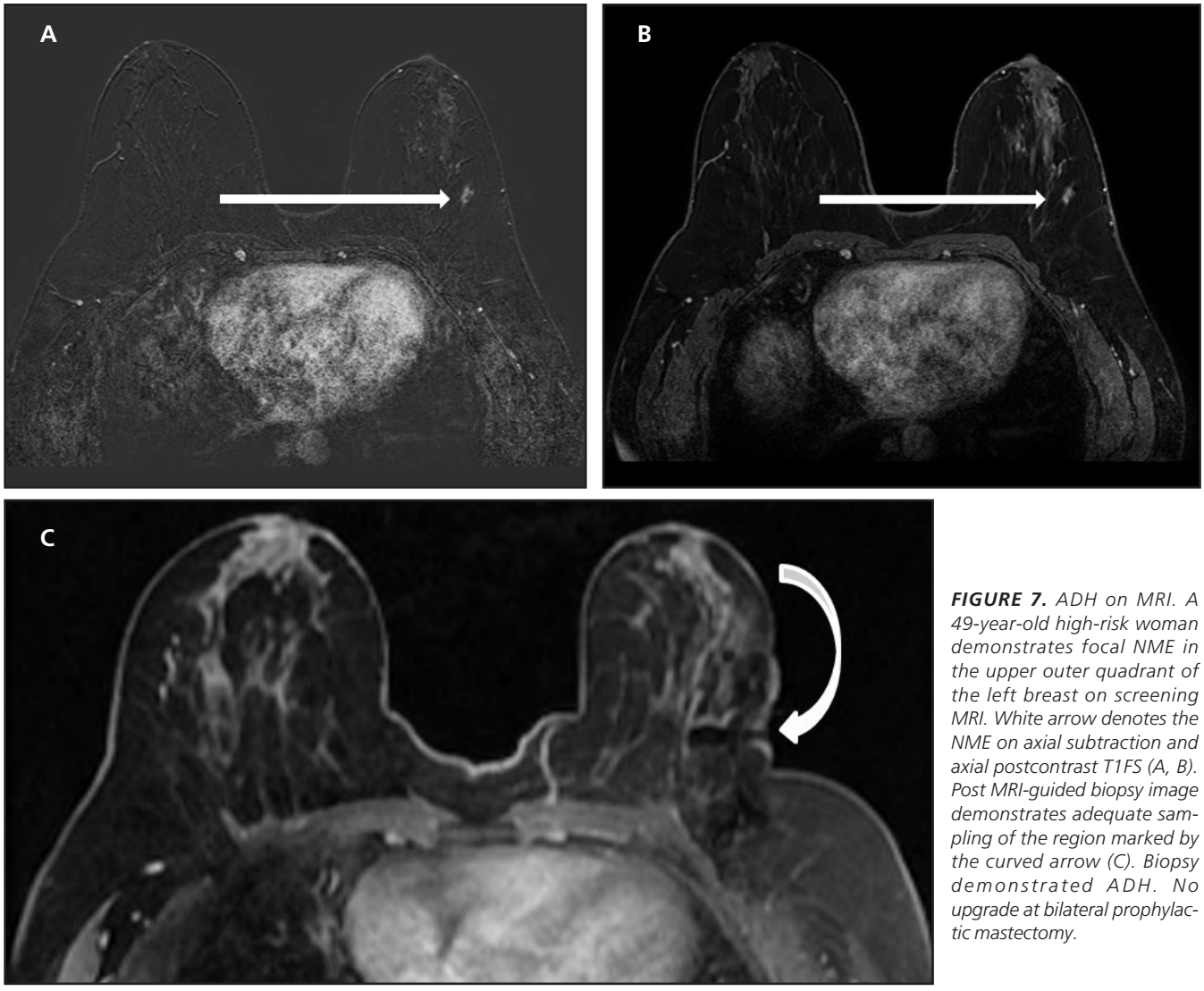

FIGURE 7. *ADH on MRI. A 49-year-old high-risk woman demonstrates focal NME in the upper outer quadrant of the left breast on screening MRI. White arrow denotes the NME on axial subtraction and axial postcontrast T1FS (A, B). Post MRI-guided biopsy image demonstrates adequate sampling of the region marked by the curved arrow (C). Biopsy demonstrated ADH. No upgrade at bilateral prophylactic mastectomy.*

relatively low and imaging follow-up is now becoming more of a consideration. LCIS is typically surgically excised. The need for clear margins is controversial but typically not essential.[13] PLCIS treatment, on the other hand, is similar to DCIS, often requiring clear margins (optimally > 2mm) with possible radiation.[13] Variants such as LCIS with necrosis or florid LCIS may be treated similarly.[18] Unfortunately, LCIS may be multifocal and margins may be difficult to clear.[13]

LN is considered a precursor lesion by the World Health Organization.[12] Lobular neoplasia carries with it increased risk for subsequent development of breast cancer. LCIS also carries a 2% per year cancer risk leading to a 26% cumulative risk over 15 years.[19] Subsequent cancers arise 3 times more frequently with LCIS than with ALH. Relative risk for the development of invasive breast cancer is 9 times higher after an LCIS diagnosis and 4 to 5 times higher after an ALH diagnosis,[20] of which approximately 77% of the subsequent cancers are ductal in origin.[11] LCIS is clonally related to synchronous invasive lobular cancer (ILC) and DCIS in 42% of cases.[21] Given this risk, excision versus imaging follow-up is not the only treatment consideration. Risk reduction with chemoprevention is often recommended. Classic LCIS is 100% estrogen receptor (ER) and progesterone receptor (PR) positive and pleomorphic LCIS is 72% to 100% ER positive.[18]

Atypical Ductal Hyperplasia

ADH presents pathologically as a neoplastic epithelial proliferative lesion of the mammary TDLU with micropapillary, tufts, bridges, or solid and cribriform patterns of evenly distributed, monomorphic cells with rounded or ovoid nuclei. ADH resembles low-grade DCIS microscopically and differs only in quantitative measurements. This similarity makes adequate sampling important. One definition of ADH is atypical cells partially or completely filling two or fewer ducts. If more than two duct spaces are involved, then DCIS is the diagnosis. An alternative definition of ADH is when the epithelial cells occupy < 2 mm in maximum dimension.

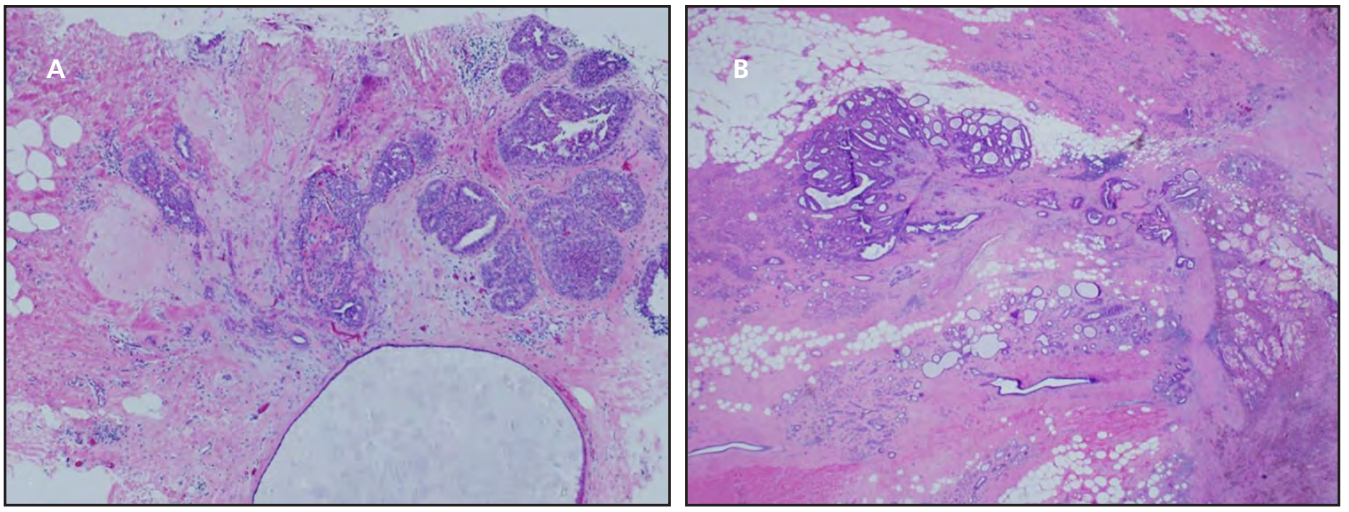

FIGURE 8. *RS/CSL pathology. RS showing central fibrosis/elastosis (A). Excisional biopsy specimen of the resection of a CSL (B). Core biopsy changes are identified on the right side of the image.*

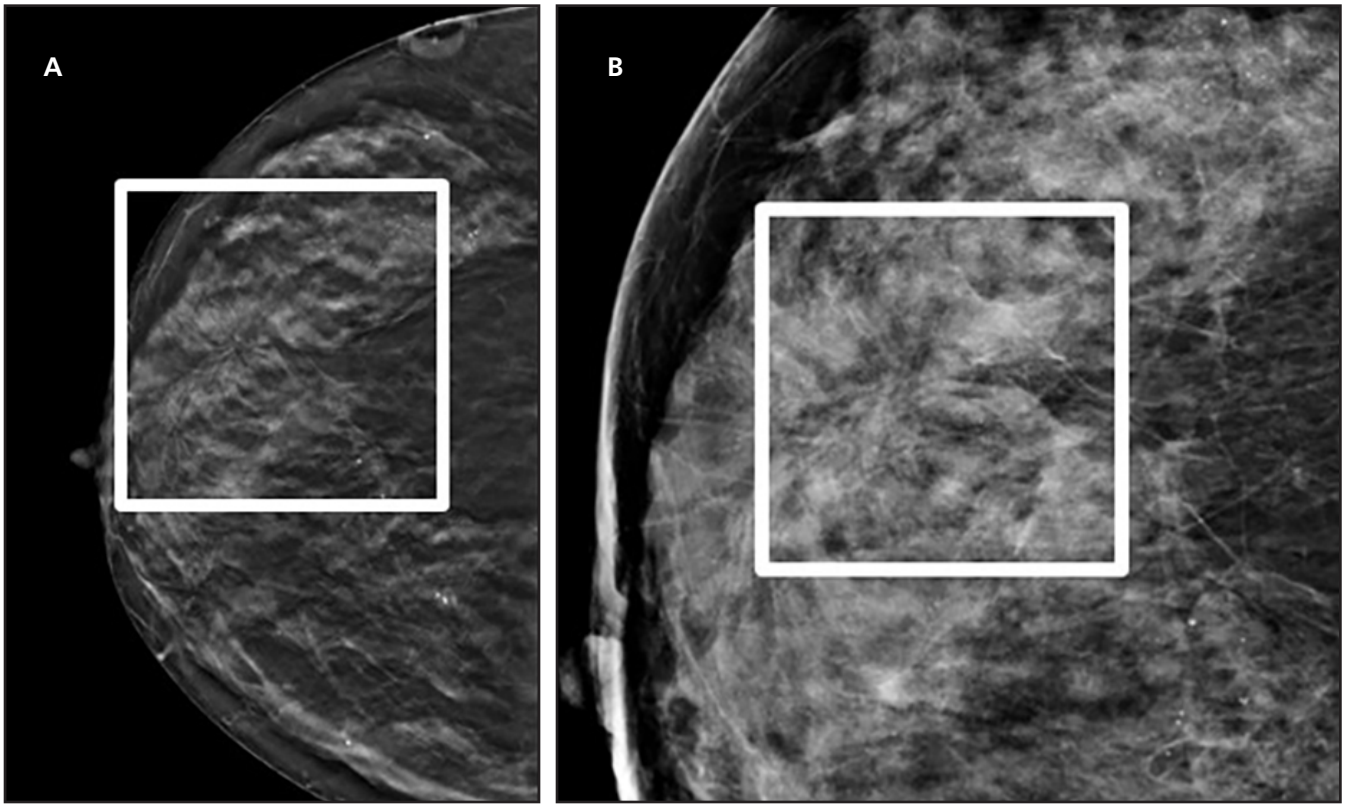

FIGURE 9. *RS/CS as architectural distortion. A 74-year-old woman presented with new architectural distortion on screening mammography in the upper outer quadrant of the right breast, seen best in the CC view (A). This was her first tomosynthesis examination. The finding was not appreciated on the full-field CC 2D view (not pictured). With spot compression, the distortion can be seen in the lateral breast at anterior depth (B).*

If the cells occupy > 2 mm, the diagnosis would be considered DCIS.

On imaging, ADH frequently presents as microcalcifications but may also present as a mass, asymmetry, or architectural distortion. An example of ADH presenting as calcifications is shown in **Figure 6**. Although ADH may be occult on ultrasound, it can rarely present as a hypoechoic mass. Often the MRI presentation of ADH is clumped linear nonmass enhancement similar to that of DCIS (**Figure 7**).

Management of ADH is debated. ADH is common and may be found in 8% to 37% of CNB specimens.[22-25] ADH has a variable upgrade rate from 22% to 65%.[22,24,25] Attempts to identify clinical, pathological or molecular biomarkers to predict risk factors for upgrade to malignancy have been unsuccessful.[23-26] Furthermore, breast cancer risk with ADH is 4 to 5 times that of the general population with a 6 times

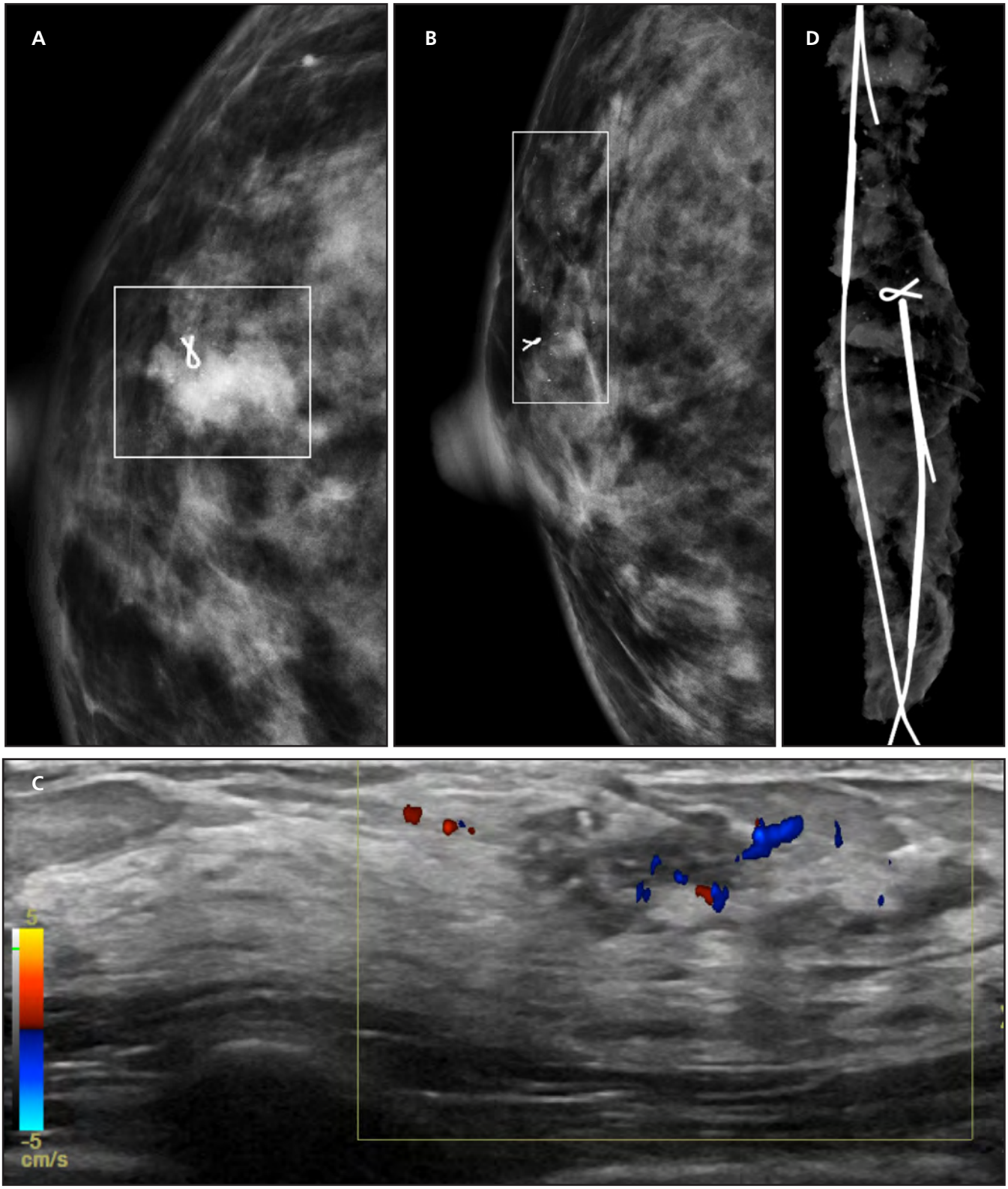

FIGURE 10. *RS/CSL with calcifications. A 41-year-old woman presented with increased segmental amorphous and punctate microcalcifications in the right breast 11 o'clock anterior depth on CC and ML magnification mammography (A and B). Ribbon clip is at prior benign biopsy site. Targeted static color Doppler ultrasound image showed an irregular hypoechoic mass with microlobulated margins and intraductal calcifications (C). Biopsy showed complex sclerosing lesion, which was excised. Bracket localization and excision demonstrated calcifications within the specimen (D). There was no upgrade at excision.*

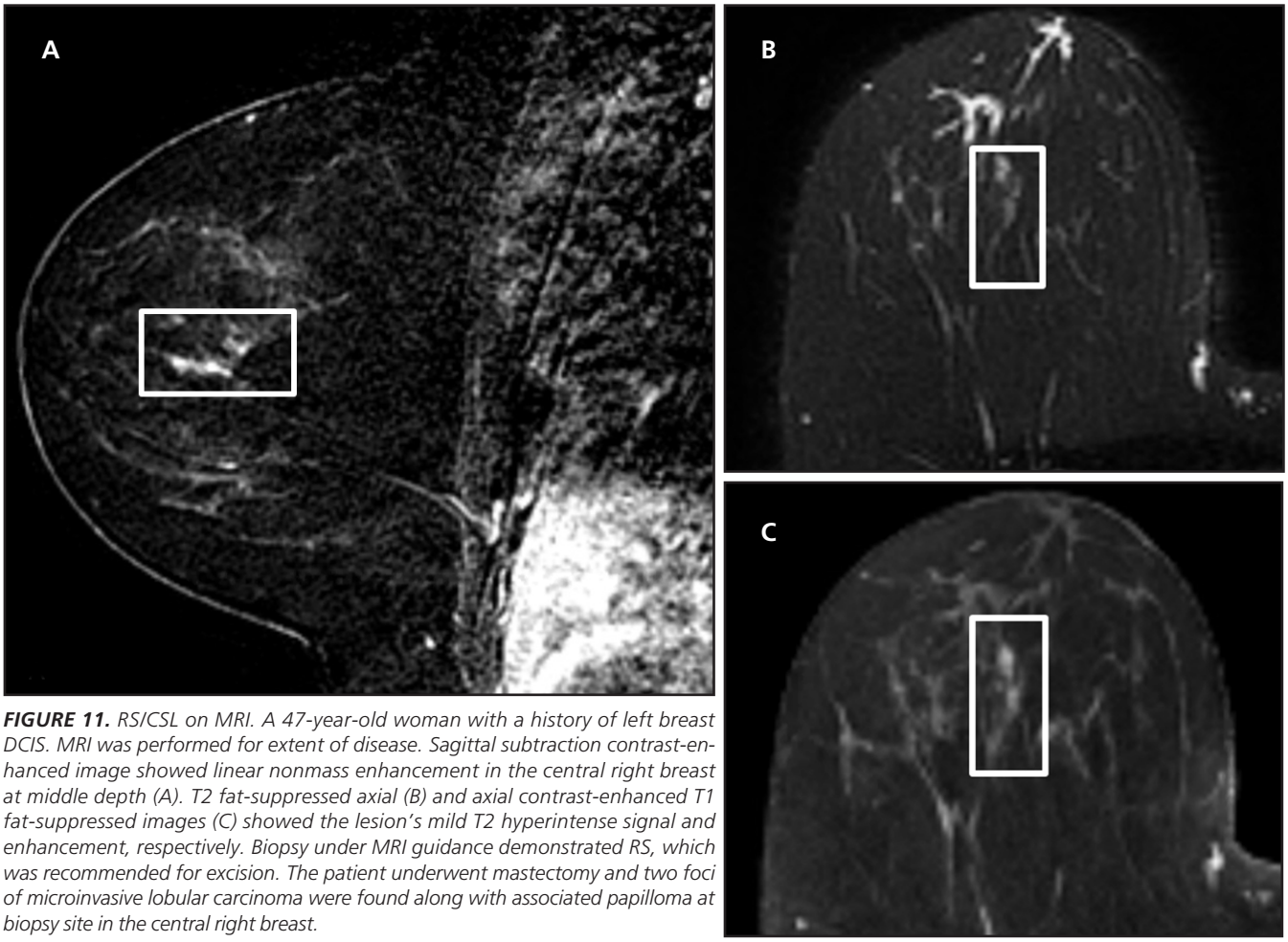

FIGURE 11. *RS/CSL on MRI. A 47-year-old woman with a history of left breast DCIS. MRI was performed for extent of disease. Sagittal subtraction contrast-enhanced image showed linear nonmass enhancement in the central right breast at middle depth (A). T2 fat-suppressed axial (B) and axial contrast-enhanced T1 fat-suppressed images (C) showed the lesion's mild T2 hyperintense signal and enhancement, respectively. Biopsy under MRI guidance demonstrated RS, which was recommended for excision. The patient underwent mastectomy and two foci of microinvasive lobular carcinoma were found along with associated papilloma at biopsy site in the central right breast.*

