Multimodality Imaging of Benign and Malignant Diseases of the Nipple-Areolar Complex

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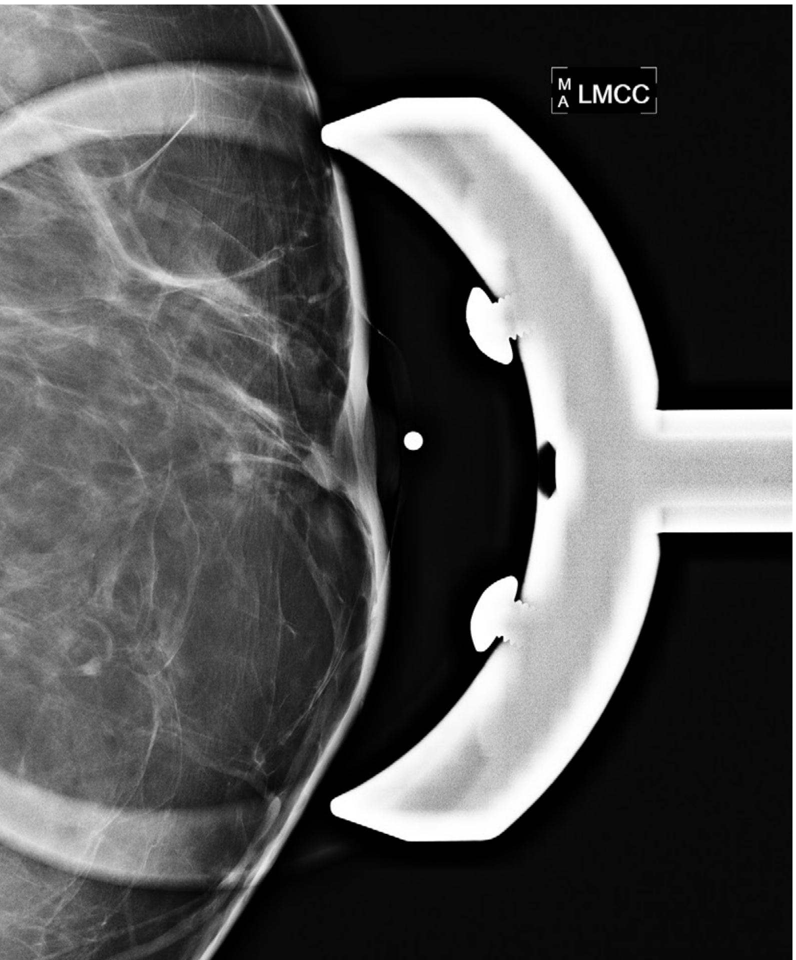

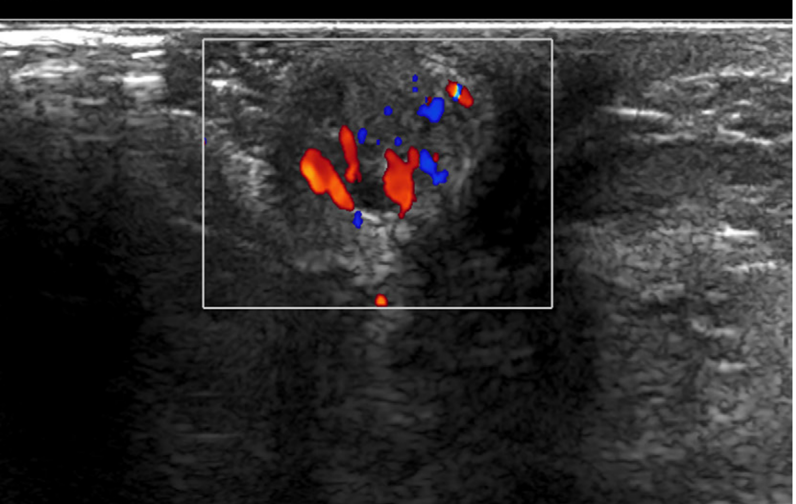

The nipple-areolar complex (NAC), a unique anatomic structure of the breast, encompasses the terminal intramammary ducts and skin appendages. Several benign and malignant diseases can arise within the NAC. As several conditions have overlapping symptoms and imaging findings, understanding the distinctive nipple anatomy, as well as the clinical and imaging features of each NAC disease process, is essential. A multimodality imaging approach is optimal in the presence or absence of clinical symptoms. The authors review the ductal anatomy and anomalies, including congenital abnormalities and nipple retraction. They then discuss the causes of nipple discharge and highlight best practices for the imaging workup of pathologic nipple discharge, a common condition that can pose a diagnostic challenge and may be the presenting symptom of breast cancer. The imaging modalities used to evaluate and differentiate benign conditions (eg, dermatologic conditions, epidermal inclusion cyst, mammary ductal ectasia, periductal mastitis, and nonpuerperal abscess), benign tumors (eg, papilloma, nipple adenoma, and syringomatous tumor of the nipple), and malignant conditions (eg, breast cancer and Paget disease of the breast) are reviewed. Breast MRI is the current preferred imaging modality used to evaluate for NAC involvement by breast cancer and select suitable candidates for nipple-sparing mastectomy. Different biopsy techniques (US -guided biopsy and stereotactic biopsy) for sampling NAC masses and calcifications are described. This multimodality imaging approach ensures an accurate diagnosis, enabling optimal clinical management and patient outcomes.

Introduction

The anatomy and diseases of the nipple-areolar complex (NAC) can make the evaluation of this anatomic region challenging. Multiple benign and malignant processes can involve the NAC and have significantly overlapping imaging appearances. Therefore, meticulous multimodality imaging evaluation is needed to assess symptomatic patients and incidental imaging findings to exclude an underlying malignancy. Understanding the spectrum of normal appearances across different imaging modalities enables accurate interpretation of the imaging and pathologic findings in this region. Correlation with the patient's symptoms is key to interpreting the imaging findings, identifying the underlying disease, and guiding clinical management.

Supplemental Material

TestYour Knowledge

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Abbreviations: CEM = contrast-enhanced mammography, DCIS = ductal carcinoma in situ, NAC = nipple-areolar complex, PD = Paget disease, PND = pathologic nipple discharge

TEACHING POINTS

- Breast MRI is more sensitive and specific for evaluating PND than is galactography. It is better tolerated by patients and less invasive compared with galactography.
- The cancer rate among women with PND ranges from 3% to 33%. As PND is the presenting symptom in 5%–12% of breast cancer cases, a thorough imaging evaluation is indicated.
- NAC eczema mimics PD of the breast. However, unlike PD of the breast, eczema of the NAC is usually bilateral.
- Breast MRI is sensitive for the detection of NAC involvement by a known malignancy. The cutoff lesion-to-nipple distance is 1 cm.
- During stereotactic biopsy of a retroareolar lesion, positioning the breast with the nipple rolled away may open a safe window for biopsy that avoids the areola.

In this article, we discuss NAC anatomy and anomalies. We review causes of nipple discharge and highlight best practices for the imaging workup of pathologic nipple discharge (PND). We review benign conditions, benign tumors, and malignant conditions of the NAC. Finally, we discuss biopsy techniques for sampling NAC masses and calcifications.