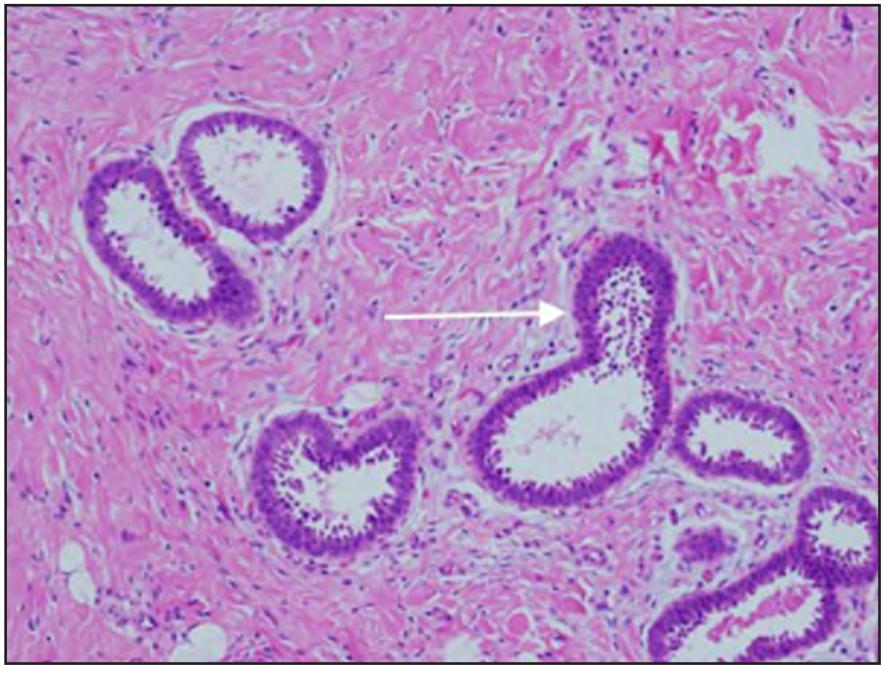

FIGURE 12. *FEA pathology. FEA biopsy specimen shows three to five layers of columnar epithelial cells with apical cytoplasmic snouts and intraluminal secretions (arrow).*

higher risk in premenopausal women and 10 times higher risk in patients with a family history of breast cancer.[22-25] Factors associated with upgrade of ADH include: age > 50, large lesion size, removal of < 95% of calcifications in the absence of an associated mass, smaller needle diameter at core biopsy (12 to 16 gauge), shorter length of biopsy core (< 2 cm), ipsilateral breast symptoms, other mammographic lesions in addition to microcalcifications, concomitant papilloma diagnosis, and severe ADH.

Excisional biopsy is the typical recommendation for ADH.[27] Identifying low-risk groups that may be safely observed is the focus of current research efforts.[25,26] Increasing evidence suggests that a small volume of ADH, if completely excised on CNB and shown to be concordant on imaging and pathology, may be observed with close follow-up.[23,24,28,29] Long-

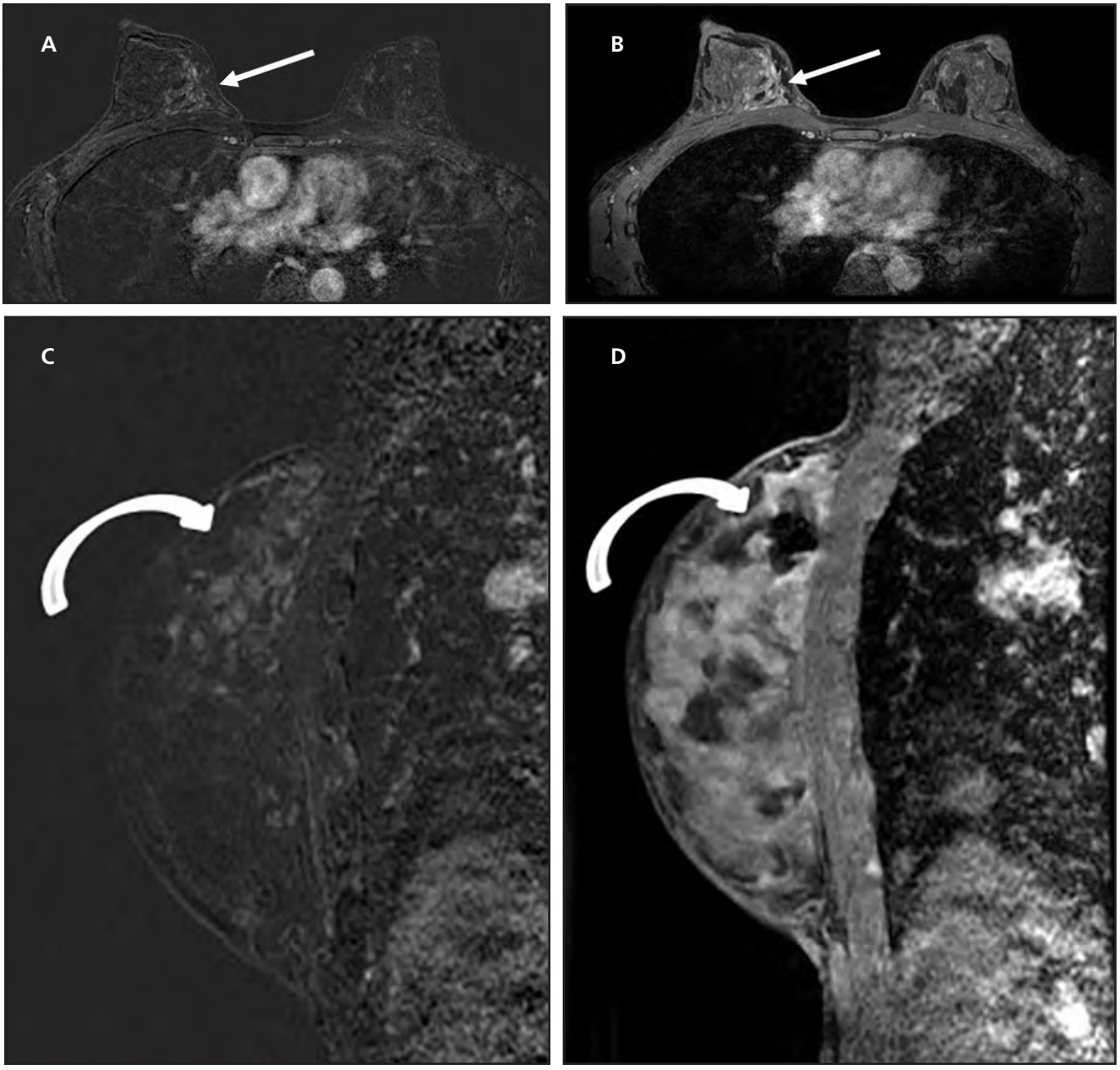

FIGURE 13. *FEA on MRI. A 34-year-old woman demonstrates regional NME in the upper inner quadrant of the right breast on postcontrast axial images marked by the white straight arrows (A, B). Biopsy was recommended and sagittal subtraction prebiopsy and sagittal postcontrast T1FS post-biopsy images demonstrates adequate sampling of the targeted area marked by the curved arrows (C, D). Pathology demonstrated FEA and ALH. No upgrade at surgical excision.*

term counseling for women with ADH should include discussion of breast cancer risk, surveillance strategies, and options for prevention therapy.

Radial Scar/Complex Sclerosing Lesions

Radial scars (RS) and complex sclerosing lesions (CSL) may arise from injury, duct ectasia or chronic inflammation. RS has a stellate pattern with a fibroelastic core surrounded by ducts and lobules that merge within the center of the lesion (**Figure 8**).[30] RSs are typically described as < 1 cm, and CSLs are > 1 cm. Sometimes they are difficult to differentiate from malignancy because of the infiltrative appearance. RSs and CSLs are frequently found as incidental lesions identified at biopsy. Patients are usually asymptomatic. The utilization of tomosynthesis has significantly increased the number of biopsies demonstrating these pathologies.

Mammographically, the classic presentation of these lesions is architectural distortion (**Figure 9**). Additionally, they may present as a focal asymmetry or mass. Infrequently, calcifications may be associated with

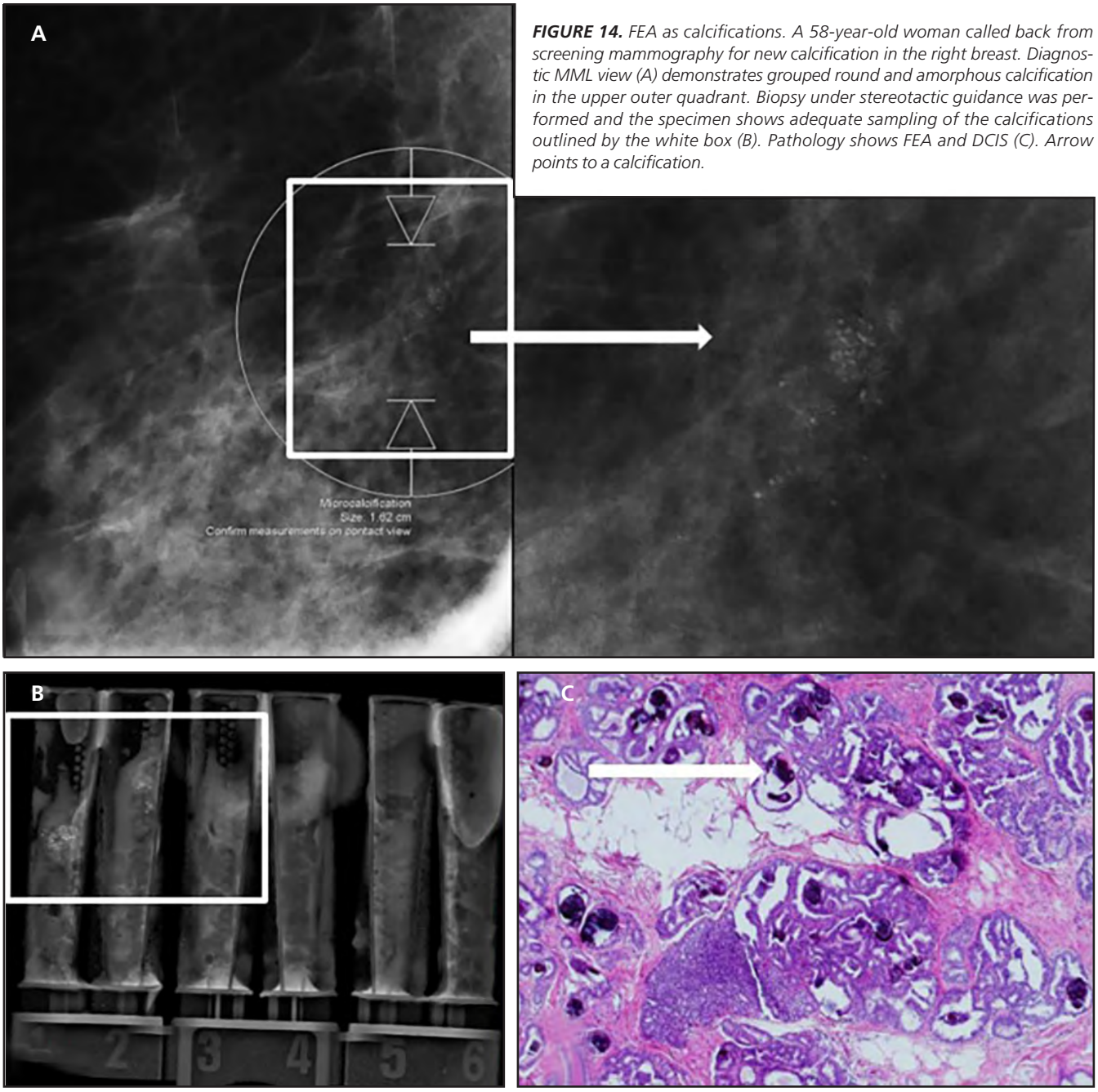

FIGURE 14. *FEA as calcifications. A 58-year-old woman called back from screening mammography for new calcification in the right breast. Diagnostic MML view (A) demonstrates grouped round and amorphous calcification in the upper outer quadrant. Biopsy under stereotactic guidance was performed and the specimen shows adequate sampling of the calcifications outlined by the white box (B). Pathology shows FEA and DCIS (C). Arrow points to a calcification.*

these lesions (**Figure 10**).[31] RSs and CSLs are often occult on ultrasound but may present as a mass with associated architectural distortion. Although the MRI appearance is variable, architectural distortion is often present. RSs and CSLs may also present as irregular masses, nonmass enhancement, or small foci of enhancement. **Figure 11** demonstrates a CSL presenting as NME on MRI. Furthermore, RSs and CSLs may be occult on MRI. This is important to note because a lack of enhancement may be a predictor of benignity.

RSs without atypia demonstrate variable upgrade rates of 0% to 40%. Factors associated with increased risk for upgrade include size > 2 cm, age > 50 years, and the presence of another high-risk lesion. Therefore, excision may be warranted in cases with these associated factors. In addition, factors that appear to be associated with a lower upgrade or no upgrade risk include biopsies performed with vacuum assistance, a larger gauge needle, and increased number of cores taken. Follow-up can be considered for smaller, incidental lesions when large-core, vacuum-assisted sampling is performed.[32] The current management of MRI-detected RSs is excision as there is a 15% upgrade rate even without atypia.[31] In addition to upgrade risk, RSs have been shown to be an independent risk factor

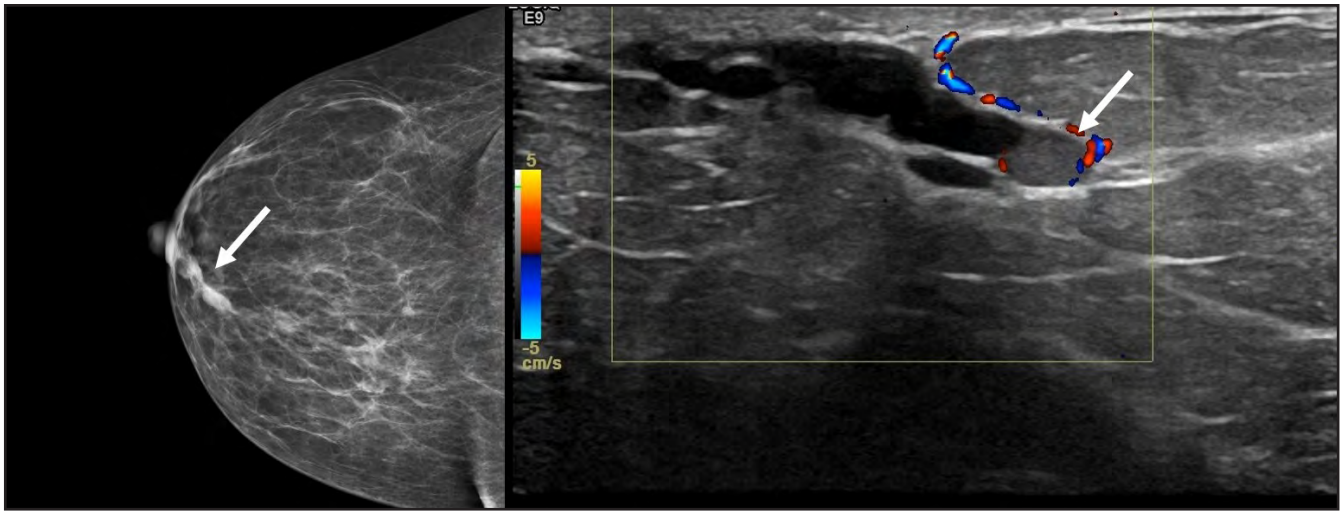

FIGURE 15. *Solitary dilated duct. A 55-year-old woman called back from screening for a solitary dilated duct. CC view from screening demonstrated a solitary dilated duct marked by the white arrow. This persisted on diagnostic mammography and targeted ultrasound was performed. Ultrasound demonstrated a dilated subareolar duct with an intraductal mass demonstrating vascularity at the base. Solitary dilated duct is a special case and should be considered a BI-RADS 4.*

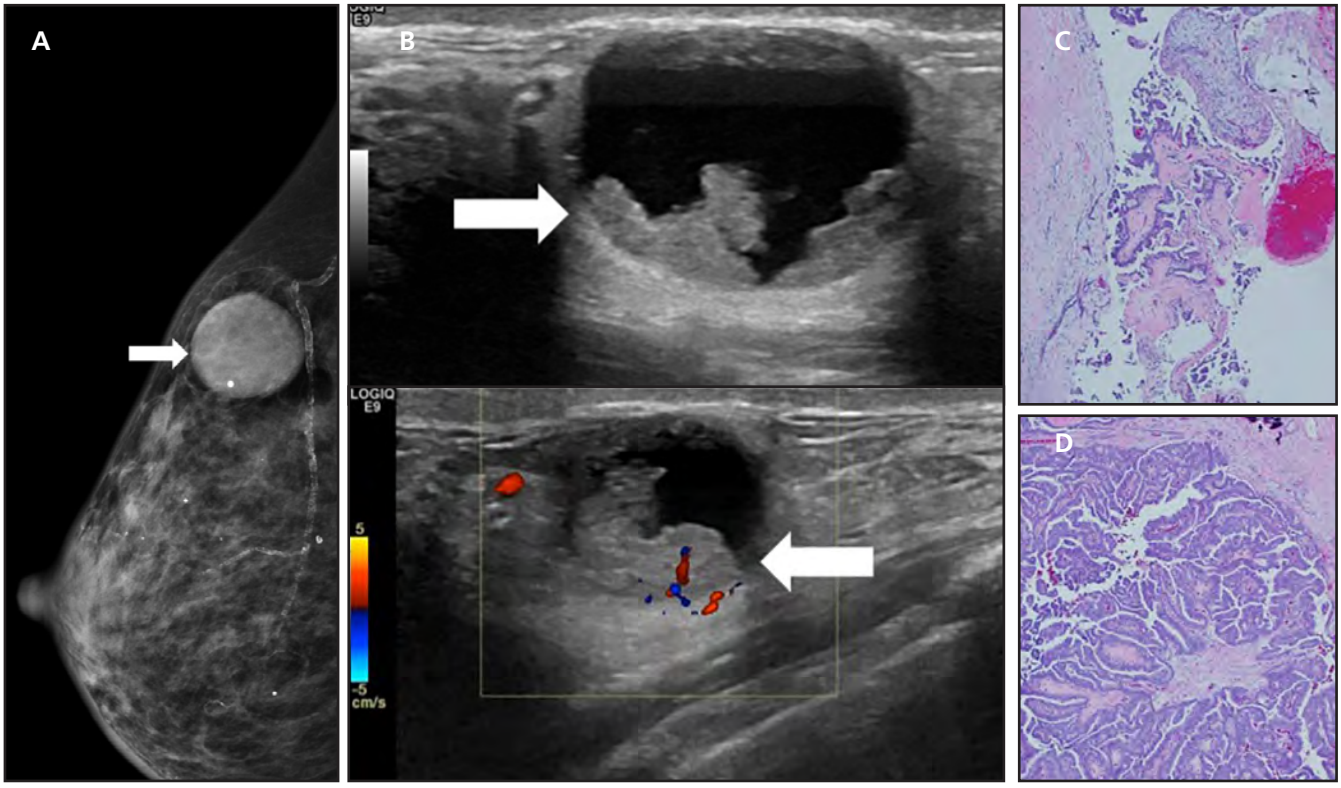

FIGURE 16. *Papillary lesion presenting as a complex cystic and solid mass. An 83-year-old woman presented for a right upper outer quadrant palpable mass. Diagnostic ML view demonstrates a round high-density mass with circumscribed margins deep to the BB placed on the skin, denoting the region of palpable concern (A). Grayscale and color flow ultrasound images demonstrate a complex cystic and solid mass in the 11:00 breast with internal vascularity identified in the solid components of the mass (B). Percutaneous biopsy was performed demonstrating papilloma with atypia. Excision was recommended and DCIS was discovered on excision. Pathology specimens demonstrate papilloma from biopsy (C) and DCIS from excision (D).*

for breast malignancy in some studies, increasing risk to 1.8 times the average breast cancer risk. If atypia is associated with an RS, the risk of malignancy is higher than with atypia alone.[32]

Flat Epithelial Atypia

Flat epithelial atypia (FEA) presents pathologically as an enlarged TDLU lined by a single or 3 to 5 layers of tightly packed columnar epithelial cells with prominent apical cytoplasmic snouts and intraluminal secretions (**Figure 12**).[33,34] Cells have clear or granular cytoplasm, increased nuclear to cytoplasmic ratio, loss of orientation, and incremental

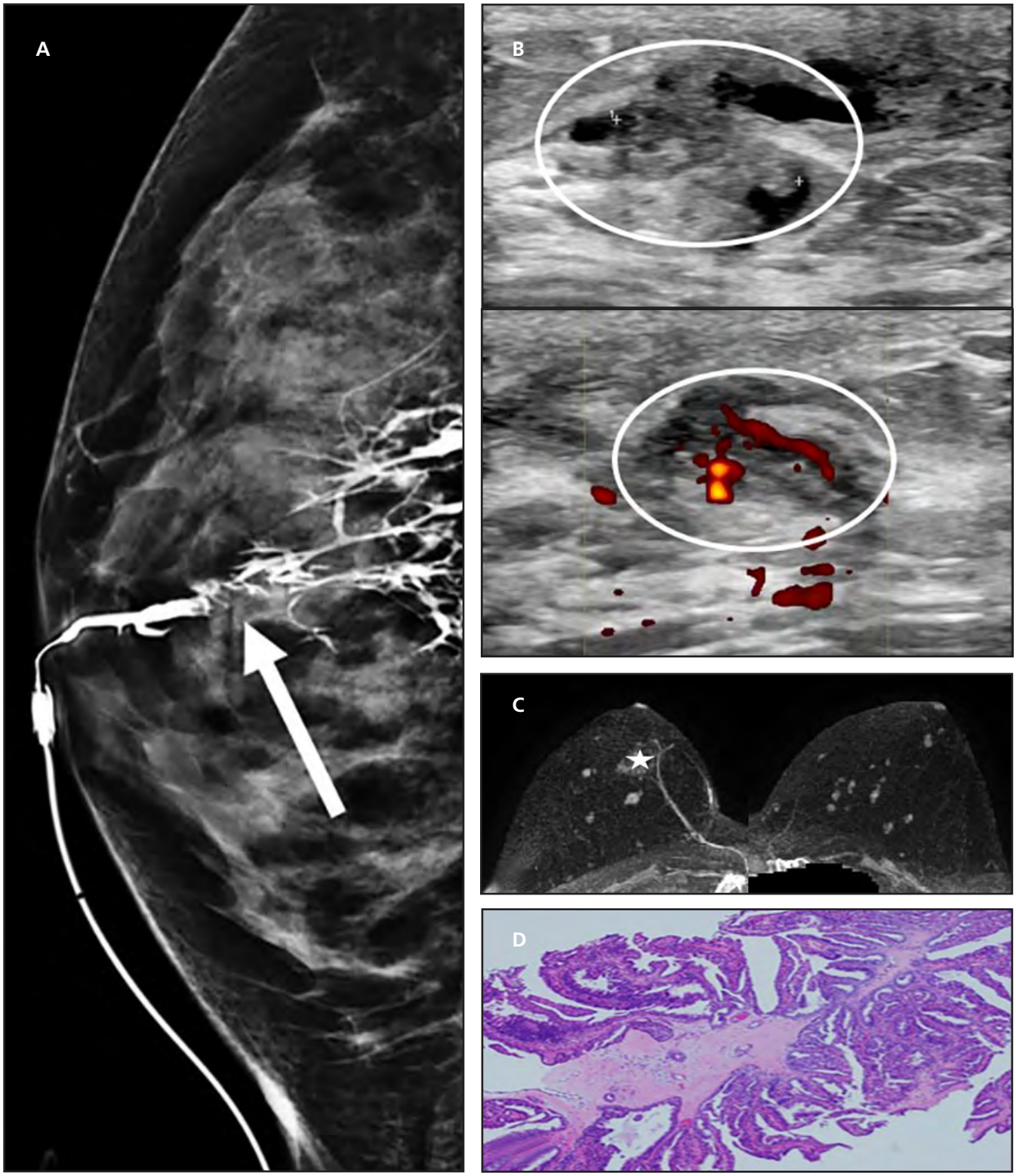

FIGURE 17. *Papilloma presenting as nipple discharge. A 23-year-old woman with spontaneous bloody nipple discharge. Ductography demonstrates an intraluminal filling defect in the subareolar right breast (arrow) (A). Transverse and sagittal ultrasound images demonstrate a corresponding intraductal mass with internal vascularity measuring 11 mm (B). Vacuum-assisted biopsy was performed demonstrating intraductal papilloma without atypia. Nipple discharge stopped after the biopsy. No surgical excision was performed. Subsequent MRI was performed demonstrating multiple bilateral masses as demonstrated on the MRI maximum projection images (C). Postbiopsy change is denoted by the white star. Pathology slide demonstrates a classic appearance of papillae with fibrovascular core (D).*

Table 1. High-risk Lesion Management

Surgical Excision[1]

- CSL
- RS with atypia
- Papilloma with atypia
- MLL with atypia
- FEA + other atypical lesion

Surgical Excision, Risk Assessment, & Counseling on Risk-Reduction Strategies[2]

- Pleomorphic LCIS
- LCIS
- ALH
- ADH

Consider Conservative Management With Follow-up Imaging in 6-12 Months[3]

- Pure FEA
- Papilloma Without Atypia
- MLL Without Atypia
- RS Without Atypia

[1]If excision is not performed, observation with follow-up imaging in 6-12 months.
[2]If excision is not performed, observation with follow-up imaging in 6-12 months, risk assessment, and counseling on reduction strategies.
[3]Patients should have a clinical evaluation, be asymptomatic, have concordant imaging findings, and be assessed for additional risk factors. Discussion within interdisciplinary team preferred.

irregularities without complex architectural atypia.

FEA frequently occurs in asymptomatic patients, detected incidentally. The most common characteristic of FEA across all imaging modalities is an occult presentation. On mammography, it can present as grouped amorphous calcifications. Less commonly, FEA is associated with fine pleomorphic and coarse heterogeneous calcifications. On ultrasound, it may present as an irregular mass, and on MRI it may be associated with nonmass enhancement as depicted in **Figure 13**.

Epithelial atypia is relatively rare, reported in 1% to 17% of breast biopsies.[35] Additionally, the upgrade rate is variable ranging 0% to 20%.[35] The rate increases with concomitant HRLs. FEA frequently coexists with ADH, lobular neoplasia, and indolent malignancies (tubular carcinoma). **Figure 14** demonstrates an example of DCIS with associated FEA presenting as calcifications. Factors associated with increased risk for upgrade rate include older age, African American race, utilization of hormone replacement therapy, and calcifications in the biopsy specimen.[35]

Management of FEA is typically excisional biopsy.[36] Patients with adequate sampling, probable compliance with follow-up, focal pure FEA in the absence of residual calcifications, radiology-pathology concordance, and without personal history of breast cancer may undergo surveillance.[37] No single factor can decide if isolated FEA on CNB should forgo excision. A multidisciplinary evaluation tailored to each patient appears to be the most feasible approach to optimize management.[36,38]

Papillary Lesions

Papillary lesions are described as the proliferation of epithelial cells surrounded by a fibrovascular stalk (**Figure 17D**). Myoepithelial cells may or may not be present. Papillary lesions may be benign but also may be associated with atypia, noninvasive malignancy, and invasive malignancy. Benign solitary central papillomas typically arise from a large central duct. Peripheral papillomas develop in smaller ducts and may be multiple.

On imaging, central papillomas can present as subareolar masses. They may also be symptomatic, presenting with spontaneous clear or bloody nipple discharge. Furthermore, approximately 25% are associated with calcifications. Papillomas may also present as solitary dilated ducts (**Figure 15**). Peripheral papillomas, on the contrary, may present as oval masses but are usually further from the nipple and not in the immediate subareolar region. Peripheral papillomas are typically asymptomatic at presentation. On ultrasound, papillary lesions may present as hypoechoic, solid, oval masses or complex cystic and solid masses (**Figure 16**). An intraductal mass or cyst with a small mural mass is also a classic presentation. Vascularity is sometimes identified in the fibrovascular stalk. Papillary lesions may be identified on MRI examination as oval or round masses that demonstrate homogeneous or heterogeneous enhancement. Galactography is sometimes used to evaluate nipple discharge. Papillomas will appear as intraluminal filling defects on this imaging modality. **Figure 17** demonstrates the imaging work-up for a patient presenting with nipple discharge.

Papillary lesions convey a twofold increased risk for breast cancer development. Papillomas without atypia have a relatively low upgrade rate around 2.3%.[39] As mentioned previously, papillomas may present with pathologic nipple discharge. If the nipple discharge persists following biopsy, excision is recommended for symptomatic treatment. However, without clinical symptoms, conservative management with follow-up imaging in 6 to 12 months may be considered. Additional factors may be utilized to determine whether conservative management is appropriate. Such factors include the following: radiologic-pathologic concordance, vacuum-assisted biopsy device utilization, small size (< 1 to 1.5 cm), being nonpalpable at presentation, and central location. Fulfillment of such criteria may support conservative management. Papillomas with atypia have a significantly higher upgrade rate of up to 36.9%.[40] Surgical excision is recommended for all papillomas with atypia.

Conclusion

Management of benign disease is an important aspect of patient care in breast imaging. Since the literature is constantly evolving, recommendations also change to reflect these updates. From this review of past and recent data, suggestions for management strategies are summarized in **Table 1**. In addition, an integrated approach is needed to consider patient factors such

as past medical history, family history, and clinical presentation. This approach ensures thorough patient evaluation and appropriate multidisciplinary care.

Disclosure

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Imaging Evaluation of Nipple Discharge: Review of Literature and Management Considerations

Stefanie Woodard, D.O.,[1] Elizabeth Allen, M.D.,[1] Kriti Ahuja, M.B.B.S. [2]

[1]Department of Radiology, The University of Alabama at Birmingham, Birmingham, AL
[2]Department of Internal Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL

Nipple discharge is a common and problematic symptom reported by many women seeking evaluation in primary care practices, surgery clinics, and breast radiology facilities. Discharge has been cited as the second to third most reported breast symptom, next to palpable lumps and tenderness.[1-3] Numerous groups have discussed management strategies regarding nipple discharge, and there has been a significant evolution away from surgical intervention.

For the radiologist, nipple discharge can be a dilemma for many reasons. For academic medical centers with the availability of a network of clinical breast care personnel, subspecialty-trained breast radiologists, and breast surgeons, a comprehensive evaluation and management strategy is more realistic. In the community setting, managing a patient with nipple discharge can be challenging due to limited time and resources. Fortunately, the vast majority of patients presenting with nipple discharge can be appropriately triaged with a thorough history and physical examination.

For those requiring imaging, mammography and ultrasound are widely available for initial work-up. MRI has also become more commonplace in recent years and has become an important tool in the evaluation process of nipple discharge. Ductography, which is decreasing in popularity, may continue to play a specific role in managing nipple discharge; however, the availability of skilled practitioners may be limited. Our aim in this review is to discuss features that differentiate physiologic from pathologic nipple discharge, provide a literature summary to guide imaging recommendations, and introduce a flow chart as an overview for step-by-step management for the radiologist.

Physiologic vs Pathologic Nipple Discharge

When evaluating a patient with nipple discharge, one of the first steps in a management approach is obtaining a clinical history as well as performing a thorough focused physical examination. In many radiology practices, this is limited given the demands of daily workflow. A clinical office visit may not occur before imaging evaluation, and the patient's history may not be routinely available upon presentation. One option for radiology practices could be to elicit specific information on a history sheet from each patient presenting with discharge to help guide management. An example of a patient survey is provided, which outlines several of the salient clinical questions pertinent to work-up (**Figure 1**).

The definitions of physiologic and pathologic nipple discharge pertain to processes that happen within epithelial cells that line the ductal system. Fluctuations in hormone levels including prolactin, estrogen, and progesterone impact the production of fluid secretions. In addition to hormone stimulation, the natural process of cell death with continuous sloughing of the epithelial lining contributes to such secretions. These processes are responsible for physiologic discharge and account for the nonmalignant etiologies.[4]

Features of physiologic nipple discharge commonly discussed throughout literature include the following: bilaterality, nonbloody (yellow, green, milky, gray) color, multiduct location, and nonspontaneous expression.[5] The consensus for work-up of this type of discharge makes the imaging algorithm fairly simple for the radiologist. Once discharge is identified as physiologic, the likelihood of malignancy significantly diminishes.[6] In addition, this type of discharge frequently resolves over 1 to 6 months.[6] Standard imaging evaluation typically involves ensuring the patient has undergone recent mammographic evaluation and performing a target ultrasound if requested; however, the American College of Radiology (ACR) appropriateness criteria does not recommend any imaging for this type of discharge.[7] For physiologic discharge, the color may direct subsequent management. For instance, lab work may be indicated in the setting of milky (prolactin level) or purulent (complete blood count [CBC]) discharge. Discharge that potentially meets these benign criteria may still cause unpleasant symptoms and warrant evaluation and treatment.

Pathologic discharge is discussed throughout literature as being serous or bloody, spontaneous, unilateral, and

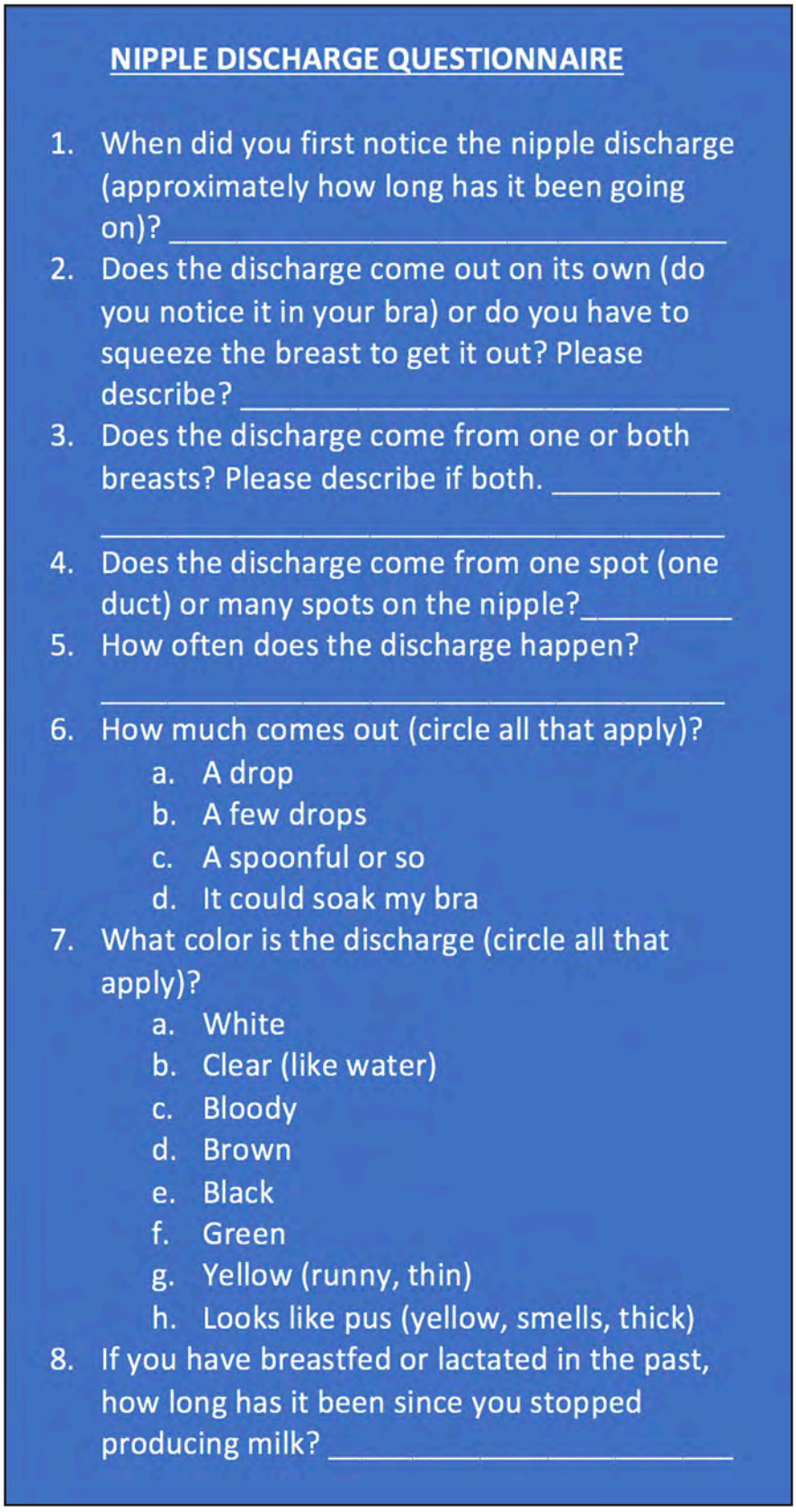

FIGURE 1. *Nipple discharge questionnaire.*

single duct.[4,5] Numerous studies discuss features of discharge and factors predictive of malignancy. Bloody discharge has been demonstrated as a significant predictor of malignancy.[8] In addition, single duct discharge is also known to have a significant association with malignancy.[9] While such factors may prompt more vigorous work-up, discharge that is persistent or copious without single duct or bloody characteristics may still raise clinical concern.

Mammography and Ultrasound

According to the ACR appropriateness criteria, the management of nipple discharge depends on numerous factors including patient age (under 30 or over 40), biological gender, characteristic of discharge (pathologic or nonpathologic), and availability of advanced imaging modalities.[7] The first specification of the appropriateness criteria separates physiologic discharge from the management tree. No imaging is recommended in the setting of physiologic discharge. Because patients are often sent for evaluation without a thorough assessment of the nature of discharge and since these patients commonly have not undergone recent mammography, they may need work-up in a diagnostic clinic to discern the type of examination needed. If possible in a breast imaging center, the ideal scenario would involve a discussion with these symptomatic patients, triaging those in need of imaging. Furthermore, physical examination may confirm discharge characteristics or redirect management strategy. This ideal setting is less common than the typical scenario, which involves a patient presenting with no provided information regarding discharge characteristics and no reported physical examination findings. For this reason, mammography is often performed in women over age 40 who have not undergone mammographic imaging for the past year. With the supportive information of physiologic discharge, this should be a screening mammogram.[4]

In the setting of pathologic discharge, the recommendation is to begin

Figures 2-5. The patient is a 66-year-old woman with a history of right breast ER-, PR- DCIS diagnosed 6 years prior. She presented with new clear single-duct left nipple discharge from a central/12 o'clock orifice.