Ductal Anatomy

The NAC marks the termination of the lactiferous ductal system. The terminal duct lobular unit is the functional unit of the breast lobule and produces milk (1–3). The lobules are oriented radially in relation to the nipple, with several lobules constituting a lobe (Fig 1) (1–4). About 15–20 lobes are present within the breast and are drained by the lactiferous ducts (1–4). The lactiferous ducts converge radially toward the nipple. In the subareolar region, the converging lactiferous ducts expand to form the lactiferous sinus (2). The skin of the NAC is hyperpigmented squamous epithelium and includes sweat glands, sebaceous glands, hair follicles, and smooth muscle (4). The NAC has a rich subareolar lymphatic plexus. This may explain why cancers near the NAC may have a faster propensity for axillary lymph node metastasis (2). The Montgomery glands, whose openings form 1- to 2-mm tubercles on the areolar skin (Fig 1), are the modified sebaceous glands of the NAC (4). The Montgomery glands are connected to the skin surfaces by way of Montgomery (or Morgagni) ducts (1,2,4). The epithelium lining the ducts is continuous with the dermis of the nipple. This anatomy explains how breast cancer cells can spread through the epithelium to involve the areolar skin, as seen in Paget disease (PD) of the breast (1,2).

Breast and Nipple Anomalies

Developmental Anomalies

During embryologic development, the ectodermal ridges (also called milk lines) form on both sides of the anterior chest, running from the axillae to the inguinal regions. These ridges give rise to several mammary buds along this line (1,2). Normally, these buds atrophy; the exceptions are the buds in the fourth intercostal space, which develop into the breast and nipple (2,4). Failure of the mammary buds to completely atrophy can lead to supernumerary nipples, which can arise anywhere along the milk line but are most common in the axillary and inframammary regions (2,4). Less common breast and NAC anomalies include athelia (absence of the nipple and areola), amazia (lack of breast tissue but with a nipple present), and amastia (absence of the breast tissue and nipple) (2).

Nipple Inversion and Nipple Retraction

Although nipple retraction and nipple inversion frequently are used interchangeably, they are distinct entities. Nipple retraction occurs when there is tethering of the nipple and areola by the subareolar tissues, resulting in a nipple that lies flat to the areola. Nipple inversion occurs when the entire nipple is deep to the breast surface (Fig S1) (4). An inverted nipple may be congenital or secondarily acquired due to a benign or malignant process. Up to 10%–20% of women have one or more inverted nipples at birth that are caused by hypoplasia and retraction of the lactiferous ducts (5). Acquired nipple inversion develops after puberty and breast development. The causes of nipple inversion or retraction include traumatic fat necrosis, an infectious process, ductal ectasia, sudden weight loss, Mondor disease, subareolar papillomatosis, breast surgery, and breast cancer (5).

Clinical Evaluation

A comprehensive clinical history and thorough physical examination are crucial components in the diagnosis of NAC diseases. They provide the framework for the breast imaging assessment. The presence of a palpable lump, changes in the appearance of the NAC, nipple discharge, and/or new nipple inversion warrant further investigation. Distinguishing physiologic nipple discharge from PND requires the acquisition of a thorough medical history. At physical examination, the health care provider should check for scaly skin, inverted or retracted nipples, nipple discharge, edema, peau d'orange, draining fluid collections, or a palpable mass.

Imaging Evaluation

The NAC is difficult to evaluate with imaging. It is superficial and highly mobile and has a wide spectrum of normal appearances (1,2). Many NAC disease processes have nonspecific overlapping imaging findings and clinical presentations, posing a diagnostic challenge.

Mammography

Mammography and digital breast tomosynthesis are usually the first imaging modalities indicated in patients with nipple symptoms or abnormalities. Although mammography has low sensitivity for identifying masses in the subareolar region, it has high sensitivity for detecting suspicious calcifications (6). Digital breast tomosynthesis can differentiate between skin lesions and masses in the nipple or retroareolar region. Nipple positioning is important when evaluating for

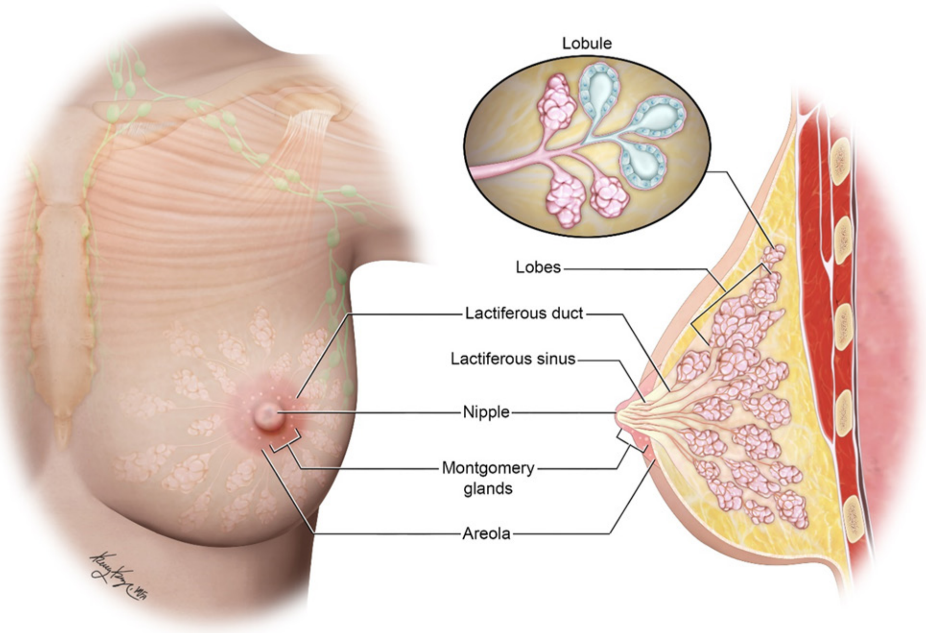


Figure 1. Breast ductal anatomy. The terminal duct lobular unit (blue cells) is the functional unit of the breast lobule that is responsible for milk production. Several lobules constitute a lobe. Lactiferous ducts drain 15–20 lobes of the mammary gland. In the subareolar region, the ducts converge and expand to form the lactiferous sinus. The ducts then drain through 9–20 orifices in the nipple. Morgagni tubercles are raised areas of the areolar skin and represent the openings of the ducts of the Montgomery glands, which are modified sebaceous glands that help lubricate the areola during lactation.

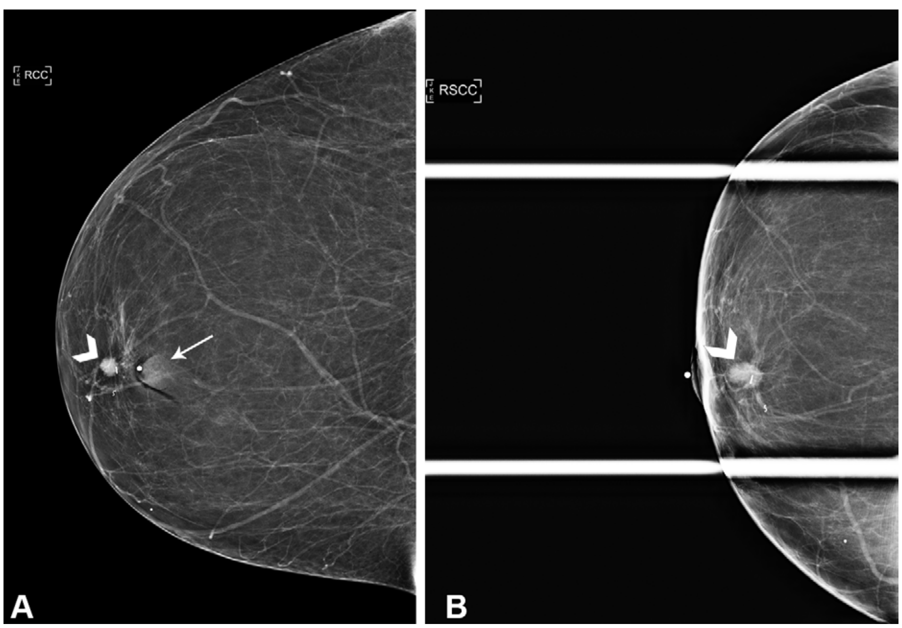


Figure 2. Mammographic positioning of the nipple in a 60-year-old woman with known invasive lobular carcinoma. **(A)** Right craniocaudal mammogram shows a rolled nipple (arrow) simulating a mass,+ and a right breast retroareolar invasive lobular carcinoma (arrowhead). **(B)** Spot compression view shows the nipple (marked with a metallic BB marker) in profile and the subareolar malignancy (arrowhead), enabling more effective evaluation of the NAC in this patient.

NAC anomalies (2). In the United States, the Enhancing Quality Using the Inspection Program (EQUIP) guidelines require that the nipple be centered within the detector and in profile in at least one mammographic projection (7). In addition, nipple markers can help to identify the nipple, distinguishing a retroareolar mass from an inverted or rolled nipple (Fig 2). Additional spot compression or magnification views of the subareolar area can help to identify NAC abnormalities in patients with nipple symptoms (Fig 3).

Ultrasonography

US of the breast with a high-frequency (at least 12 MHz) linear transducer is the optimal modality for evaluating the retroareolar region (8). It provides excellent spatial resolution of this superficial anatomy (2,8). Placing a gel-filled pad, also known as a standoff pad, between the ultrasound probe and the skin, or the use of ample gel (Fig 4), is helpful in evaluating the mobile and superficial anatomy of the NAC (2,8). Significant acoustic shadowing is usually seen while scanning the subareolar region. This shadowing is multifactorial due to uneven areolar skin, protuberance of the nipple, and convergence of the ducts (8). Angling the probe or using one of several compression techniques (peripheral compression, rolled nipple, two-handed compression) can help eliminate the shadowing (Fig S2) (1,2,8).

The NAC has a spectrum of normal appearances. Comparing the affected nipple with the contralateral nipple is often useful and easily feasible. Sonographically, the mammary ducts are anechoic tubular structures that may be completely collapsed or measure 1–2 mm if they are visible (Fig 4) (1).

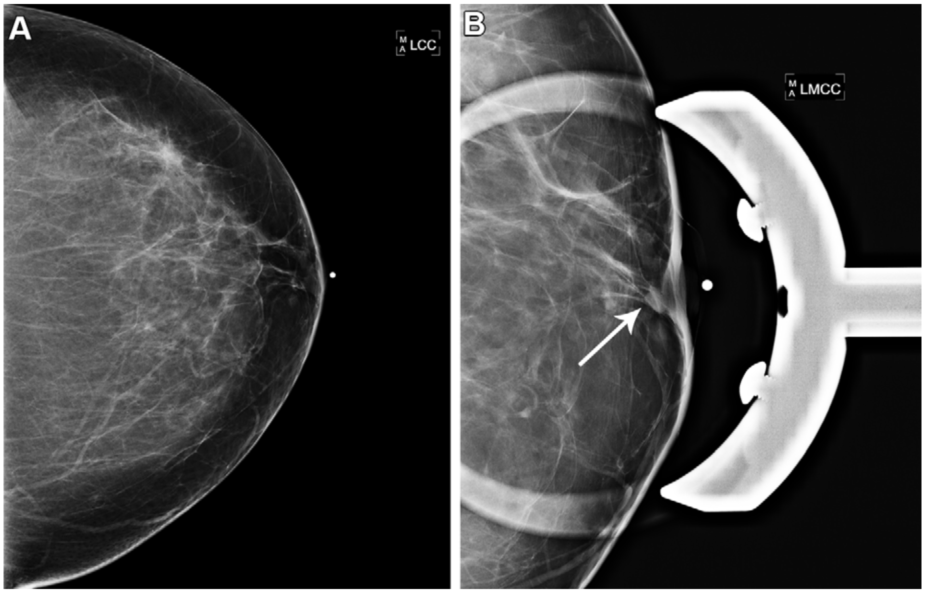


Figure 3. Mammographic workup of nipple symptoms in a 65-year-old woman who presented with bloody left breast nipple discharge. A full-field craniocaudal left breast mammogram **(A)** and then a spot craniocaudal mammogram **(B)** were obtained for further evaluation of the discharge. The spot view **(B)** shows a retroareolar mass (arrow) that was not evident in **A.** The nipple is marked by a metallic BB marker.

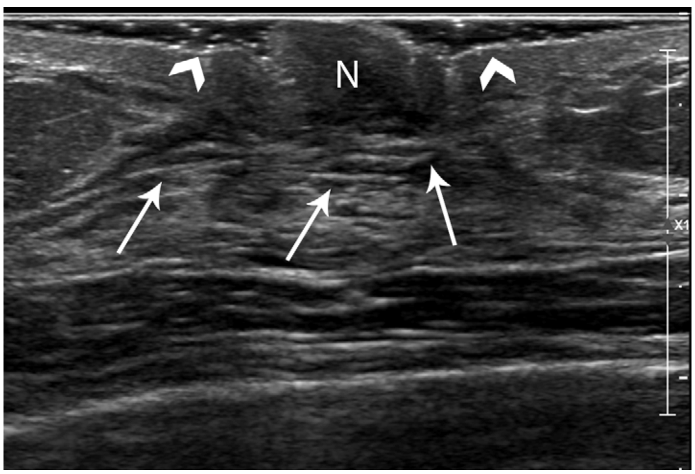


Figure 4. US appearance of normal retroareolar ducts. Transverse US image in a 41-year-old asymptomatic woman who presented for screening US shows nearly collapsed retroareolar ducts (arrows) converging in the retroareolar region. Ample gel (arrowheads) was used to evaluate the nipple *(N).*

Once a dilated duct is identified, the ultrasound beam can be aligned radially and antiradially with the duct to determine whether an intraductal mass is present. Ductal dilatation should be interrogated with color Doppler US to distinguish secretions, which lack color flow, from intraductal masses (1).