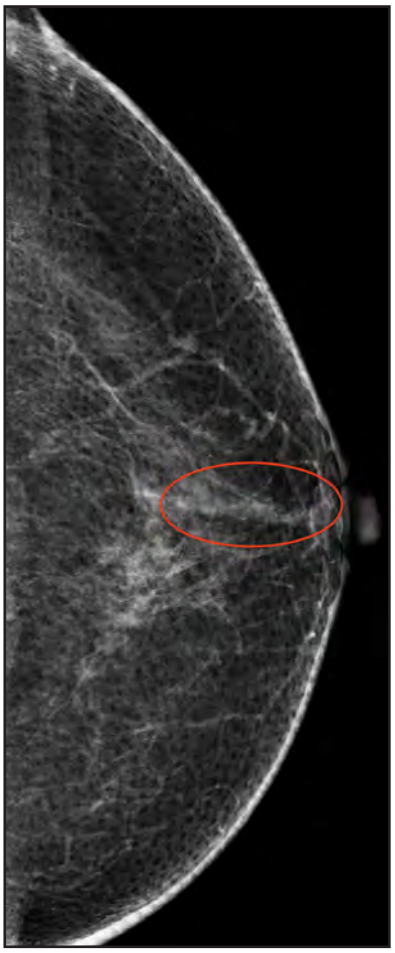

FIGURE 2. *Left CC view full-field mammogram demonstrates a solitary dilated duct (oval) in the central breast at anterior depth.*

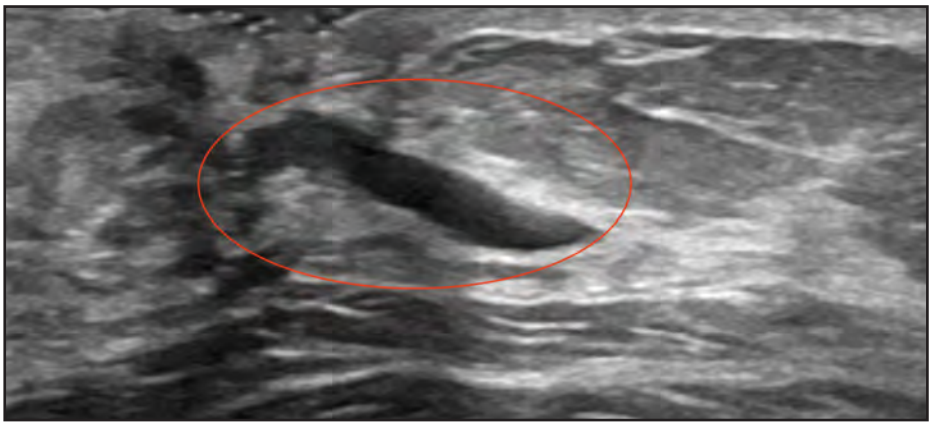

FIGURE 3. *Targeted B-mode ultrasound of the subareolar region of the left breast in the transverse plane demonstrates a dilated duct with internal echoes (oval) corresponding to the mammographic finding. The differential considerations include a duct with debris vs an intraductal mass distending a duct.*

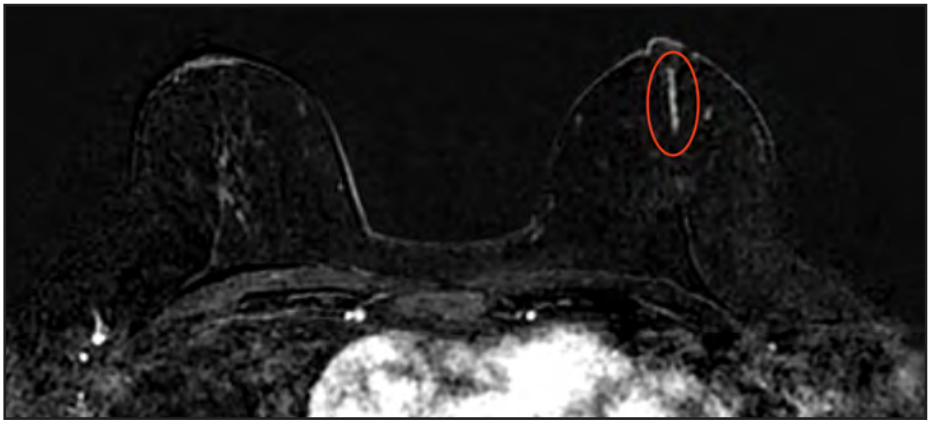

FIGURE 4. *Bilateral T1-weighted, contrast-enhanced subtraction breast MRI in the axial plane; first postcontrast phase demonstrated linear nonmass enhancement in the left central breast at anterior depth (oval). Ultimately, biopsy performed under MRI guidance demonstrated a papilloma.*

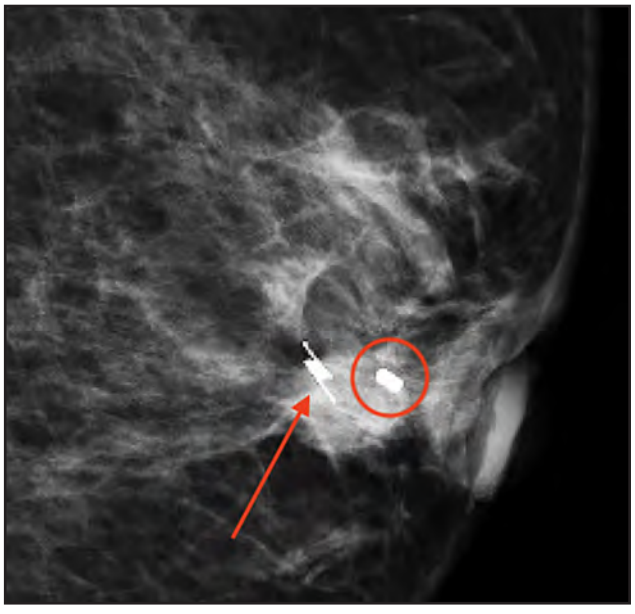

FIGURE 5. *Full-field ML mammogram from a Savi Scout localization procedure demonstrates the Savi device (arrow) just posterior to the biopsy clip (circle), demarcating the lesion location. No upgrade was noted at the time of excision.*

with diagnostic mammography and ultrasound in patients over age 30. Under age 30, the recommendation supports ultrasound as the initial imaging modality.[7] Although mammography is not the most sensitive modality in the assessment of nipple discharge, normal mammography and ultrasound imaging combined with an otherwise normal physical examination (no palpable abnormality) have been shown to be predictive in confirming benignity with only 1 out of 287 malignancies found by Sabel et al.[10] In this study, the 1 malignancy was found in a patient who had a history of breast cancer. Excluding this history resulted in no malignancies diagnosed in patients with normal diagnostic mammosonography.[10] Gray et al had a similar experience in 204

Figures 6-8. The patient is a 66-year-old woman who presented with right single-duct bloody nipple discharge.

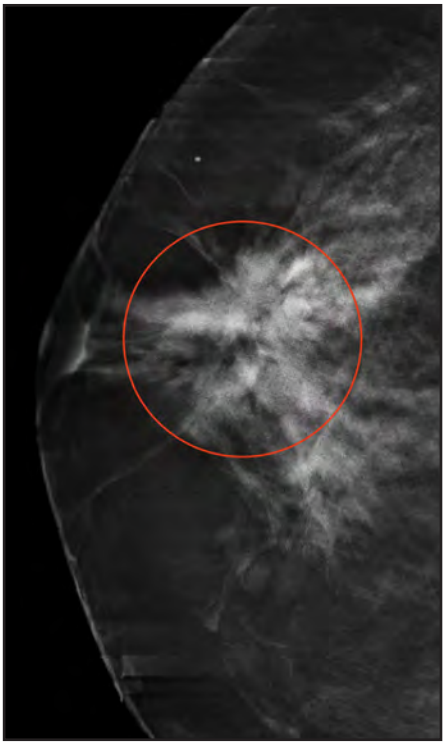

FIGURE 6. *Right breast spot CC tomosynthesis demonstrates architectural distortion in the central breast anterior depth (circle).*

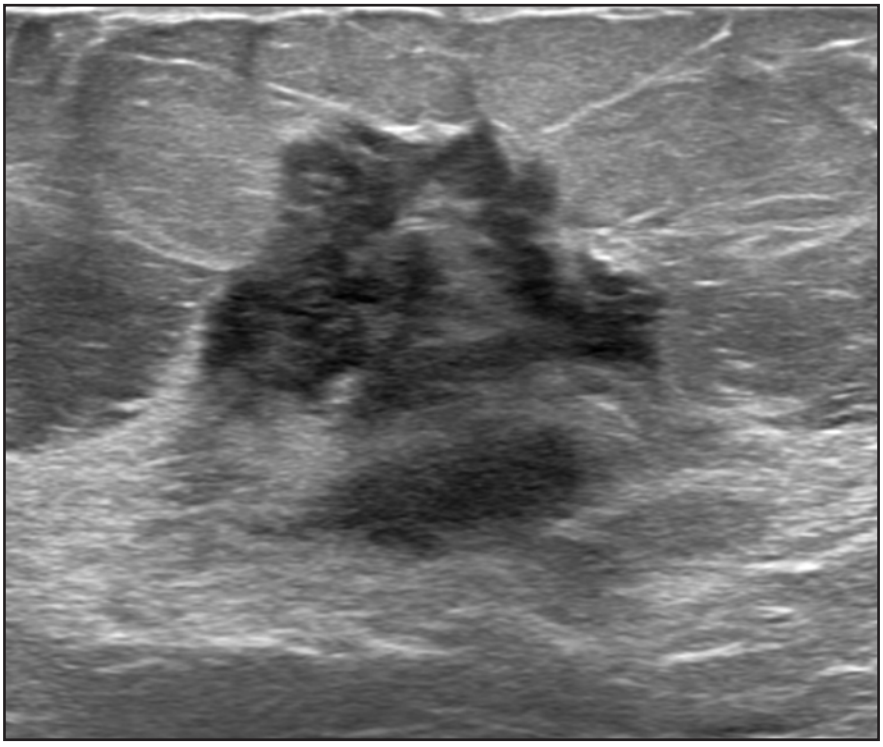

FIGURE 7. *Right breast targeted B-mode grayscale ultrasound image in the transverse plane demonstrates an irregular mass at 12 o'clock in the subareolar location.*

patients, finding that abnormal mammograms and ultrasounds were predictive of malignancy. In addition, suspicious discharge (in this study, spontaneous, bloody, unilateral, or serous) in the setting of a negative mammogram resulted in an overall risk of malignancy of 3%. When combined with a subareolar ultrasound, the risk was 0%.[11]

Ultrasound has also been widely used in assessing nipple discharge with studies showing increased cancer detection when added to mammography.[12] During routine investigation of discharge, ultrasound plus mammography significantly increases sensitivity.[13] Elastography has been investigated as a tool to better characterize intraductal masses. In a study by Zhu et al, supplemental elastography increased both specificity and accuracy compared with ultrasound alone.[14] Numerous studies have also documented the benefit of ultrasound in conjunction with galactography[15,16] as well as combining ultrasound with galactography and MRI.[17]

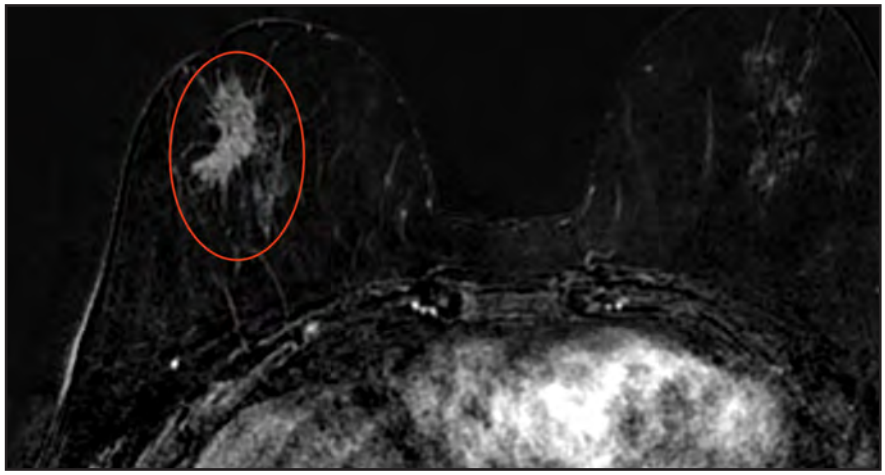

FIGURE 8. *Bilateral T1-weighted, contrast-enhanced subtraction breast MRI in the axial plane, first postcontrast phase, demonstrates an irregular mass with spiculated margins, spanning 11 and 12 o'clock at anterior and middle depth. Pathology of biopsy demonstrated estrogen receptor positive and progesterone receptor positive (ER+ PR+) high-grade ductal carcinoma in situ (DCIS). On mastectomy, no upgrade was noted.*

Imaging with mammography in cases of nipple discharge, whether due to benign or malignant causes, is often normal. Several mammographic findings have been described including the following: mass, duct ectasia, focal asymmetry, solitary dilated duct, and microcalcifications. Pathologic causes of nipple discharge manifest on ultrasound as masses (sometimes intraductal, typical of papillomas or ductal carcinoma in situ [DCIS]), duct ectasia, or cysts. Calcifications can also be seen on ultrasound, either within a mass,

outside of a mass, or inside the ductal system. A fluid collection can also be seen in cases of nipple discharge. For example, cases of nipple discharge with infectious causes may detect an abscess and cases of postoperative discharge may find seromas or hematomas. Characteristics of malignant ultrasound-detected masses have been reported more commonly as hypoechoic with irregular margins. Benign characteristics tend to favor anechoic and hypoechoic masses with circumscribed margins. Heterogeneity and complex cystic solid features can be seen in both benign and malignant cases but tend to be more common in the malignant category.[18] **Figures 2-14** demonstrate mammographic and sonographic findings from initial work-up of three cases of pathologic discharge, one due to a papilloma (**Figures 2-5**), one due to high-grade DCIS (**Figures 6-8**), and one case of low-grade DCIS (**Figures 9-14**). Each of these cases also underwent MRI evaluation (**Figures 4, 8, and 14**).

Figures 9-14. The patient is a 49-year-old woman presenting with persistent two-duct discharge in the upper outer nipple duct system, involving ducts at approximately 10 and 11 o'clock. She underwent mammographic imaging followed by ultrasound evaluation. MRI was then performed.

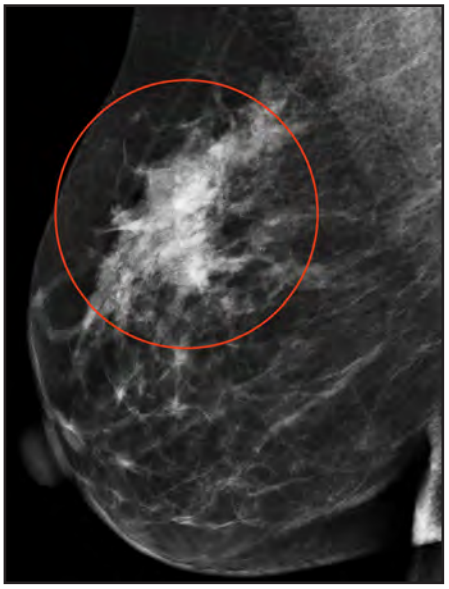

FIGURE 9. *Right full-field MLO*

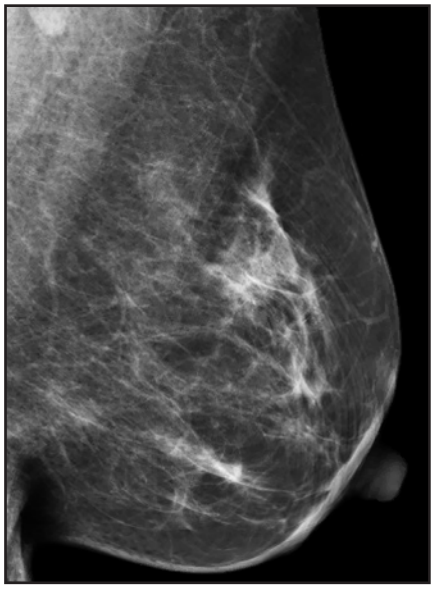

FIGURE 10. *Left full-field MLO*

Figure 9 and Figure 10 demonstrate a right breast MLO-view asymmetry in the superior breast at middle depth. Figure 9 compared to Figure 10 demonstrates an overall increase in tissue density in the superior breast middle depth. Finding is only seen in MLO view (CC not shown), and this was the patient's baseline exam.

MRI

Although for over 20 years the role of MRI has been studied in the assessment in nipple discharge,[19] many radiologists still debate its utility. The added value of MRI to the work-up of nipple discharge is supported by multiple studies, including a 2011 study by Lorenzon et al, which showed better sensitivity and specificity compared with mammography and ultrasound.[20] A 2015 study by Bahl et al showed that in patients with benign sonomammography, negative/benign/probably benign MRI assessments had 100% sensitivity and 100% negative predictive value (NPV).[21] In 2017, a retrospective review by Bahl et al confirmed these findings (those with MRI of BI-RADS 1, 2, or 3) with demonstrating a < 4% risk of malignancy in women with negative or inconclusive mammograms.[22] Recently, Zacharioudakis et al discussed the use of MRI in the management of nipple discharge in a prospective study involving 82 patients over a 9-year period who underwent mammography and ultrasound examinations with the detection of malignancy in 14 patients who had normal mammographic and sonographic evaluation. MRI was performed on all patients as a part of standard protocol and demonstrated sensitivity, specificity, positive predictive value (PPV), and NPV of 85.71%, 98.53%, 92.31%, and 97.1%, respectively.[23] In 2019, a similar study by Zaky et al reported these measures as 100%, 83.3%, 63.6%, and 100%, respectively.[24]

The ACR appropriateness criteria addresses the use of MRI in the evaluation of nipple discharge; however, for the variants listed in the appropriateness criteria, MRI is listed as a 'usually not appropriate' radiologic procedure. This rating is given because each variant addresses only the initial imaging examination for the given scenario. The literature summary in the ACR Appropriateness Criteria goes on to discuss MRI as a valuable tool.[7]

MRI has been compared with numerous other imaging modalities. In 2003, Nakahara et al reported that compared with galactography and ultrasound, MRI better demonstrated the imaging features of ductal carcinoma DCIS in patients presenting with bloody nipple discharge.[25] In 2015, Manganaro et al concluded that MRI had higher sensitivity and specificity compared to galactography in those with clear or bloody discharge.[26] Berger et al performed a review of MRI compared to galactography, published in AJR in 2017. They reviewed 10 studies involving 921 patients. Their findings support the use of MRI over galactography in the setting of negative mammosonography.[27] In 2014, Lubina et al reported a prospective study of patients with nipple discharge performed using a 3 Tesla (3T) MRI and compared findings to galactography. Based on their results, the recommendation was to replace galactography with 3T MRI due to the improved correlation with lesion size.[28]

On MRI, various features have been described to correlate with suspicious

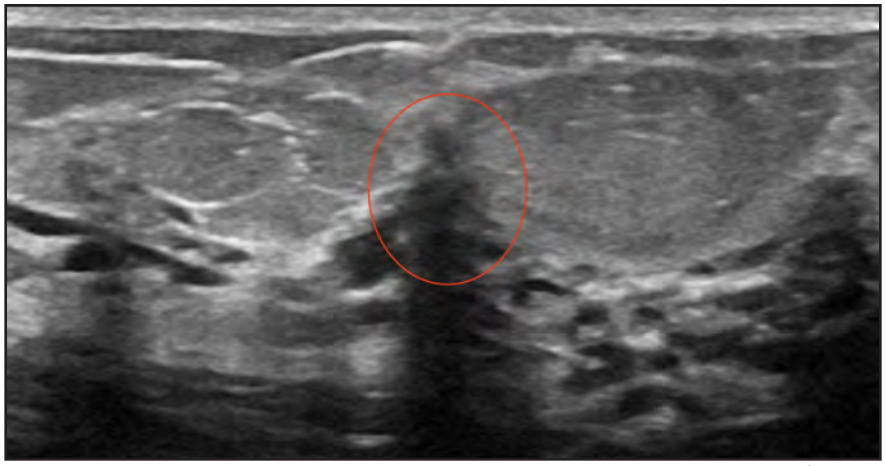

FIGURE 11. *B-mode grayscale targeted ultrasound in the right breast at 12 o'clock 2 cm from the nipple in the transverse plane.*

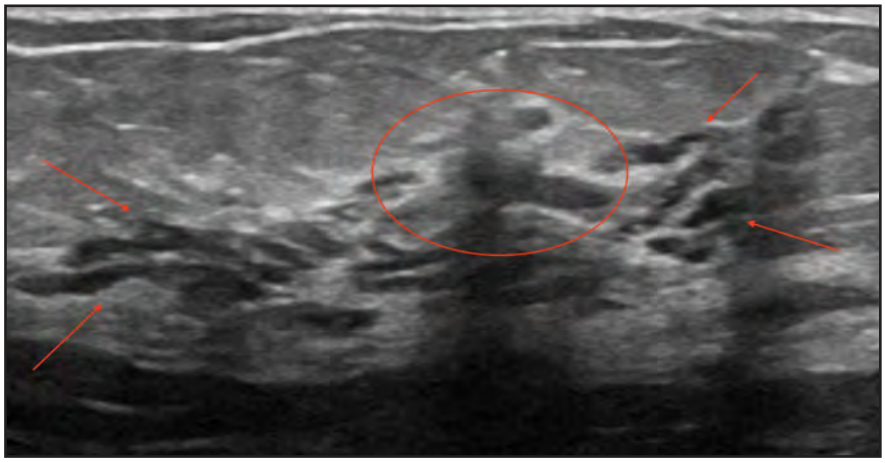

FIGURE 12. *B-mode grayscale targeted ultrasound in the right breast at 12 o'clock 2 cm from the nipple in the sagittal plane.*

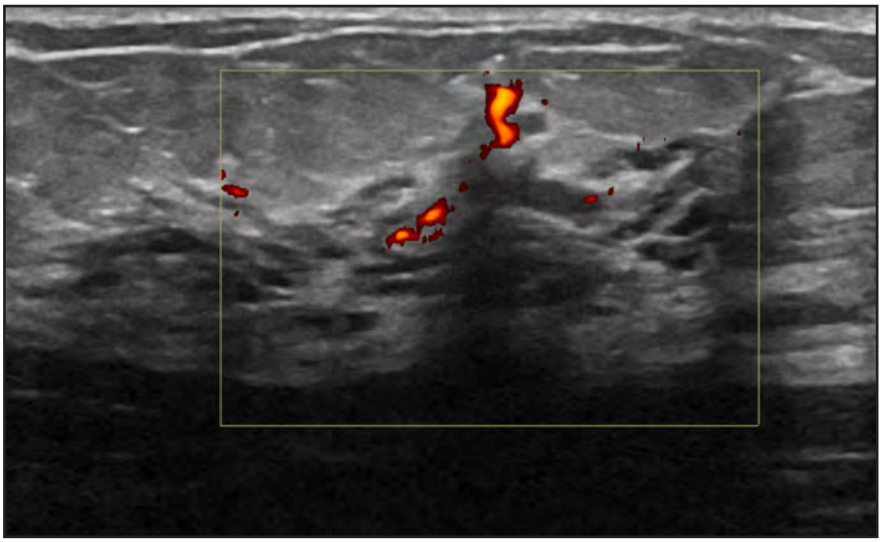

FIGURE 13. *Power Doppler imaging in the sagittal plane*

Figure 11 and Figure 12 demonstrate an irregular hypoechoic not parallel mass with indistinct margins (oval). There is posterior shadowing. Associated abnormal duct changes are noted in a segmental distribution (arrows). Figure 13 demonstrates internal vascularity involving the mass.