Galactography

Galactography can be performed when mammography, US, and MRI findings are inconclusive, especially in the setting of PND. During galactography, contrast material is injected through a cannula into the discharging duct. Normal ducts have a thin wall and taper smoothly, unlike diseased ducts, which may have an abrupt cutoff sign or a filling defect (1). Galactography is invasive, time consuming, and technically challenging (9). Successful duct cannulation requires the nipple discharge to be visible on the day of the examination and the absence of contrast material extravasation (9). In recent years, breast MRI has replaced galactography as the preferred modality for evaluating PND (9).

Breast MRI

Breast MRI can be used as an adjunctive modality when findings at conventional imaging are inconclusive or if they are negative in the setting of suspicious NAC symptoms or examination findings. As mentioned, MRI has become the preferred method for evaluating PND (9). In addition, MRI can be used to accurately assess NAC involvement by breast cancer. (See the "Breast Cancer" section of "Malignant Tumors of the NAC" in this article.) Breast MRI is more sensitive and specific for evaluating PND than is galactography. It is better tolerated by patients and less invasive compared with galactography.

On MR images, normal ducts are often indistinguishable from the surrounding breast parenchyma. When the ducts are dilated with fluid, they appear as branching tubular structures with low to high T1 signal intensity, depending on the proteinaceous or hemorrhagic content (2). The walls of normal ducts can show no or thin enhancement.

Physiologic enhancement of the NAC is usually symmetric (Fig 5A), but in some cases, it can be asymmetric in the early phase, becoming more symmetric in the delayed phase (Fig 5B) (10). Gao et al (10) found that 96% of NACs had symmetric enhancement and that the nipple was more commonly everted (75%) and less commonly flat (23%) or inverted (2%). They classified physiologic nipple enhancement as *(a)* superficial linear enhancement—that is, the linear enhancement at the skin level; *(b)* the nonenhancing zone—that is, the nonenhancing line immediately below the superficial linear enhancement; and *(c)* internal nipple enhancement—that is, the enhancement between the nonenhancing zone and the base of the nipple (Fig 6) (10).

Contrast-enhanced Mammography

Contrast-enhanced mammography (CEM) has emerged as a breast imaging modality that has improved accuracy compared with the accuracy of mammography and US (11). In a

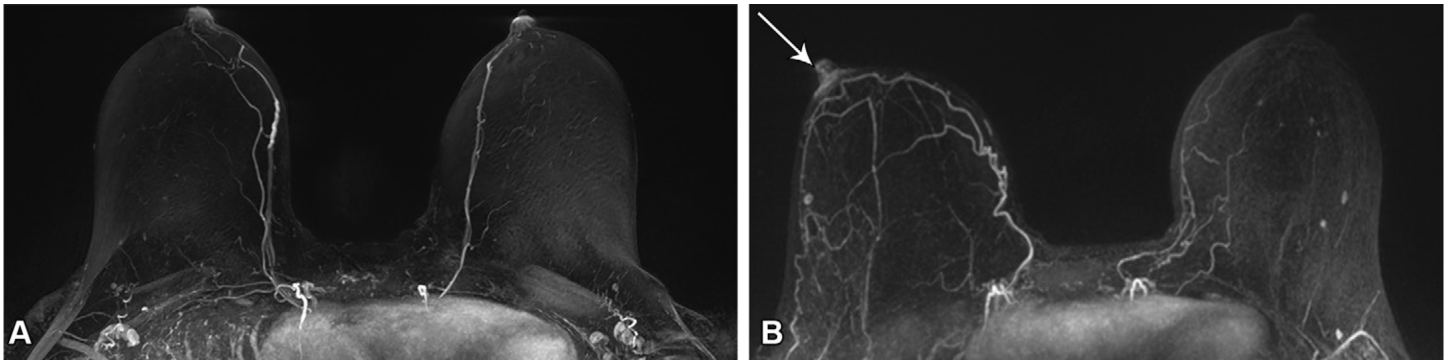


Figure 5. Physiologic nipple enhancement at mammography in two patients. **(A)** Physiologic nipple enhancement is more likely to be symmetric, as in this case of a 50-year-old woman with a family history of breast cancer who presented for screening breast MRI. Maximum intensity projection breast MR image shows mild physiologic symmetric nipple enhancement and no suspicious findings. **(B)** Asymmetric physiologic enhancement is a less common variant that is more conspicuous during the early contrast enhancement phase, becoming less prominent during more delayed phases. In this case of asymmetric physiologic enhancement, a 53-year-old woman with a 15-year history of right breast ductal carcinoma in situ (DCIS) who underwent breast-conserving treatment presented for surveillance. Maximum intensity projection breast MR image shows asymmetric early phase enhancement of the right nipple (arrow), as compared with the appearance of the left nipple.

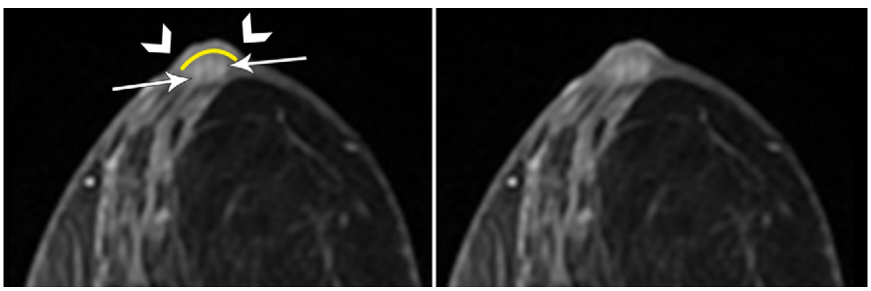


Figure 6. Zones of physiologic NAC enhancement. Axial T1-weighted MR images of the right nipple, with (left) and without (right) annotations, show the zones of normal nipple enhancement. The superficial linear enhancement (arrowheads) is the thin linear enhancement at the level of the skin. This enhancement is usually more intense than the skin enhancement in the rest of the breast. The nonenhancing zone (yellow arc) is the thin nonenhancing area immediately below the superficial linear enhancement. The internal nipple enhancement (arrows) is located below the nonenhancing zone and can be patchy or linear. The images in this patient show a linear internal nipple enhancement pattern.

study examining the use of CEM in cases of PND by Fakhry et al (12), CEM had higher sensitivity and diagnostic accuracy than those of combined mammography and US. Also, unlike MRI, CEM can also depict suspicious calcifications (13). For patients with contraindications to breast MRI, CEM may be an alternative and less expensive imaging modality (Fig 7) (13).

Imaging Evaluation of Nipple Discharge

Nipple discharge is the third most common breast symptom, second only to breast pain and breast lump (14). Although nipple discharge is often benign, it is an alarming symptom. Benign nipple discharge can be physiologic or caused by an underlying hormonal etiology such as galactorrhea. Physiologic nipple discharge is nonspontaneous, bilateral, and intermittent or long standing and arises from multiple ducts. It is characteristically green, yellow, or milky. Conversely, PND is unilateral, spontaneous, and characteristically serous or bloody, and it arises from a single duct. The cancer rate among women with PND ranges from 3% to 33% (14).

As PND is the presenting symptom in 5%–12% of breast cancer cases, a thorough imaging evaluation is indicated (14). In adult men and women aged 40 years or older, mammography is the first-line imaging modality for patients with PND. However, mammography has low sensitivity (15%–68%) and a low positive predictive value (16.7%) for breast cancer, especially in cases of dense breasts (14). Further evaluation with breast US is indicated as a complementary examination, at which lesions that are not found on mammograms are identified 63%–69% of the time. Compared with mammography, US has higher sensitivity (56%–80%) but lower specificity (61%–75% vs 38%–98%) (14). In women younger than 30 years, breast US is the initial modality of choice, while in women between the ages of 30 and 40 years, mammography or US can be the initial imaging study (14).

Historically, galactography has been the imaging modality of choice for PND. However, it yields incomplete results in 10%–15% of cases and cannot reliably exclude malignancy; thus, further evaluation with breast MRI is necessary in many cases (9). MRI has higher sensitivity (92%) and specificity

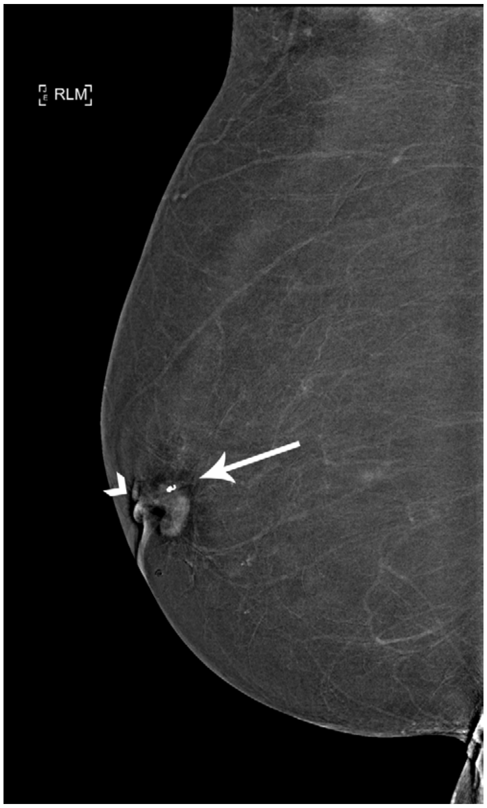


Figure 7. CEM performed for staging in a 58-year-old woman with newly diagnosed right breast invasive ductal carcinoma who presented with a palpable mass and new nipple retraction. Mediolateral CEM subtraction image shows an irregular avidly enhancing mass (arrow) with indistinct margins and an associated clip marker. The mass appears to be continuous with the nipple (arrowhead), which is retracted.

Figure 8. Changes after breast reduction in a 48-year-old woman. Mediolateral mammogram of the right breast shows nipple elevation (solid arrow), retraction of the lower portion of the breast (arrowhead), and retroareolar fibrotic bands (dashed arrows) with associated benign fat necrosis calcifications.

(76%) rates than those of galactography (69% and 39%, respectively) (9,14). In patients with negative imaging findings, major duct excision remains the reference standard for excluding malignancy (14). When imaging findings, including those of MRI, are negative, galactography may still be useful to localize intraductal lesions and aid surgery in patients with PND. Patients who undergo galactography-guided surgery are significantly more likely to have a specific underlying lesion identified than are patients who undergo central duct excision alone (15). Although nipple-smear cytology is performed in many centers as part of the workup of PND, it should not be used as a diagnostic method. Pooled data from multiple studies suggest that nipple-smear cytology has limited diagnostic accuracy (16).

Postoperative Changes of Native and Reconstructed Nipples

Mastopexy and reduction mammoplasty are common aesthetic surgeries performed for cosmetic reasons, including to correct breast asymmetries following breast cancer surgery. Typical mammographic findings seen after reduction mammoplasty and mastopexy include nipple elevation, retraction of the lower breast, skin thickening, retroareolar fibrotic bands, downward shifting of the glandular tissue, and areolar skin calcifications (Fig 8) (17,18).

In patients who have undergone mastectomy, NAC reconstruction is the final phase of breast reconstruction and is typically performed 4–6 months after the reconstruction (19). Varying techniques are used to reconstruct the nipple and areola, which can be reconstructed with local flaps, a composite of local flaps with augmentation grafts, or composite tissue graft placement. The recreated areola is tattooed 6–12 weeks following surgery. On breast MR images, enhancement of the reconstructed nipple is similar to that of the adjacent skin (Fig 9). The characteristic native nipple enhancement is absent (19). (See the "Breast MRI" section.)

Nipple Calcifications

Calcifications in the nipple are not common and typically have a benign cause such as obstructed hair follicles or glands, intraductal papilloma, or fat necrosis, which most often occurs secondary to reduction mammoplasty (Fig 10) (1). Calcifications in the NAC can also be related to a malignant process such as PD of the breast, invasive carcinoma, or ductal carcinoma in situ (DCIS) (Fig 11) (1,3,20). Like debris artifact encountered elsewhere in the breast, topical ointments and radiopaque debris can mimic calcifications (1). Debris artifact can be distinguished from true calcifications by having the patient thoroughly cleanse the NAC before reimaging.

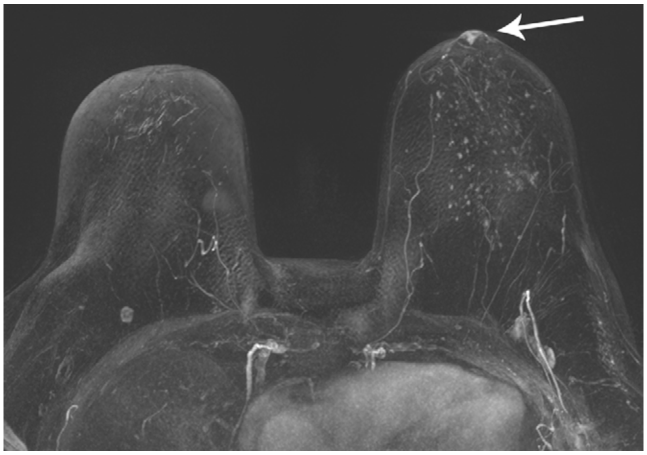


Figure 9. Reconstructed nipple after central segmentectomy 3 years previously in a 54-year-old woman with right breast cancer who presented for surveillance breast MRI. Axial maximum intensity projection MR image shows the enhancement of the native nipple on the left (arrow), as compared with the enhancement of the reconstructed right nipple, which appears flatter with enhancement similar to that of the adjacent skin. Note the asymmetry of the background parenchymal enhancement, which is greater on the left than on the right, compatible with prior radiation therapy.