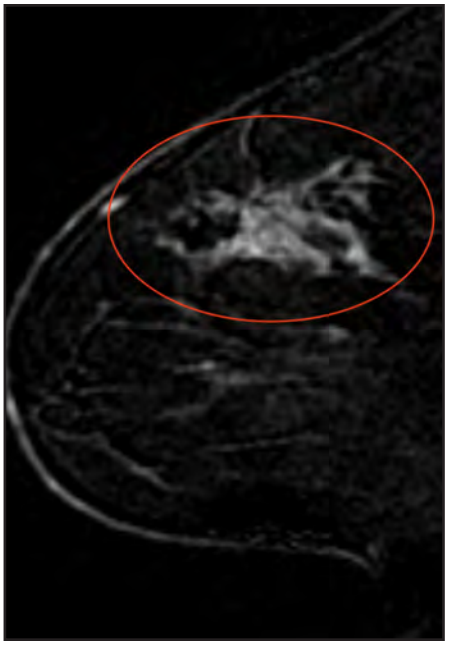

FIGURE 14. *Sagittal T1-weighted, contrast-enhanced subtraction MRI of the right breast demonstrates clumped segmental nonmass enhancement at 12 o'clock middle depth. Pathology demonstrated ER+ PR+ DCIS with micropapillary and cribiform patterns.*

nipple discharge. Nonmass enhancement (previously described as nonmass-like enhancement) was most common with a segmental distribution, heterogeneous internal enhancement, and plateau kinetics. Additional malignant appearance included clustered-ring enhancement.[29] Benign features responsible for pathologic discharge may include nonenhancing proteinaceous debris within the ducts, duct ectasia, cysts, and fluid collections (similar to ultrasound). Other common MRI findings that have been reported in patients presenting with nipple discharge include masses that vary in appearance from those with irregular margins to those with circumscribed margins. Diffuse enhancement has also been noted, which is by far a benign characteristic.[18] **Figures 4, 8, and 14** are selected images from MRIs performed in patients experiencing nipple discharge. Characteristics include linear nonmass enhancement (**Figure 4**) corresponding to a papilloma, an irregular mass (**Figure 8**) corresponding to high-grade DCIS, and clumped segmental nonmass enhancement (**Figure 14**) corresponding to low-grade DCIS. In **Figures 15-23**, the use of

Figures 15-17. The patient is a 23-year-old woman with a history of unilateral one-duct spontaneous discharge initially nonspontaneous. She presented for evaluation, which was first performed with ultrasound.

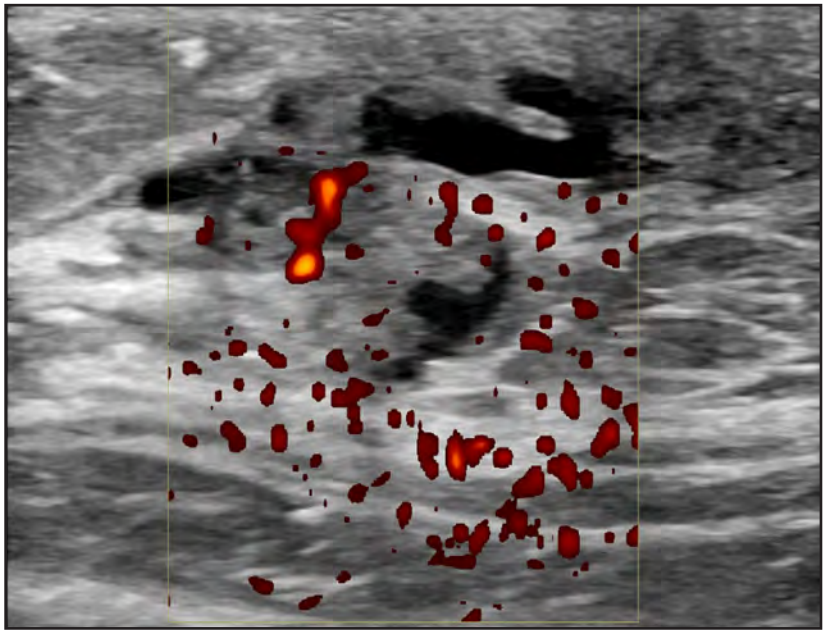

FIGURE 15. *Power Doppler imaging in the sagittal plane demonstrates an intraductal mass in the right breast 1 o'clock subareolar location showing internal vascularity.*

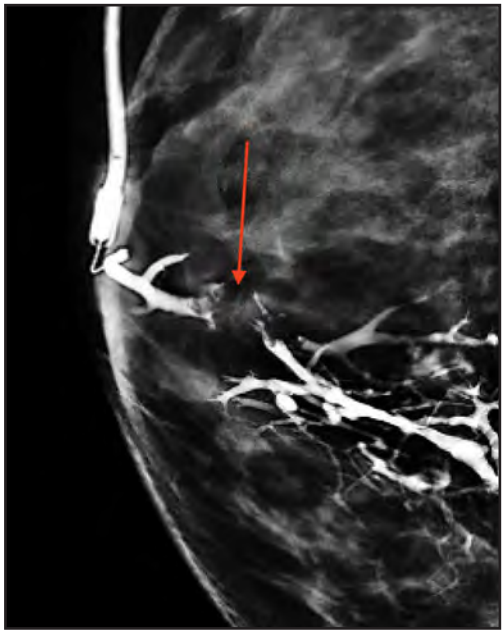

FIGURE 16*. Right CC ductogram demonstrates an intraductal filling defect (arrow) at 1 o'clock anterior depth. Biopsy demonstrated intraductal papilloma without atypia.*

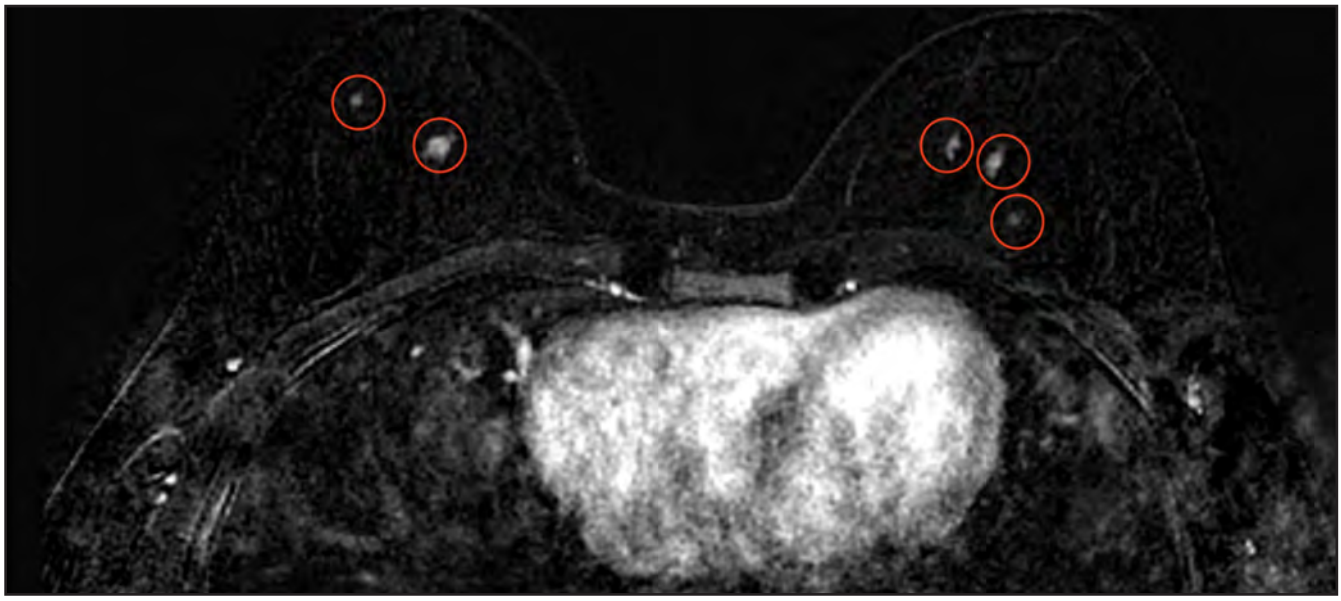

FIGURE 17. *Bilateral T1-weighted, contrast-enhanced subtraction breast MRI in the axial plane; first postcontrast phase demonstrates multiple bilateral oval enhancing masses (circles). No discrete enhancement could be seen at the site of right 1 o'clock biopsy (not shown). Ultimately, the decision was for surveillance due to the number and similarity of lesions. A follow-up MRI in six months demonstrated stability. Discharge did not recur after biopsy.*

MRI is illustrated in both benign and malignant scenarios. In **Figure 17**, MRI was utilized for management purposes in a 23-year-old woman who underwent biopsy of a papilloma (producing nonspontaneous single-duct unilateral bloody nipple discharge) with vacuum-assistance. **Figures 15** (ultrasound) **and 16** (ductogram) provided depiction of the lesion of interest, which was the intraductal mass (papilloma). MRI (**Figure 17**) changed management when numerous bilateral similar-appearing enhancing masses were seen, any of which could represent additional papillomas. Discharge had resolved after biopsy and no enhancement was seen at the biopsy site. Surveillance with MRI was, therefore, chosen instead of surgical excision.

Figures 18, 19. The patient is a 66-year-old woman with a history of right breast, single-duct brown nipple discharge.

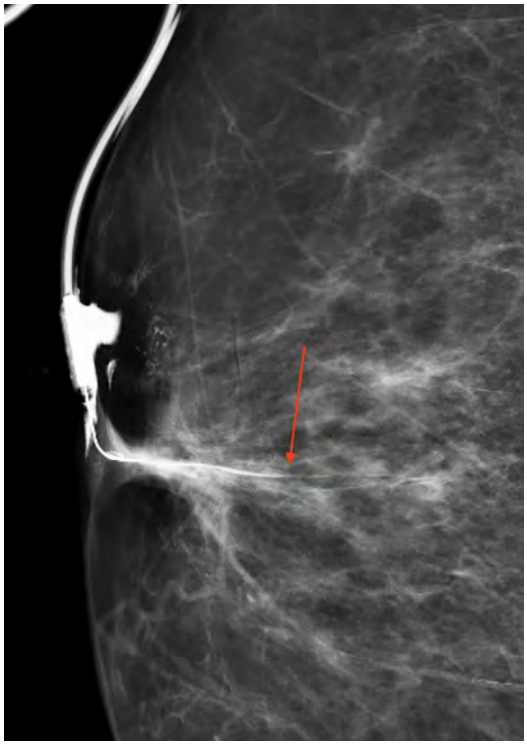

FIGURE 18. *Right ML ductogram demonstrates poor filling and opacification of the central duct system with duct cut-off (arrow).*

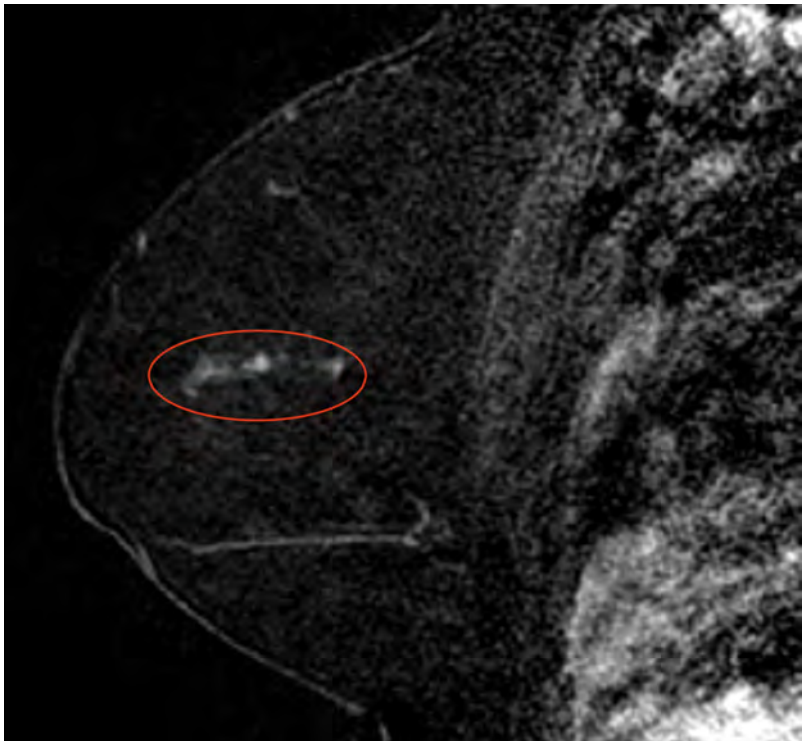

FIGURE 19. *Sagittal T1-weighted, contrast-enhanced subtraction MRI of the right breast demonstrates linear clumped nonmass enhancement in the right central breast at middle depth (oval). This abnormal enhancement initiates at the site of duct cut-off seen on galactogram (A), and biopsy was performed under MRI guidance. Pathology yielded papillary DCIS.*

Ductography

Ductography, or galactography, involves injection of a contrast agent into the discharging duct followed by mammography. The utility of ductography has been questioned in recent years with several publications documenting the improved performance of other imaging modalities. Ductography has been utilized for decades in the assessment of nipple discharge. While it may not be needed for many cases, galactography provides anatomic information that can guide surgical management.

A clear benefit of galactography is the concept of isolating a specific ductal system. This has been supported throughout literature; for example in 1983 by Tabar et al, demonstrating the less invasive surgical measures needed with use of ductography.[30] In assessing the use of galactography in unilateral discharge, Florio et al in 1999 noted an improved detection of malignancy and high-risk lesions,[31] and in 2001 Hou et al showed similar benefits.[32]As more studies investigated the utility of galactography, metrics were found to be less impressive, showing a sensitivity and specificity of 31.2% and 97.4%, respectively, according to Dinkel et al.[33] Additional investigation in 2003 described certain features on galactography that had varying predictors with the following sensitivity/specificities: filling defect 55.6% and 62.1%, duct ectasia 22.2% and 94%, filling stop (termination of the duct) 5.6% and 77.6%. In contrast, a normal ductogram was 93% specific for absence of disease but only 78% sensitive.[34] A similar description of such imaging features of galactography was supported by Kim et al in 2008.[35] More recently in 2018, Istomin et al sought to revisit the role of galactography in the evaluation of pathologic nipple discharge in 146 patients. These patients underwent standard imaging as well as breast MRI, and the calculated sensitivity and specificity of those tests included 77.4%, 75.7% (galactogram) vs 85.7% and 71.4% (MRI).[36]

Galactography can isolate the site of interest specifically; however, internal features of the causative lesion itself are not assessed. Galactography does assess the changes of the ductal system that occur due to mass effect. Reported galactogram findings include most commonly a solitary filling defect. Other reported findings include irregular appearance of the duct wall, multiple filling defects, and a duct cut-off. Normal ductography as well as a limited or incomplete galactogram are also reported.[18] **Figures 16, 18, 24, and 27** demonstrate ductography findings in patients with pathologic nipple discharge. The pathologies include papilloma, papillary DCIS, atypical ductal hyperplasia (ADH) with other high-risk lesions (radial scar, complex sclerosing

Figures 20-23. Patient is a 50-year-old woman who presented with new unilateral right spontaneous green nipple discharge. She had a history of right breast invasive ductal carcinoma (IDC) and DCIS, triple positive, treated with lumpectomy and radiation 13 years ago.

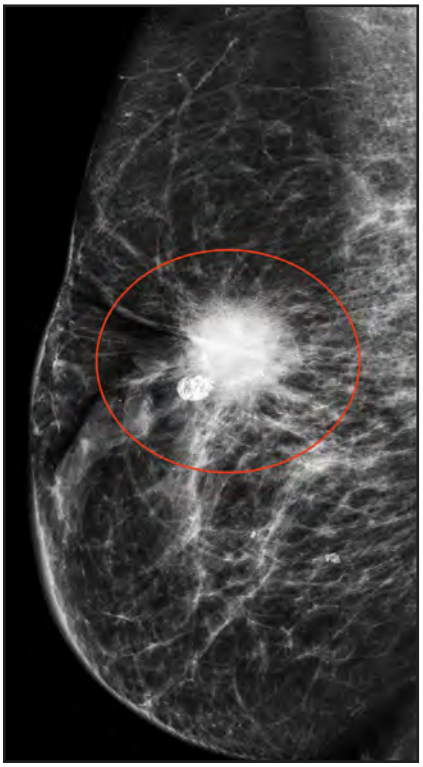

FIGURE 20. *Right MLO view full-field mammogram (current))*

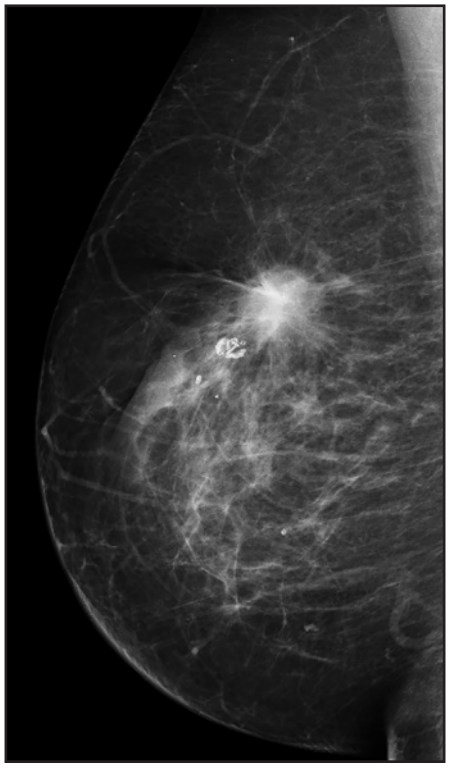

FIGURE 21. *Rght MLO view full-field mammogram (3-year prior)*

Figure 20 and Figure 21 demonstrate a developing asymmetry (oval) at 12 o'clock middle depth. There is also increased trabecular thickening and overall shrinking of the breast.

lesion and papilloma), and papilloma with atypia, respectively. **Figures 24-26** demonstrate a work-up of unilateral single-duct bloody nipple discharge, for which mammography and initial ultrasound were negative. After ductogram (**Figure 24**), ultrasound (**Figure 25**) was able to appropriately identify a small intraductal mass corresponding to a filling defect. Ductogram also aided in localizing the abnormal ductal system for surgery. **Figures 27-29** provide a similar management technique. Neither case underwent MRI evaluation, which may have impacted management.

Less Commonly Used Imaging Modalities

Molecular breast imaging (MBI) and positron emission mammography (PEM) currently are not recommended in the evaluation of nipple discharge per the ACR appropriateness criteria.[7] Both modalities can identify metabolically active processes within the breast; however, evidence is lacking for their routine use in the evaluation or management of discharge.