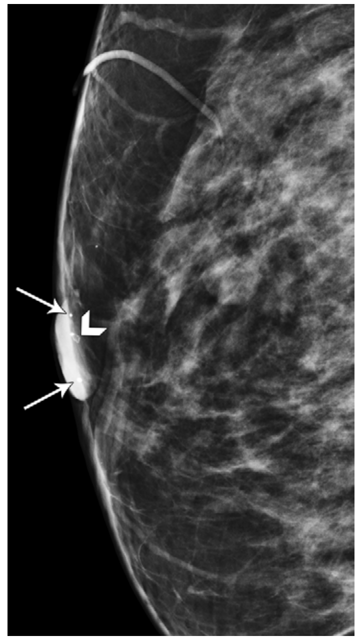


Figure 10. Benign nipple calcifications in a 65-year-old woman with a history of breast reduction who presented for screening mammography. Zoomed right breast mediolateral oblique mammogram shows round (arrows) and lucent centered (arrowhead) calcifications within the nipple, consistent with benign calcifications.

Benign Diseases of the NAC

Eczema

Eczema of the NAC is generally bilateral, predominantly seen in individuals with atopy, and frequently associated with severe pruritis (3,4,20,21). Often, only the areola is affected while the area adjacent to the base of the nipple is spared (4,20,21). The breast is less likely to be involved, and the nipple is rarely affected (20). Physical examination reveals scratched, thickened, cracked, dry, and scaly skin, which can appear raw or inflamed (Fig 12A) (4). Small raised bumps can leak fluid and can crust over due to scratching. Chronic eczema can become lichenoid (21). US findings include skin thickening and increased vascularity (Fig 12B) (21). In contrast to PD of the breast, eczema of the NAC advances more quickly, is almost always bilateral, and responds rapidly to corticosteroid treatment (21). If there is clinical uncertainty, skin punch biopsy should be considered to exclude PD of the breast (21). Psoriasis of the NAC may also cause excoriation and ulceration (3). NAC eczema mimics PD of the breast. However, unlike PD of the breast, eczema of the NAC is usually bilateral.

Epidermal Inclusion Cyst

Epidermal inclusion cyst (EIC) is a benign cutaneous or subcutaneous lesion that develops secondary to the proliferation of epidermal elements within the dermis (22). The cysts grow owing to the accumulation of epithelial and keratinous debris (22). Although EICs are more common in the trunk and extremities, they can rarely occur in the breast, including the nipple or areola cutaneously or the subareolar or periareolar regions intraparenchymally (Fig 13) (22,23). Associated nipple discharge, which can be bloody due to a ruptured EIC, has been reported (23). The most common clinical presentation is a superficial palpable lump (22,23). US is considered the diagnostic tool of choice, typically showing a circumscribed mass with posterior acoustic enhancement and complex cystic and solid or heterogeneous internal echogenicity (23). An “onion ring” sign, created by alternating concentric hyper- and hypoechoic rings corresponding to lamellate keratin, has been reported (24). At mammography, a circumscribed mass with or without microcalcifications can be seen (23). MRI shows a circumscribed mass with variable T2 signal intensity, with or without peripheral rim enhancement (23). Surgical excision is recommended when the cyst is larger than 2 cm and palpable or when it causes patient discomfort (22). Removal of the entire cyst wall is recommended to prevent recurrence or malignant transformation (22). If the cyst is asymptomatic, is small (<2 cm), and has typical imaging features, intervention is not required (22).

Mammary Ductal Ectasia

Mammary ductal ectasia, defined as benign dilatation (>3 mm) of the ductal system, is one of the most common benign NAC pathologic conditions (1). With the onset of menopause, the breast undergoes involution, causing ductal shortening and dilatation (25). Nipple discharge, nipple retraction, noncyclical breast pain, and a palpable lump are the most common symptoms (1).

On mammograms, nonspecific focal asymmetry, dilated branching subareolar asymmetry, and/or large rodlike calcifications can be seen (Fig 14A) (1,2). Sonographic findings include one or more anechoic distended ducts without an obstructing intraductal mass (Fig 14B). Similar findings are seen at MRI (1). The duct walls typically do not enhance, although smooth thin enhancement can be seen and may indicate intraductal inflammation (2). Bilateral ductal ectasia is usually benign. While unilateral ductal ectasia may also be benign, certain sonographic findings, including a nonsubareolar location, hypoechoic intraluminal contents, irregularity of the

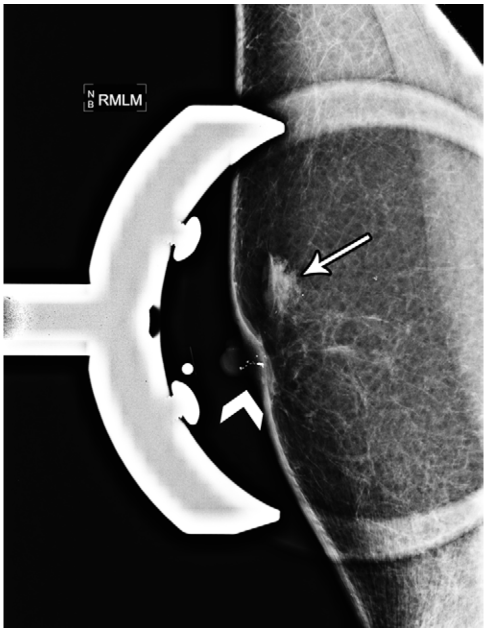


Figure 11. Breast cancer with associated nipple calcifications in an 81-year-old man with a palpable mass and nonbloody right nipple discharge. Right breast lateromedial spot magnification mammogram shows an irregular mass (arrow) in the retroareolar region, with associated fine linear branching calcifications (arrowhead), which are seen extending in a linear distribution into the nipple. Core-needle biopsy and surgical excision revealed invasive ductal carcinoma and DCIS in a background of solid papillary carcinoma, with involvement of the nipple.

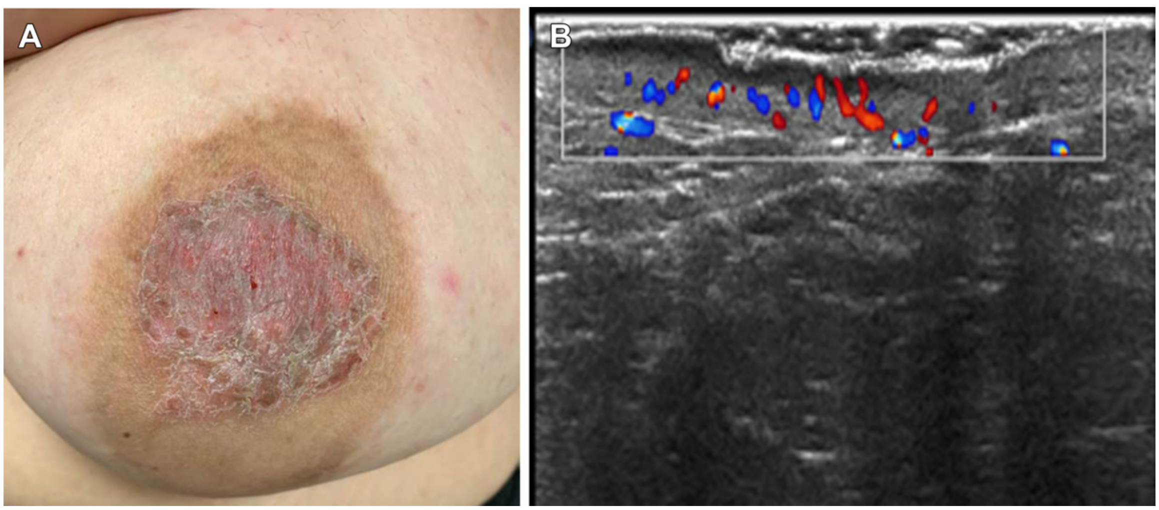


Figure 12. NAC eczema in a 21-year-old woman with bilateral nipple discharge, itching, and erythema. **(A)** Photograph of the left breast shows thickened, cracked, scaly skin involving the areola. **(B)** Longitudinal left breast color Doppler US image shows a mild increase in vascularity. Similar findings were seen at clinical examination and US of the right breast (not shown). The clinical diagnosis was consistent with eczema, with prompt response to corticosteroid treatment.