Contrast-enhanced spectral mammography (CESM) has not been widely studied in patients presenting with nipple discharge. Certain causes of nipple dis-

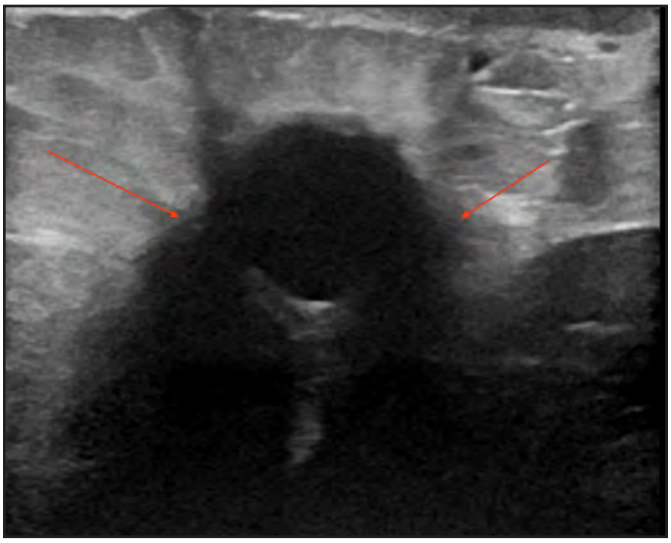

FIGURE 22. *Targeted B-mode ultrasound of the 12 o'clock subareolar region of the right breast in the transverse plane demonstrates a fluid collection with indistinct margins (arrows) corresponding to the mammographic finding.*

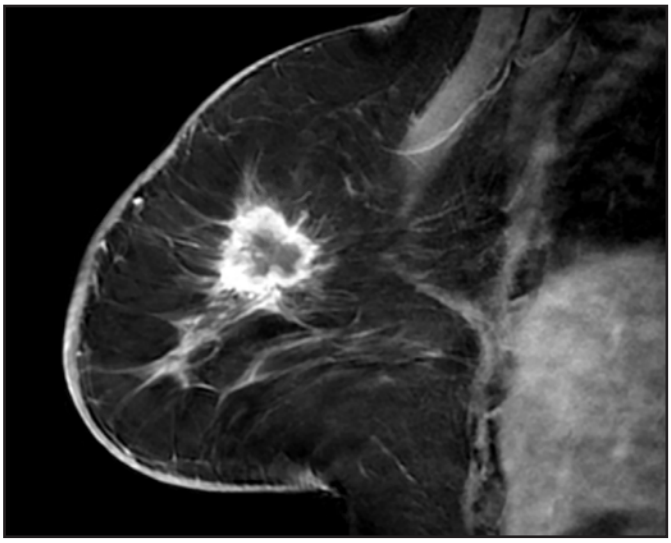

FIGURE 23. *Sagittal T1-weighted, contrast-enhanced fat-subtraction MRI of the right breast demonstrates an irregular fluid collection with thick rim enhancement immediately adjacent to the finding on ultrasound. This was not seen on ultrasound. Biopsy of her lumpectomy bed ultimately showed recurrent IDC.*

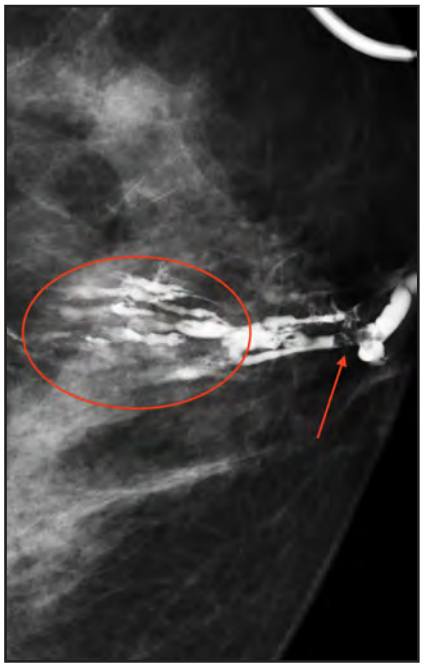

FIGURE 24. *Left CC full-field mammogram obtained after the administration of intraductal contrast. An intraductal filling defect can be seen in the central breast (arrow) at anterior depth along with an overall irregularity of the ductal system (oval).*

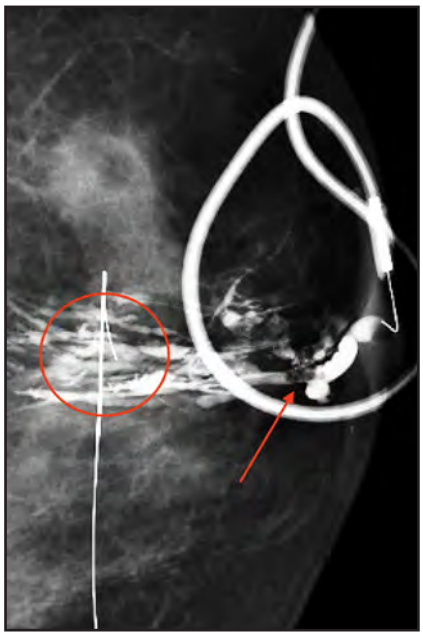

FIGURE 26. *Ductogram localization in the CC projection demonstrating filling defect (arrow) again in the central breast anterior depth. The posterior extent of the irregular ductal system (oval) is marked by the thick portion and hook of the wire. Pathology after duct excision demonstrated atypical ductal hyperplasia (ADH), radial scar, complex sclerosing lesion, and papilloma.*

Figures 24-26. The patient is a 48-year-old woman presenting with a history of bloody left nipple discharge. Initial mammographic and ultrasound imaging were noncontributory. Intraductal administration of a water-soluble iodinated contrast (Iohexol, Omnipaque 350) is required for obtaining galactography imaging. A lidocaine/prilocaine (EMLA) cream is applied to the nipple followed by a warm compress prior to the procedure. The nipple is cleansed and the duct is cannulated with a 30-gauge sialogram catheter. Approximately 1 mL of contrast is injected and mammography images are obtained, typically first with full-field imaging followed by magnification views.

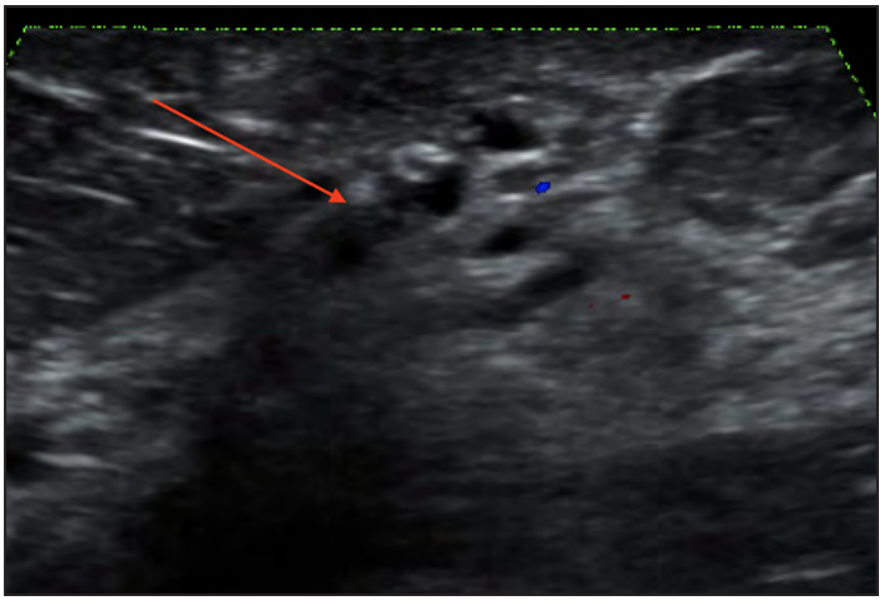

FIGURE 25. *Target ultrasound of the left retroareolar region at the level of the nipple demonstrates an intraductal mass (arrow). Images obtained with color flow, which does not demonstrate internal vascularity. The sonographic findings were thought to represent debris.*

charge, such as papillomas and DCIS, are known to be visualized with CESM. The performance of CESM compared with MRI was evaluated by Hegazy et al in a 2020 retrospective review of 37 biopsy-proven papillomas. This study reported that CESM was significantly lacking in specificity for papillomas of all sizes and sensitivity for lesions < 5 mm.[37] At this time, CESM is not recommended in the routine evaluation of nipple discharge.[7]

MR ductography, which uses a heavily T2-weighted sequence to better identify intraductal lesions, has been described by several authors. It can be performed in conjunction with the administration of IV contrast and, subsequently, the T2-weighted and contrast-enhanced images are fused.[38] In 2010, this technique was compared to conventional galactography and was proposed as a comparable alternative by Wenkel et al.[39] In 2015, Nicholson et al similarly used contrast-enhanced MRI, conventional galactography, and MR galactography to evaluate a small group of patients (n = 20) in a feasibility study. They reported sensitivity, specificity, PPV, and NPV as 65, 33.3, 76.5, and 22.2 for conventional galactography, vs 95, 66.7, 90.5, and 80.8 for contrast-enhanced MRI, and 55, 66.7, 84.6, and 30.8 for MR galactography.[40] As recently as 2020, the use of MR ductography was retrospectively evaluated by a group in Thailand, showing a sensitivity of 100%, NPV of 100%, but specificity of 38%.[41] Currently, the use of MR ductography for evaluating nipple discharge is not endorsed by the ACR appropriateness criteria.[7]

Figures 27-29. The patient is a 57-year old woman who presented with unilateral spontaneous clear nipple discharge. Yellow-tinged discharge elicited from one duct upon physical examination.

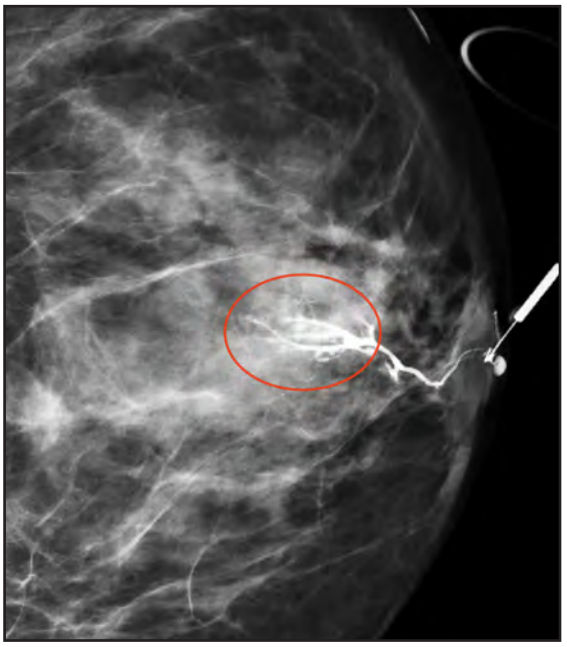

FIGURE 27. *Left full-field CC ductogram demonstrates irregularity of the 12 o'clock ductal system with termination of the ductal system.*

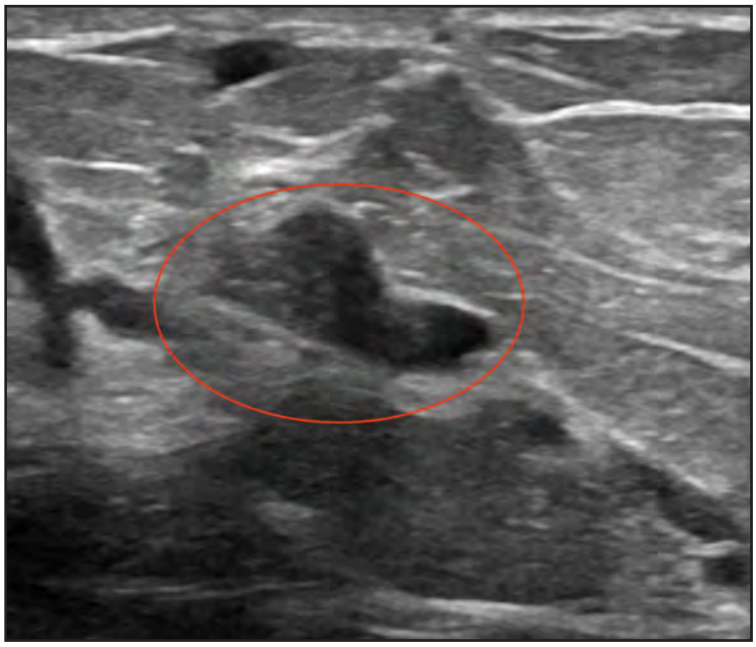

FIGURE 28. *Targeted B-mode ultrasound of the 12 o'clock subareolar region of the left breast in the sagittal plane demonstrates an intraductal mass (oval) corresponding to the ductogram location. Distinct filling defect correlating with this intraductal mass was not seen on ductogram. Biopsy under ultrasound guidance ultimately demonstrated a papilloma with atypia.*

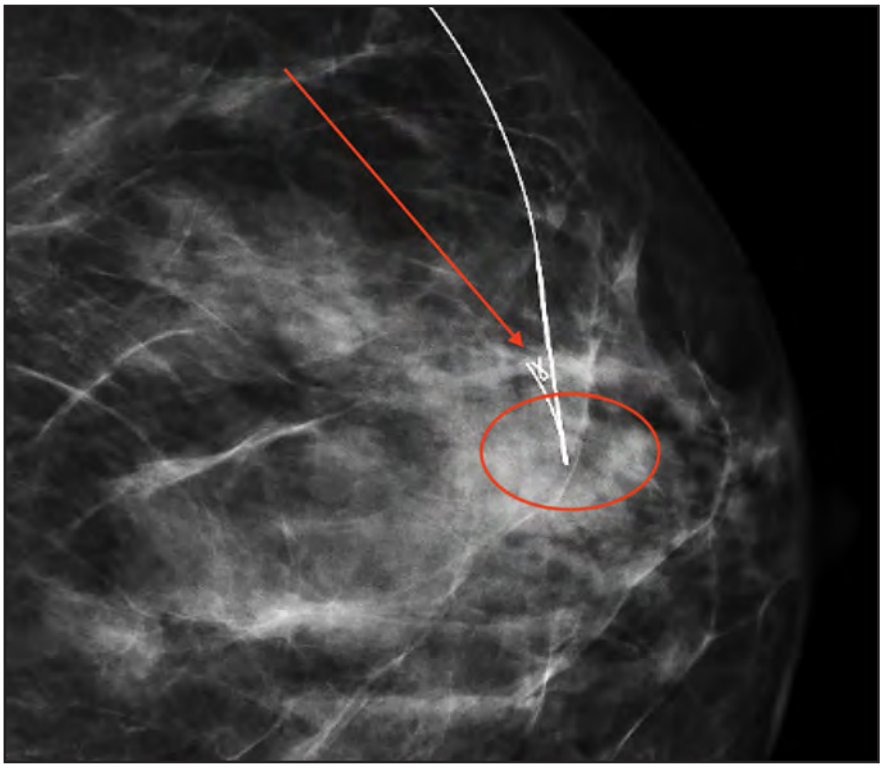

FIGURE 29. *Full-field CC mammogram from needle and wire localization procedure demonstrates the ribbon clip (arrow) at site of biopsy and hook of wire (circle) at the site of irregular ducts. No upgrade was found with excision.*

CESM has not been utilized for large volume studies in evaluating nipple discharge at this time, but findings on CESM have been reported in cases involving patients with nipple discharge, most recently by Hegazy et al as previously referenced.[37] In studying papillomas for which 84% presented with nipple discharge, the contrast mammography findings were most commonly described as nonmass enhancement, followed by no enhancement and, least commonly, an enhancing mass.[37] Specific use of MBI or PEM to evaluate nipple discharge may be available in case reports or pictorial reviews; however, no large studies have been designed to evaluate imaging characteristics of nipple discharge with these modalities.

Surgery

For many years, central duct excision (CDE or subareolar excision, SAE) was the mainstay of treatment for pathologic nipple discharge. The various imaging modalities previously

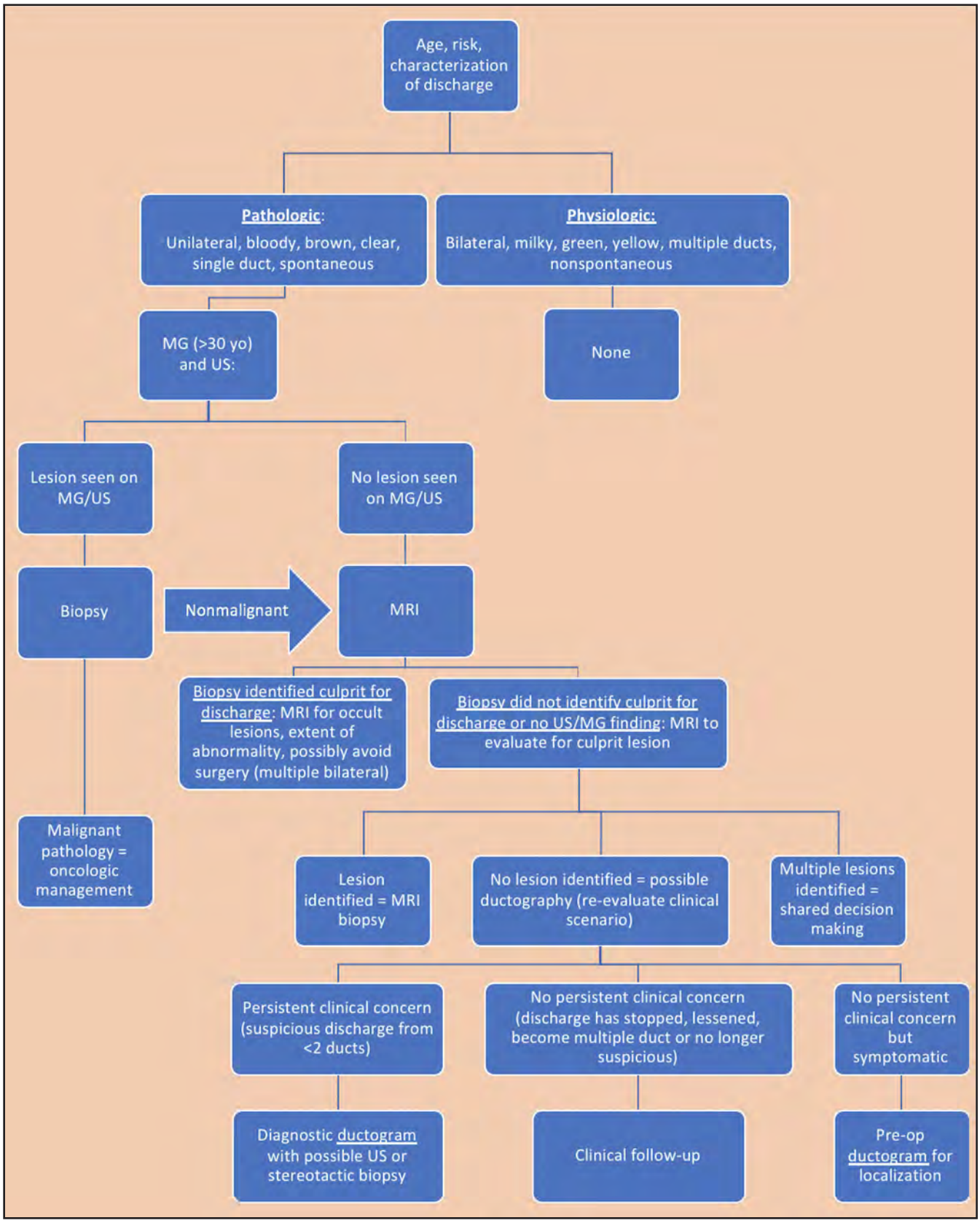

FIGURE 30. *A flow chart to assist radiologists caring for patients who present with nipple discharge.*

described, primarily mammography, ultrasound, galactography, and MRI, have been used to localize and guide surgical intervention. Prior to the wide use of MRI, the lack of imaging to provide a consistently high negative predictive value prompted routine CDE due to the rate of malignancy in patients presenting with nipple discharge, up to 12.7% in postmenopausal females according to Lau et al.[42] A review from a 20-year follow-up in patients presenting with pathologic nipple discharge reported outcomes from CDE, citing no missed malignancies.[43] In 2010, Alcock and Layer also retrospectively evaluated patients with pathologic nipple discharge with a final recommendation of either major or minor duct excision as the recommended diagnostic and therapeutic intervention.[44] Morrogh et al echoed this recommendation after review of 287 cases.[45] Sabel et al contradicted these recommendations more recently in 2011, only finding one malignancy in follow-up of a group of 142 patients with pathologic nipple discharge after complete imaging work-up and surgical intervention appropriately diagnosed and treated malignancy in seven.[46] One suggested alternative to surgery is the use of interventional ductoscopy in the treatment of nipple discharge; however, this is not as widely reported. Filipe et al described this procedure involving 215 patients (60 eventually undergoing surgery), and reported no major complications.[47] Recently, CDE has become less favored due to the improved diagnostic capabilities of imaging combined with appropriate triage of symptomatic patients.

Risk Stratification

Risk stratification of patients has been discussed as a means of potentially averting surgery. A study by Gray et al in 2007 found that age (≥ 50 years) and abnormal imaging (mammography and ultrasound) were factors predictive of malignancy.[48] Cytologic examination has also been evaluated and found to have a PPV of 85% when breast imaging was abnormal.[49] Regarding the characteristics of discharge, unilateral, bloody, and single-duct discharge have strong associations with malignancy according to Wong Chung et al. Unfortunately, they found that the lack of such characteristics alone was not sufficient to exclude malignancy. It is important to note that the advanced imaging modalities discussed above were not utilized for work-up in this study.[50]

Throughout literature, risk stratification has been discussed when concerning management strategies. In 2015, Dupont et al found that a prior history of ipsilateral breast cancer, BRCA mutation, or atypia on core-needle biopsy were associated with malignancy. Without these findings, the cancer risk was < 2%.[51] The presence of symptoms other than nipple discharge has also been associated with higher risk for breast cancer, noted by Li et al who found that palpable masses were independently associated with suspicious malignancy in patients presenting with pathologic nipple discharge.[52]

Management Algorithm

Considering the data regarding the imaging options discussed, **Figure 30** provides a flow chart geared toward radiologists caring for patients presenting with nipple discharge. Using the questionnaire provided in **Figure 1**, the characterization of discharge can be categorized into either pathologic or physiologic. It is important to note that if any one of the suspicious characteristics of discharge is present (unilateral, bloody, brown, clear, single-duct, or spontaneous), the pathologic algorithm should be considered. Mammography and ultrasound are recommended in accordance with ACR appropriateness criteria, and if no lesion is identified, MRI is recommended if available. If a lesion is identified, biopsy should follow, and malignant results should be handled as oncologic guidance deems appropriate. Depending on breast density and patient age, this may include MRI. If no malignancy or culprit for discharge is found or if a papilloma or other high-risk lesion is identified, MRI is suggested. As indicated in the algorithm, MRI should be considered for preoperative evaluation even in nonmalignant cases. MRI may identify occult lesions that could need work-up, may delineate greater extent of disease than expected (change surgical planning), or may provide information that could allow for nonsurgical management altogether (in the setting of multiple bilateral similar-appearing masses). In the setting of mammographically and sonographically occult lesions, MRI has an obvious role for evaluation. If the culprit mass is identified, MRI also provides a method for biopsy. If no mass is identified, symptoms should be re-addressed and management determined by the clinical scenario. Ductography provides the additional step needed in cases where nonmalignant but clinically problematic issues continue (such as surgical localization for cases of persistent yet benign discharge), primarily if there is involvement of only one or two ducts. Unfortunately, clinically problematic cases of multiduct (greater than two) discharge may still warrant CDE for symptomatic relief.