duct wall, and a solid intraductal mass, raise suspicion for malignancy (25).

Periductal Mastitis

Although periductal mastitis has distinct causes, it has clinical and imaging features that are similar to those of mammary ductal ectasia. Periductal mastitis is a suppurative inflammatory condition that occurs in nonlactating premenopausal women (1,2). The causes of this condition remain unknown but may include bacterial infection, inflammation, and ductal obstruction. Risk factors include smoking, diabetes, and obesity (1,2). The areola may be erythematous and painful, and nipple discharge or inversion may be part of the clinical presentation, mimicking mammary ductal ectasia and breast cancer (2). Treatment includes symptom relief and antibiotics when there is an associated infection (26).

Breast Abscess

Although breast abscesses are benign, they can cause long-term morbidity (27). They result from lactiferous duct or periareolar follicle obstruction and stasis, causing subsequent inflammation and infection (27). A fistulous track forms when the abscess ruptures through the skin (27). Unlike lactational abscesses, nonpuerperal abscesses affect patients of a wider age range and recur more frequently (28).

Symptoms include swelling and pain. Other symptoms are pus, skin warmth, nipple discharge, a palpable lump, and fever (28). At mammography, a mass with obscured or indistinct

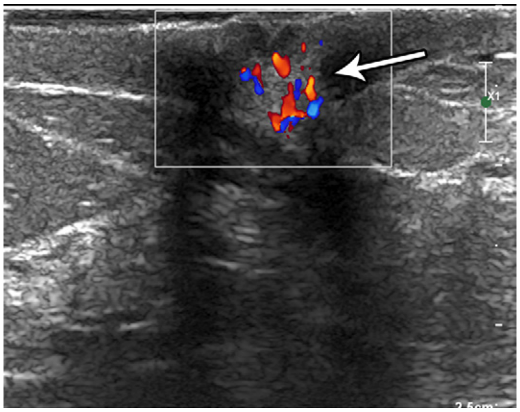


Figure 13. Epidermal inclusion cyst in a 71-year-old woman with a history of contralateral breast cancer who presented for assessment of a palpable lesion in the right nipple. Color Doppler US image shows an isoechoic round mass (arrow) within the nipple with circumscribed margins and increased vascularity. Fine-needle aspiration was performed. Cytologic findings were consistent with an epidermal inclusion cyst.

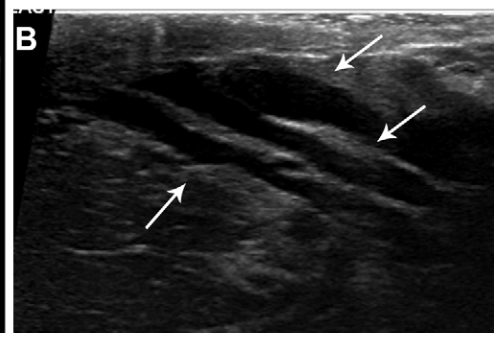


Figure 14. Mammary ductal ectasia in a 69-year-old woman with a 10-year history of intermittent bilateral clear nipple discharge. **(A)** Left breast mediolateral oblique tomosynthesis section shows asymmetries (arrows) resembling dilated ducts in the central portion of the breast. **(B)** Radial US image shows nonspecific dilatation of the retroareolar ducts (arrows).

margins and focal or global asymmetry is seen (Fig 15A) (28). At US, a complex solid cystic mass, heterogeneous hypoechoic mass, or nonmass lesion can be seen (Fig 15B) (28). The clinical and imaging presentations can mimic those of inflammatory breast cancer, which should be carefully excluded. Treatment includes antibiotics, image-guided aspiration, or surgical incision and drainage (27). Recurrent subareolar abscesses, also known as squamous metaplasia of lactiferous ducts (SMOLD), are relatively common. Inappropriate management of these abscesses can lead to prolonged disease and disfigurement (29). Complete surgical excision is usually indicated for SMOLD (29,30).

Benign Tumors of the NAC

Papilloma

Papillomas are intraductal masses consisting of a proliferation of epithelial cells with a fibrovascular stalk. Central papillomas typically are subareolar solitary lesions arising from the main ducts. Peripheral papillomas involve the peripheral ducts and tend to be multiple, occupying a quadrant within the breast. Papillomas can be associated with atypia or malignancy, and higher prevalences of both atypia and malignancy have been identified among patients with multiple peripheral papillomas (1,31).

Patients commonly present with spontaneous, unilateral, and clear or bloody nipple discharge. However, papillomas may also be incidental imaging findings that are most frequently detected on US images (31). A circumscribed, complex, solid or cystic intraductal mass with associated internal vascularity is usually seen (Fig 16A). Papillomas are often mammographically occult. When they are seen, findings include circumscribed round or oval masses, sometimes with microcalcifications (31). A round or oval enhancing mass with associated high T2 signal intensity and variable enhancement kinetics are common MRI findings (Fig 16B). An associated dilated duct may be visible. The current management of papillomas is evolving, with recent evidence indicating that surveillance may be an option for patients—specifically, those without atypia (Fig 16C) (1,32). The most recent American Society of Breast Surgeons consensus guidelines (33) recommend excision for papillomas that involve atypia owing to an upgrade in disease stage at the time of surgical excision up to 67% of the time. Papillomatosis is a rarer entity defined by the presence of multiple intraductal papillomas that usually occurs in the distal duct-lobular units and in younger patients. The association of papillomatosis with malignancy is still debatable, with no clear imaging and follow-up guidelines (34).

Nipple Adenoma

Nipple adenomas form when the epithelium of the lactiferous ducts and duct orifice proliferates (35–37). Although some of these adenomas are asymptomatic, the clinical presentation includes palpable or visible changes of the nipple with friable tissue or erosion and focal ulceration, resulting in simulation of bloody nipple discharge (35–37). Nipple adenomas are often mammographically occult (1,35). Asymmetric enlargement of the nipple may be identified at mammography (35). Calcifications are not typically seen (35). The US depiction of nipple adenoma may be technically challenging owing to the superficial nature of this tumor. The expected findings, if identified at US, include circumscribed hypoechoic masses within the nipple with increased vascularity (1,35). On MR images, increased T1 and T2 signal intensity with washout kinetics may be present with focal nipple enhancement (Fig 17) (1). Traditional management includes complete surgical excision due to nonspecific clinical findings that overlap with PD of the breast (nipple adenocarcinoma) (36).