Conclusion

The evaluation, management, and treatment of nipple discharge has evolved significantly to allow for less invasive measures while appropriately identifying those with malignancy. For this strategy to be effective, all elements of work-up must be addressed, beginning with the basic patient history, including characterization of discharge, personal history of breast cancer, and elevated lifetime risk of breast cancer, and ideally this should be followed by physical examination of discharge. Furthermore, an imaging strategy can be introduced to allow for appropriate triage of patients in need of more advanced imaging. The role of MRI has altered the course of nipple discharge management due to the high negative predictive value in certain cases. For many patients, surgical management

can be averted due to MRI's contribution to the imaging algorithm. For certain types of discharge, primarily involving one or possibly two ducts, galactography can not only minimize surgical intervention but can isolate a specific duct system that may be problematic yet not malignant. For this reason, none of the aforementioned primary imaging modalities should be obsolete when discussing nipple discharge.

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Benign Inflammatory Conditions of the Breast

Bhargavi Guddanti, M.D., Juan Guerrero-Calderon, M.D., Elizabeth Allen, M.D., Stefanie A. Woodard, D.O.

Department of Radiology, The University of Alabama at Birmingham, Birmingham, AL

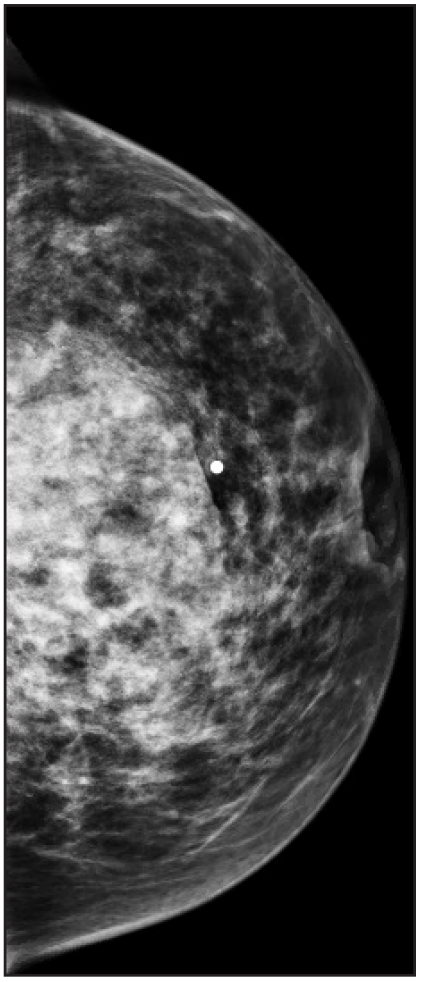

FIGURE 1. *Left breast full-field CC mammography demonstrates a global asymmetry (right breast is not shown). A BB marks the site of palpable concern.*

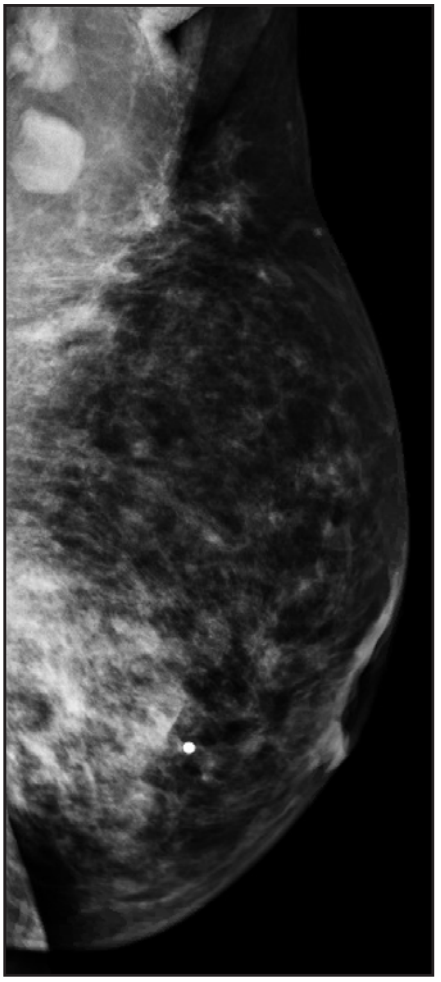

FIGURE 2. *Left breast full-field MLO view shows the global asymmetry involving the central and inferior breast. BB indicates the palpable site. A prominent left axillary node can be seen.*

Case Presentation

A 54-year-old African-American woman presented with a history of a persistent palpable lump, pain, and intermittent generalized swelling of the left breast for approximately 7 months. She had not noticed nipple discharge or nipple inversion, and there was no history of previous biopsy. She had no personal or family history of breast cancer. Pertinent obstetrical history included one prior pregnancy with a year of breast feeding. She had no significant past medical history. Upon presentation, work-up included bilateral mammogram and ultrasound (**Figures 1-3**). An aspirate was obtained, demonstrating no growth after 5 days. Ultimately, an ultrasound-guided biopsy was performed followed by bilateral breast MRI (**Figure 4**).

Key Clinical Findings

Unilateral or bilateral breast pain and erythema often with an associated palpable lump

Key Imaging Findings

Nonspecific mammographic findings, irregular masses or fluid collections on ultrasound, and masses, nonmass enhancement, sinus tracts, and fluid collections on MRI

Differential Diagnosis

Idiopathic granulomatous mastitis
Abscess
Diabetic mastopathy
Postsurgical fat necrosis
Lupus mastitis
Sarcoid
Mondor's

Discussion

Inflammatory conditions of the breast include a wide array of causes, which are broadly divided into 3 categories: infectious mastitis, noninfectious inflammatory mastitis and inflammation secondary to underlying breast cancer (inflammatory breast cancer, IBC). There is significant overlap of the clinical and radiologic features of benign mastitis with IBC, which often delays diagnosis and treatment.

Mastitis refers to inflammation of the breast parenchyma. The most common

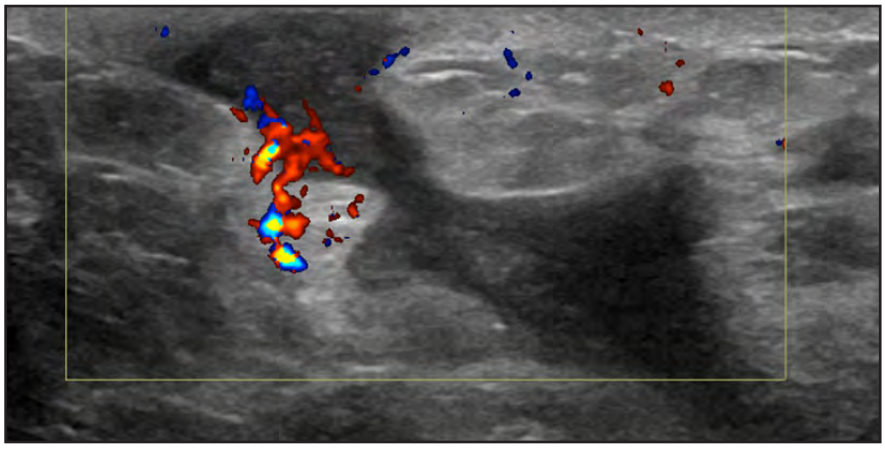

FIGURE 3. *Targeted color Doppler ultrasound image at the site of concern demonstrates a hypoechoic fluid collection that insinuates throughout the fatty tissue with a tract that extends to the skin. Vessels in a rim are noted. No internal vascularity is appreciated.*

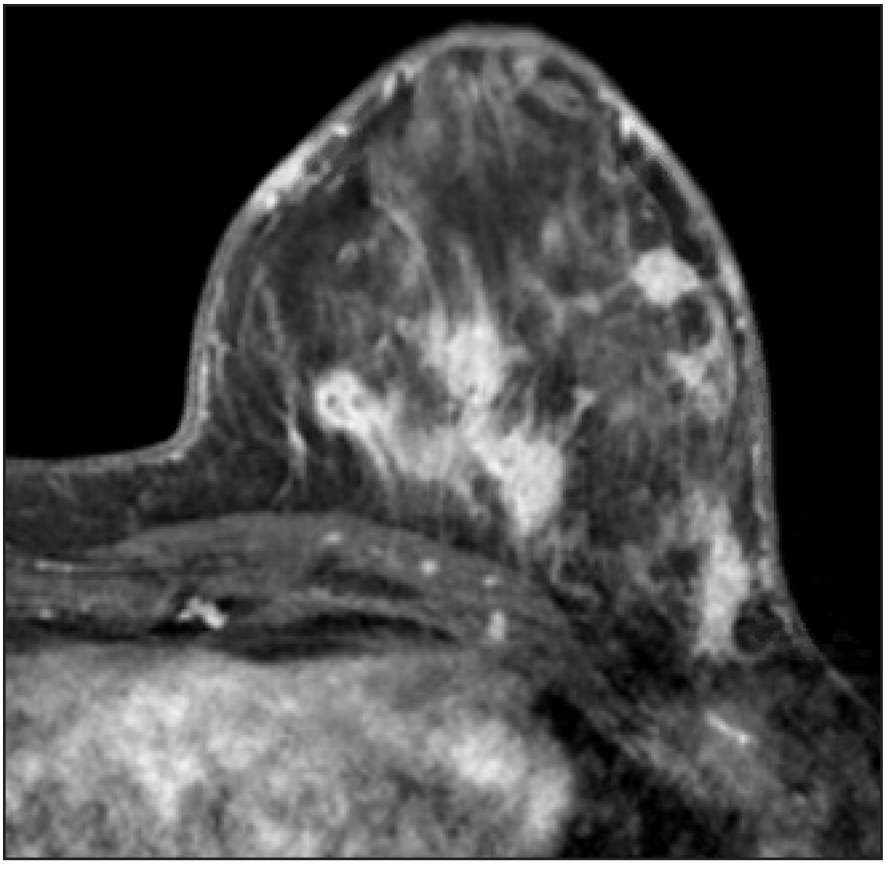

FIGURE 4. *Axial T1-weighted fat-subtracted postcontrast MRI depicts the left breast at the level of the site of concern in the inferior breast. Multiple sites of nonmass enhancement are appreciated along with several distinct sites of skin enhancement.*

clinical presentation of mastitis includes pain, redness, warmth, subcutaneous edema and skin thickening. The radiologic features are often nonspecific and can mimic those of IBC. The focus of this paper is benign inflammatory conditions of the breast.

Differential Diagnosis

Idiopathic Granulomatous Mastitis

Idiopathic granulomatous mastitis (IGM) or granulomatous lobular mastitis is an uncommon, benign chronic inflammatory condition, first described in literature by Kessler and Wolloch in 1972.[1] The definitive cause is unknown, but an autoimmune reaction is the most postulated etiology, possibly resulting from initial insult to the ductal epithelial cells with leakage of luminal protein secretions into the lobular breast stroma.[2] IGM is a diagnosis of exclusion since certain types of breast cancer are included in the malignant differential. IGM usually presents with a recurrent or persistent disease course, resulting in significant patient morbidity. It most commonly affects parous premenopausal women of reproductive age with a history lactation. There is data suggesting a clinical association with hyperprolactinemia.[2] It is mostly unilateral and commonly involves the periphery of the breast.

Imaging of IGM is variable with a focal asymmetry as the typical mammographic finding.[3] Other less common mammographic findings include an irregular mass and global asymmetry. Skin and trabecular thickening can also be seen. On ultrasound, the most common presentation is an irregular hypoechoic mass with associated duct changes. Occasionally, the sonographic features of IGM may mimic an intraductal papilloma, especially if located in a retroareolar region. MRI findings of IGM most often include clustered ring enhancement and clumped nonmass enhancement (NME). The second most described finding is an enhancing mass with the most common enhancement pattern being rim enhancement. Additional associated features of architectural distortion, focal skin enhancement, skin thickening, sinus tracts, skin ulceration, nipple retraction and axillary lymphadenopathy have also been reported.[4]

Definitive diagnosis is usually made by histopathology as the clinical and imaging features are nonspecific. Ultrasound-guided core biopsy has higher diagnostic efficacy compared to fine-needle aspiration (FNA), especially in cases of abscess and fat necrosis. On histopathology, IGM is characterized by the presence of noncaseating granulomas with varying

degrees of fibrosis around the breast lobules.

There is no definitive treatment for IGM; therefore, treatment should be tailored to each patient's clinical presentation. The treatment options include conservative measures such as close clinical and imaging surveillance, medication therapy with antibiotics, corticosteroids and/or immunosuppressants such as methotrexate. The more aggressive surgical approach is wide local excision.

Abscess (Puerperal, Nonpuerperal)

One common cause of a tender breast lump is an infected fluid collection or abscess. Most breast abscesses are complications of infectious mastitis. They usually occur in the first 3 months postpartum or at weaning; thus, named puerperal abscesses.[5] They are caused by bacteria, most commonly *Staphylococcus aureus,* that enter through small skin lacerations into stagnant lactiferous ducts. Although less common, nonpuerperal breast abscesses occur from lactiferous stagnation due to ductal obstruction by keratin plugs. Risk factors for the development of nonpuerperal breast abscesses, particularly those in the central breast, include Black race, obesity, and tobacco smoking. Peripheral abscesses are associated with chronic medical conditions, steroids, or recent breast interventions.[5] Ultrasound and mammography are typically performed in the evaluation of patients over age 30; however, ultrasound is usually the first-line modality as patients are often in pain. The typical sonographic findings include a hypoechoic fluid collection with increased peripheral vascularity. Edema and hypervascularity of the tissue are also often noted throughout the adjacent breast parenchyma. Ultrasound-guided aspiration and drainage with antibiotic therapy has been found effective in the treatment of both puerperal and nonpuerperal abscesses.[6] When outside the peripartum period or when the clinical course is prolonged, underlying inflammatory breast cancer should be considered.[5]

Postsurgical Fat Necrosis

Another common finding in patients presenting with a tender palpable lump is fat necrosis. Histologically, fat necrosis appears as foamy histiocytes and giant cells that surround lipid vacuoles and adipocytes.[7] This can vary based on the time of patient presentation since fat necrosis tends to result from trauma. It occurs after vascular damage causes inflammation in the fatty tissue. There are resultant edematous changes that ensue as the interstitium becomes engorged with fluid. With time, fibrosis can occur, leading to formation of granulation tissue and fibrous scarring. When fat is encapsulated in calcified granulation tissue, an oil cyst results, mammographically presenting as a rim calcification. Prior to calcified oil cysts, fat necrosis may appear as a focal asymmetry, asymmetry, or mass. Sonographically, fat necrosis follows the histologic timeline, initially seen as edema throughout the tissues. This is accompanied by increased echogenicity of the fat or even discrete cyst formation with hyperechoic masses throughout the parenchyma. Later, findings of a cyst with peripheral calcification (oil cyst) or architectural distortion from fibrosis can follow. MRI T2-weighted images may demonstrate hyperintense signal from edema and, later, T1-weighted images without fat saturation often demonstrate central hyperintense signal.[8]

Diabetic Mastopathy

Diabetic mastopathy is an uncommon benign inflammatory condition predominantly seen in premenopausal women with long-standing insulin-dependent diabetes. The typical presentation is single or multiple palpable breast masses that are firm but mobile. Patients typically have other diabetic complications such as retinopathy or neuropathy. Although the pathophysiology is not clear, the proposed mechanism is a localized autoimmune reaction. An inflammatory response leads to lymphocyte infiltration of the periductal, perilobular, and perivascular spaces resulting in dense keloid-like fibrosis that is seen on histopathology.[9,10] Because of the typical clinical presentation, diabetic mastopathy is usually evaluated with mammogram and ultrasound. Mammography may demonstrate various types of asymmetries or, less likely, a high-density mass. Ultrasound will show a nonvascular, irregular, hypoechoic mass with margins that are not circumscribed. Prominent posterior acoustic shadowing is characteristic. MRI findings are not well established and typically noncontributory in diagnosis. Both the clinical and imaging features of diabetic mastopathy mimic those of breast cancer and core-needle biopsy is necessary for diagnosis.[10,11]

Lupus Mastitis

Certain autoimmune processes may also present with breast symptoms. A rare breast phenomenon manifesting in patients with systemic lupus erythematosus (SLE) is lupus mastitis, which can present as a painful palpable lump or unilateral swelling. Lupus mastitis should remain in the differential diagnoses of patients with SLE; however, it needs to be a diagnosis of exclusion, and tissue sampling should exclude other more common etiologies. Patients presenting with lupus mastitis may note one or many discrete palpable lumps that wax and wane, occasionally even ulcerating through skin. Other clinical presentations include an overall asymmetric, enlarged, and painful affected breast. Histologically, lupus mastitis involves hyaline fat necrosis with intervening lymphoid cells. Fibrotic changes eventually ensue. Immunofluorescence may show IgG and C3 along the basement membranes of vessels and along the junction of the dermis and epidermis.[12] Mammographic findings range from discrete masses to global asymmetries. Sonographically, irregular masses are indistinguishable from malignancy. In many cases fluid collections occur, sometimes mimicking abscesses. MRI is nonspecific with fluid collections and nonmass enhancement being most common.[13]

Sarcoid

A rare differential diagnosis for a tender breast lump includes breast involvement in sarcoidosis. Sarcoidosis is a systemic inflammatory disease of unknown etiology that generates non-necrotizing granulomas in affected organs.[14] It generally manifests in the third and fourth decades of life. Breast involvement with sarcoidosis is rare and primary breast sarcoid is even more infrequent. On histopathologic examination, parenchymal granulomas can be seen among breast lobules and ducts. A similar pathologic process may affect lymph nodes, causing nodal enlargement.[15] Imaging findings of breast sarcoidosis are often concerning for malignancy. Mammography commonly shows irregular, spiculated masses. Ultrasound correlates are often irregular hypoechoic masses. Small, circumscribed, round masses have also been described. Calcifications within the breast parenchyma are typically absent.[15] Diagnosis requires exclusion of other causes, including biopsy with negative stains and cultures for bacteria, mycobacteria, and fungus. The clinical evidence of sarcoidosis elsewhere in the body is most helpful in reaching this diagnosis.[14]

Mondor's Disease

Mondor's disease is an acute thrombophlebitis of one or more superficial breast veins and is most common in middle-aged women. The typical presentation is a palpable cord or mass with associated focal breast pain and redness. Although many cases are idiopathic, the disease is frequently associated with prior trauma, such as surgery.[16] Ultrasound is almost always diagnostic, but because of the typical presenting symptoms, both mammogram and ultrasound are usually performed. On mammography, the thrombosed vein can be seen as a tubular-shaped focal asymmetry in the superficial breast. Ultrasound will show a dilated superficial vessel with a lack of compressibility and no intraluminal flow on Doppler imaging.[10]

Diagnosis

Idiopathic granulomatous mastitis

Summary

Granulomatous lobular mastitis is a benign, rare, chronic inflammatory condition of the breast with a nonspecific clinical presentation. There is significant overlap between the imaging features of IGM, other benign inflammatory entities, and malignancy. This overlap can lead to misdiagnosis; however, additional imaging and tissue sampling help ensure exclusion of the main differential entities. Ultimately, the goal is to reach the correct diagnosis and prevent treatment delay. Correlation with clinical presentation and risk factors may be helpful. The final diagnosis relies on exclusion of other causes and the appropriate pathologic findings on biopsy.

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Enhancing Foci on Breast MRI

Angela Choe, M.D., Rebecca Sivarajah, M.D.

Penn State Health Milton S. Hershey Medical Center, Hershey, PA

Case Presentation

A 32-year-old woman presented for high-risk screening with an International Breast Cancer Intervention Study (IBIS) tool lifetime risk of 23.1%. A new enhancing focus was noted on MRI at 11 o'clock, 4 cm from the nipple, measuring 4 mm (**Figure 1**). This focus stands out despite marked background parenchymal enhancement. The focus demonstrates rapid uptake with plateau and persistent kinetics and is not hyperintense on T2-weighted imaging (T2WI) (**Figure 2**). MR-guided biopsy was performed.

Key Imaging Findings

A small nonspace-occupying distinct enhancing dot on MRI with no describable morphologic features

Differential Diagnosis

Mass
Focal nonmass enhancement
Background enhancement
Focus

Discussion

In the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) Atlas, the breast MRI lexicon defines a focus as a unique enhancing dot that is too small to characterize further morphologically as a mass or nonmass enhancement. It is not a space-occupying lesion. In the fourth edition, mass and foci were differentiated by size. Findings smaller than 5 mm were defined as a focus, while findings larger than 5 mm were defined as a mass. The fifth edition no longer uses size criteria but instead uses morphology.[1] The presence of margins and shape defines a mass, and a focus is a specific, isolated, enhancing dot that is too small to be assigned morphologic descriptors. Because of its small size, a focus in breast MRI must be evaluated based on characteristics other than morphologic features. Patient-related factors in conjunction with lesion features should be used for decision-making.

A focus is usually too small to apply enhancement quantitative analysis with kinetic curves. The enhancement intensity and presence of washout must be visually analyzed. Mammography and ultrasound are not usually helpful to further evaluate MRI-detected foci as correlation is challenging due to their small size. The strategy must be based on the patient's risk factors and other MRI findings.

Differential Diagnosis

Mass

The first step when evaluating a small enhancing lesion in the breast is to decide whether an enhancing area represents a true focus, focal nonmass enhancement (NME), mass, or background parenchymal enhancement. A small mass may be misinterpreted as a focus. Masses are space-occupying lesions and are 3-dimensional. Masses can be described in terms of morphology, margins, and internal enhancement characteristics. The pathologic differential considerations for masses and foci may have significant overlap; however, management of these entities is different and based on their respective imaging features. If an enhancing finding can be defined by morphology, margins, or internal enhancement characteristics, it should be described as a mass. These imaging characteristics of masses help guide management and determine predictive value of malignancy.[1] Foci are not able to be managed based on imaging characteristics alone.

Focal Nonmass Enhancement

NME is defined as a discrete site of enhancement that cannot be defined as a mass or focus. It is characterized in terms of distribution and internal enhancement pattern. The types of distribution include focal, linear, segmental, regional, multiple regions, and diffuse. While most types of NME are not confused with foci, focal NME, which entails enhancement of less than a quadrant of breast tissue at a discrete site, may be difficult to differentiate from a single focus since the size cutoff of 5 mm is no longer used as a defining criterion for a focus.[1] Focal NME represents an area of enhancement distinct from the surrounding parenchyma but is not a space-occupying mass and is typically interspersed with nonenhancing fatty or glandular tissue. These

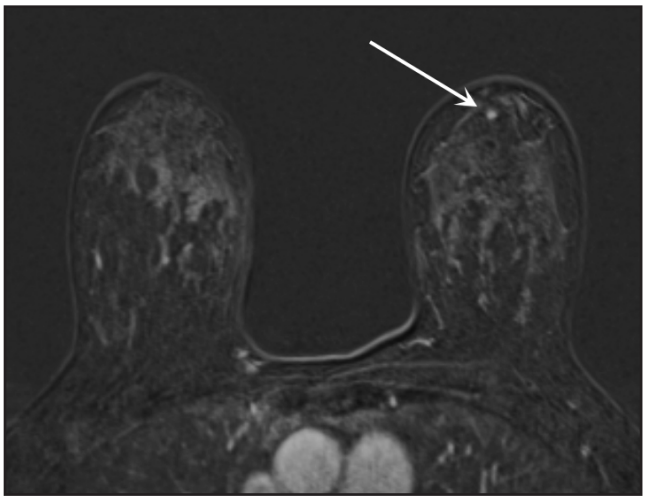

FIGURE 1. *T1 fat-saturated postcontrast axial subtraction MRI (time-point 1) demonstrating an enhancing focus in the left breast at 11 o'clock anterior depth.*

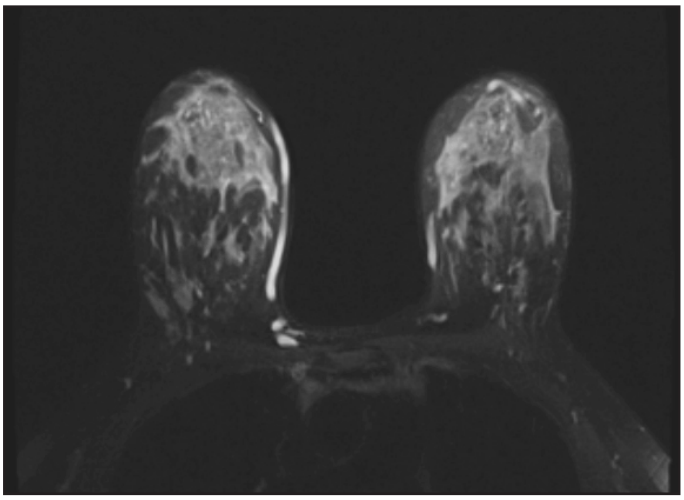

FIGURE 2. *T2-weighted image shows no corresponding hyperintense signal at the site of the focus in the left breast at 11 o'clock anterior depth.*

Table 1. Malignancy Rates of Enhancing Focus

Study	Number of Foci < 5 mm	Malignancy Rate n/N (%)
Liberman[2] 2006	74	7/74 (9.5)
Han[7] 2008	21	4/21 (19
Eby[3] 2009	168	1/168 (0.6)
Abe[5] 2010	50	3/50 (15)
Weinstein[4] 2010	47	1/47 (2.1)
Jansen[6] 2011	39	9/39 (23)
Raza[8] 2012	68	14/68 (20.6)
Total	**467**	**39/467 (8.4)**

areas appear normal on nonenhanced T1-weighted images and usually have no correlate on T2-weighted images. As with masses, the descriptive features of NME assist in management, whereas the assessment of foci cannot solely rely on imaging features.

Background Enhancement

It is important to differentiate a focus from background parenchymal enhancement (BPE), which is defined as the normal enhancement of a patient's fibroglandular breast tissue, according to the BI-RADS Atlas.[1] BPE is divided into four categories based on the amount of glandular contrast uptake, and the category assessment is usually determined on the first postcontrast dynamic image (about 90 seconds after contrast administration). Normal background parenchymal enhancement may fluctuate in pattern and degree of enhancement, depending on various physiologic factors. The management of a focus depends on the degree of BPE. If a focus does not stand out from other background foci, it should be considered as normal BPE. Conversely, if there is no significant BPE and the enhancing finding is small, a focus should be considered suspicious.

Focus: Benign and Malignant Pathologies

A focus commonly represents a benign process. The benign differential diagnoses include papilloma, lymph node, fibroadenoma, stromal fibrosis, adenosis or fibrocystic change. Malignancy rate of an enhancing focus is widely variable at 1% to 23%.

In 2006, Liberman and colleagues studied 666 consecutive nonpalpable, mammographic occult lesions detected by MRI. The malignancy rate of lesions 4 mm or less was 2.7%.[2] In 2009, Eby and colleagues showed the overall cancer yield for foci was low at 0.6%.[3] Weinstein and colleagues in 2010 found the overall malignancy rate of foci was 2.1%.[4] Higher malignancy rates were observed in more recent studies from 15% to 21%.[5-7] The overall malignancy rate of an enhancing focus was 8.4% combining the results of all these studies (**Table 1**).

Kinetic analysis was reviewed for a potential role in evaluating enhancing foci in five studies by Han et al (2008), Eby et al (2009), Abe et al (2010), Jansen et al (2011), and Raza et al (2012).[3,5-8] These studies showed no statistical difference between groups of foci showing persistent enhancement and foci with washout enhancement. Foci with washout enhancement and plateau enhancement also showed no statistical difference. In a study evaluating probable benign breast MRI lesions, no malignancy was shown in the follow-up of foci with persistent enhancement. The presence of a washout pattern and older age were found to be significant predictors of malignancy for an enhancing focus in a study by Youichi et al (2017).[9] The main decisive node on the decision tree was

Table 2. Features to Help Manage Enhancing Focus on MRI

	T2 Signal	Kinetics	Number of Foci	Size	Age
Benign features	Hyperintense	Persistent	Multiple	Stable	Younger age
Suspicious features	Isointense or hypointense	Wash-out	Single	New or increasing	Older age > 63

the presence of a washout pattern, followed by whether the patient's age was > 63 years. Small malignant lesions do not always show an expected enhancement pattern. Kinetic analysis is not specific for malignancy and should not be used alone to guide management.

In 1999, Kuhl and colleagues studied the role of using T2 signal characteristics to improve positive predictive value of breast MRI. They found that breast cancers were T2 isointense or T2 hypointense in relation to breast parenchyma in 87% of cases and fibroadenomas were T2 hyperintense in 71% of the cases.[10] However, there are breast cancers that show high T2 signal including triple negative cancers, mucinous tumors, and papillary carcinomas. More studies are needed to determine if an enhancing focus with a corresponding T2-hyperintensity can be managed as a benign finding; therefore, this should be managed with a short interval follow-up MRI. These prior studies suggest that an enhancing focus with T2-hypointensity may warrant a biopsy or at minimum a 6-month follow-up.

Interval change is an important characteristic to consider in evaluating an enhancing focus. An enhancing focus that is new or enlarging has a significant malignant potential. Ha and colleagues found the malignancy rate was 27.2% when combined with the T2 hypointensity of the lesion. They also found that malignancy was detected only when 1 or 2 foci were followed. When 3 or more foci were present, no malignancy was present.[11]

The presence of a genetic mutation is a crucial consideration for management of enhancing foci on MRI. BRCA1-associated breast cancers showed more benign morphologic features, but exhibited aggressive pathologic features, such as the triple-negative phenotype. Compared with sporadic breast cancers, BRCA-associated breast cancers also exhibit different morphologic features at imaging. Kuhl et al reported that 23% to 38% of genetic breast cancers exhibited benign morphologic features, particularly BRCA1-associated breast cancers that appear similar to fibroadenoma or cysts.[12] Since BRCA-associated breast cancers have been shown to have more benign findings on MRI, patients with a known mutation should be referred for biopsy rather than short interval follow-up.

Diagnosis

Focus: Adenosis and pseudoangiomatous stromal hyperplasia

Summary

An enhancing focus is a common finding on breast MRI, and a management strategy is important. When there are numerous foci and/or bilateral foci, these should be considered BI-RADS 2, representing background parenchymal enhancement. An isolated focus with T2 hyperintensity without washout is considered BI-RADS 3 in patients not BRCA positive. If a patient has a known BRCA mutation, a benign-appearing focus should be considered suspicious as foci in these patients may represent aggressive cancers. A new or enlarging isolated focus with T2 hypointensity should be considered BI-RADS 4, for which biopsy should be performed under MRI guidance (**Table 2**).

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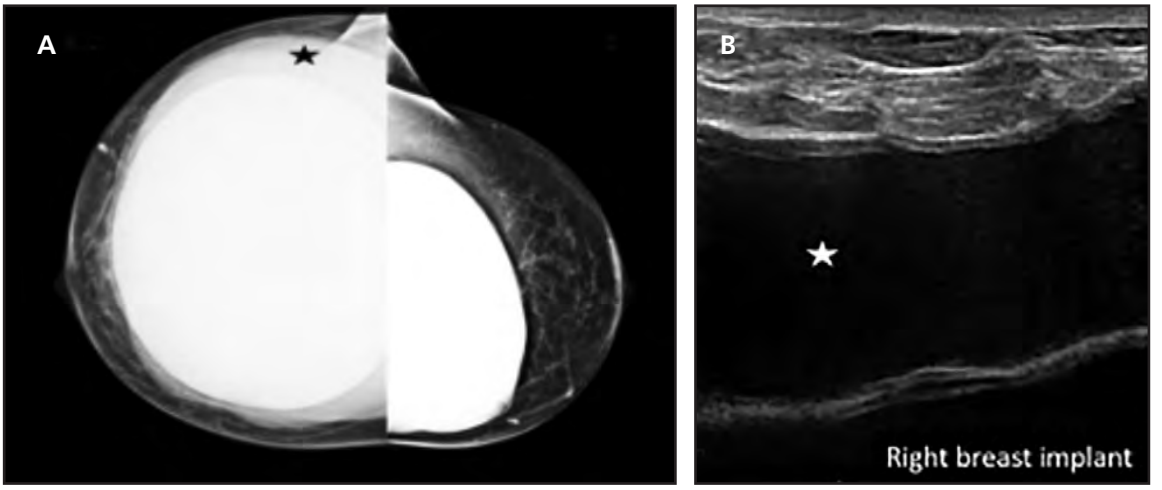
Megha M. Kapoor, M.D., Gary J. Whitman, M.D.

Department of Breast Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX



Breast Implant-Associated Anaplastic Large Cell Lymphoma

A 65-year-old woman with bilateral breast implants complained of increased right breast swelling. The patient had textured breast implants placed 14 years earlier, and approximately 10 years after surgery she began to have right breast swelling. Bilateral diagnostic mammograms (**A**) demonstrate a curvilinear focal asymmetry (star) surrounding the right breast implant, asymmetric from the left, suggestive of peri-implant fluid. Ultrasound (**B**) confirmed a moderate amount of homogeneous peri-implant fluid (star). This patient underwent surgical removal of bilateral implants and bilateral capsulectomies with pathology demonstrating breast-implant associated anaplastic large cell lymphoma (BIA-ALCL).

BIA-ALCL is a rare T-cell lymphoma typically occurring in the setting of a late-onset (defined as >1 year after surgery) fluid collection around a textured breast implant.[1] The most common clinical presentation is swelling of the affected breast related to the periprosthetic effusion.[1] Less commonly, the condition presents as a palpable mass.[1] The late-onset large spontaneous periprosthetic fluid collection occurs on average 8 to 10 years following implantation with a textured surface breast implant.[2] Mammography generally demonstrates nonspecific findings while ultrasound has high sensitivity to detect a peri-implant fluid collection or a mass.[1] When an effusion is present, fine-needle aspiration is indicated with at least 50 mL of fluid sent to pathology.[1] Indicating suspicion for BIA-ALCL is important for the pathologist because specific immunophenotyping markers must be tested to confirm the diagnosis.[1] When BIA-ALCL presents as a periprosthetic mass in the affected breast, percutaneous needle biopsy or surgical excisional biopsy can be performed to establish the diagnosis.[1] When ultrasound yields indeterminate results, breast MRI is the second imaging test of choice that can evaluate for capsule integrity, presence of effusion, and masses.[1,2] Although the majority of cases may be treated with surgery alone, extent of disease and/or lymph node involvement may also necessitate radiation and/or systemic therapy.[2]

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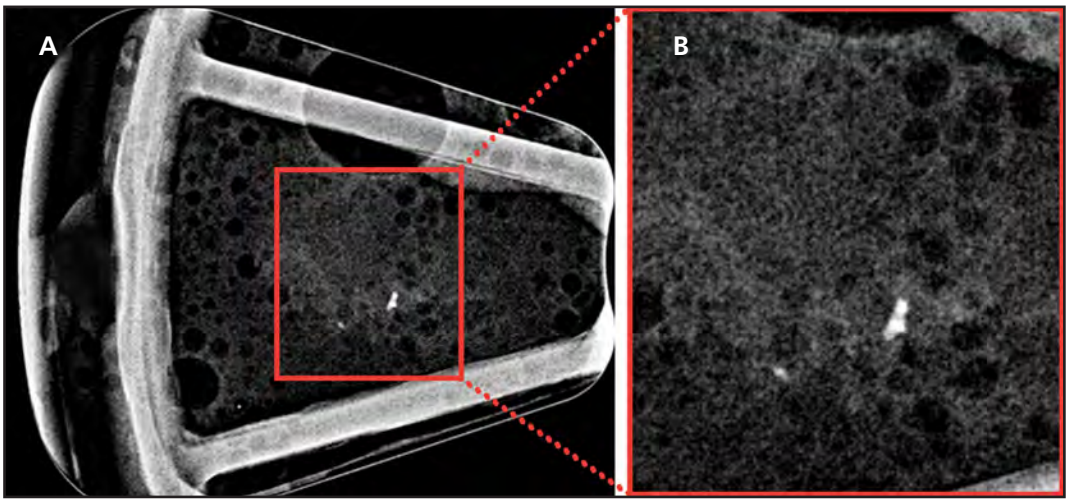
Neha Udayakumar, B.S.,[1] Claudia Kasales, M.D., M.H.A., F.A.C.R.[2]

[1]School of Medicine, University of Alabama at Birmingham, Birmingham, AL
[2]Department of Diagnostic Imaging, Fox Chase Cancer Center, Philadelphia, PA



Amyloid Calcifications in Breast

A screening mammogram in a 68-year-old with a history of idiopathic thrombocytopenic purpura (ITP) showed coarse heterogeneous calcifications in the right breast at 1200 (**A, B**). Stereotactic biopsy returned negative for malignancy, showing amyloid deposits associated with microcalcifications.

Amyloidosis is characterized by systemic or localized deposition of abnormally folded proteins, or amyloid, in the extracellular tissue matrix. Systemic amyloidosis includes primary amyloidosis (AL) caused by the deposition of immunoglobulin light chain associated with plasma cell neoplasms and secondary amyloidosis (AA) that is associated with chronic inflammatory and autoimmune conditions.[1]

Amyloid deposition in the breast is exceptionally rare and is most commonly a manifestation of underlying breast cancer, B-cell lymphoproliferative disorders, plasma cell dyscrasias, or other systemic inflammatory processes. A large amyloid center in Boston reported that only 0.5% of patients presented with localized amyloidosis, all of which had microcalcifications largely within the breast lobule.[2] The Mayo Clinic reported 40 cases seen over 16 years, 47% of which had systemic amyloidosis, mainly of the AL type and likely originating from infiltrative plasma cells secreting immunoglobulins.[1]

Mammary amyloidosis typically presents on screening mammography as microcalcifications, asymmetry, and/or a palpable mass. Histologic examination, showing apple-green birefringence under polarized light when stained with Congo red, is essential to confirm the diagnosis of amyloidosis. When identified, a work-up for possible hematologic malignancy and systemic amyloidosis should be initiated. Breast malignancy must also be excluded by performing in-depth radiologic-pathologic correlation to avoid unnecessary excisional biopsy. Amyloid should be included in the differential of all mammographic masses and calcifications.

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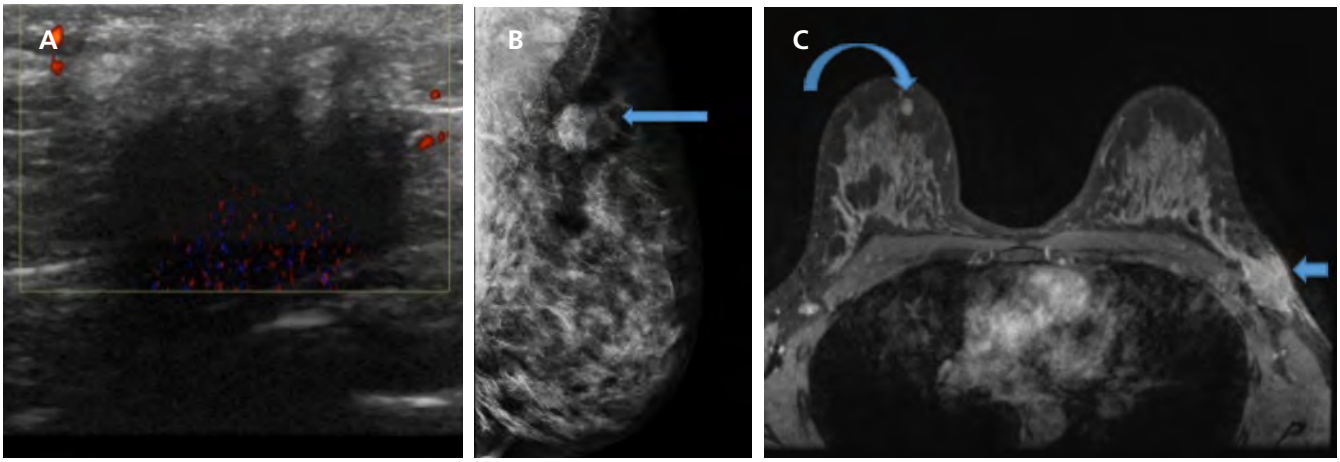
Glenn Irby, B.A.,[1] Kathryn Zamora, M.D.[2]

[1]The University of Alabama at Birmingham School of Medicine, Birmingham, AL
[2]Department of Radiology, The University of Alabama at Birmingham, Birmingham, AL



Multiple Granular Cell Tumors

A 26-year-old Black woman presented with a palpable left axillary mass. Targeted ultrasound was initially performed demonstrating a 27 × 22 × 28-mm oval hypoechoic mass with indistinct margins and peripheral vascularity (**A**). Diagnostic mammography demonstrated a round high-density mass with indistinct margins on MLO view (**B**). Ultrasound-guided biopsy yielded granular cell tumor (GCT). Subsequent MRI for surgical planning (**C**) demonstrated the GCT in the left axillary tail on postcontrast T1-weighted fat-suppressed (T1FS) imaging (**arrow**) and revealed an additional GCT in the anterior right breast (**curved arrow**).

GCTs are generally benign lesions likely of neuroectodermal origin. Most commonly they arise in the tongue followed by skin and the more distal gastrointestinal system.[1] Only 5% to 6% of GCTs occur in the breast and are commonly found in the upper inner quadrant. As exemplified above, they most frequently occur in premenopausal Black women but may occur in men.[2] Most GCTs are solitary lesions but may be multiple. The incidence of multiple tumors is 5.4% to 17.6%.[1,2]

Mammography and ultrasound are the primary imaging modalities used to evaluate GCTs of the breast. Mammography findings are nonspecific and range from round, circumscribed masses to spiculated masses with poorly defined margins. Ultrasound findings are similarly variable ranging from benign-appearing circumscribed solid masses resembling fibroadenomas to malignant appearing masses with indistinct margins and posterior shadowing.[2] GCTs lack a capsule, allowing them to appear grossly infiltrative.

The concerning imaging features of GCTs frequently lead to core biopsy. After diagnosis, preferred treatment is surgery with negative margins to decrease the chance of local recurrence. Chemotherapy and radiation therapy have not been shown effective for GCTs.

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