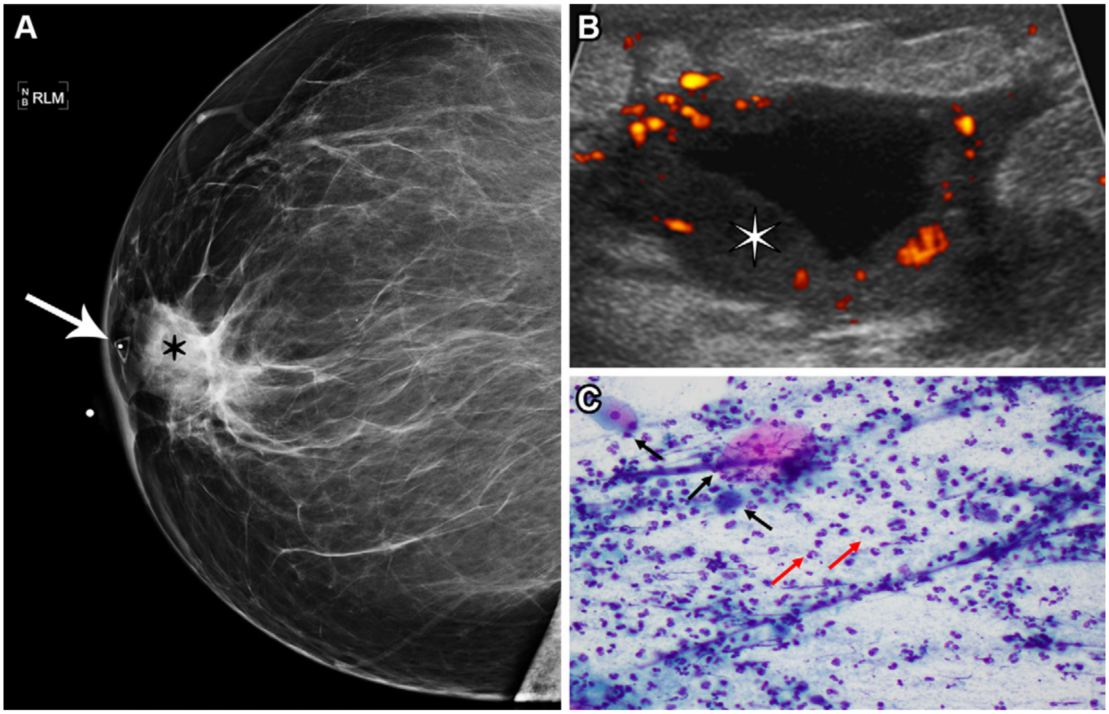
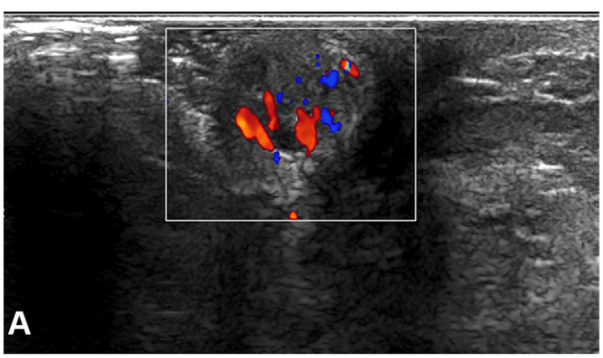


Figure 15. Subareolar breast abscess in a 26-year-old woman who had an enlarging retroareolar mass for 2 months. Most recently, the mass became enlarged, swollen, and inflamed. **(A)** Right breast lateromedial mammogram shows a high-density palpable, irregular, retroareolar mass (*) with indistinct margins. A triangular marker (arrow) was placed on the skin before imaging to mark the palpable lump and guide the radiologist. **(B)** Longitudinal color Doppler US image shows a complex cystic and solid mass (*) and increased vascularity. Cytologic analysis revealed marked acute inflammation associated with mature nucleated and rare multinucleated giant cells. **(C)** Papanicolaou test specimen shows abundant neutrophils (red arrows) and a few mature squamous cells (black arrows). (Papanicolaou stain; original magnification, ×40.) The culture specimen (not shown) revealed several organisms consistent with mastitis and abscess. The patient was treated with antibiotics, after which her symptoms improved.



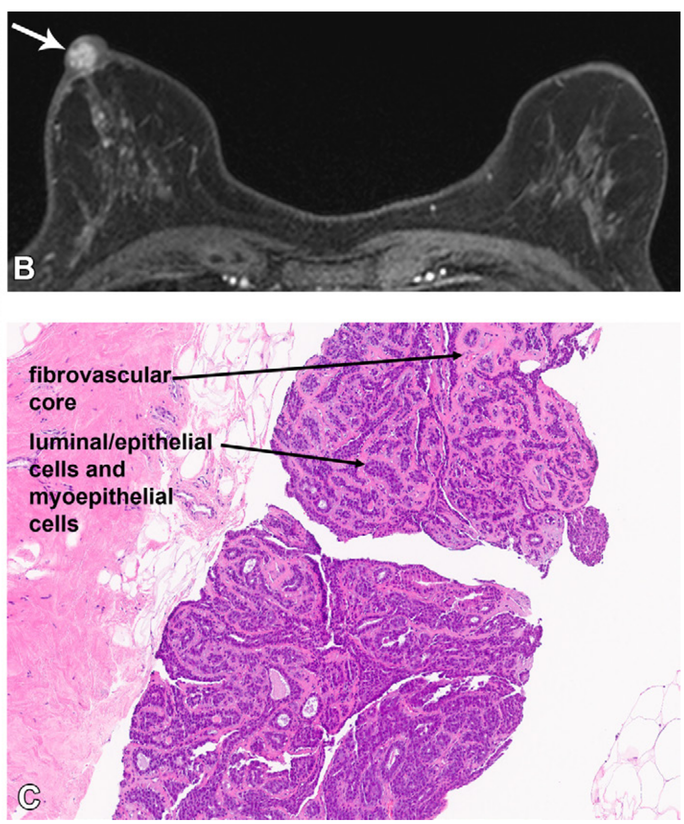


Figure 16. Papilloma in an 82-year-old woman who presented with spontaneous clear nipple discharge. **(A)** Longitudinal color Doppler US image shows a vascular retroareolar nipple mass. **(B)** Axial postcontrast T1-weighted MR image shows an enhancing mass (arrow) within the nipple. Core-needle biopsy was performed by using a semiautomated device, which was advanced to the retroareolar mass, with ample lidocaine used. The deeper part of the mass was sampled. **(C)** Stained core-needle biopsy specimen shows a benign papillary lesion with a fibrovascular core, consistent with papilloma. (Hematoxylin-eosin stain; original magnification, ×4.)

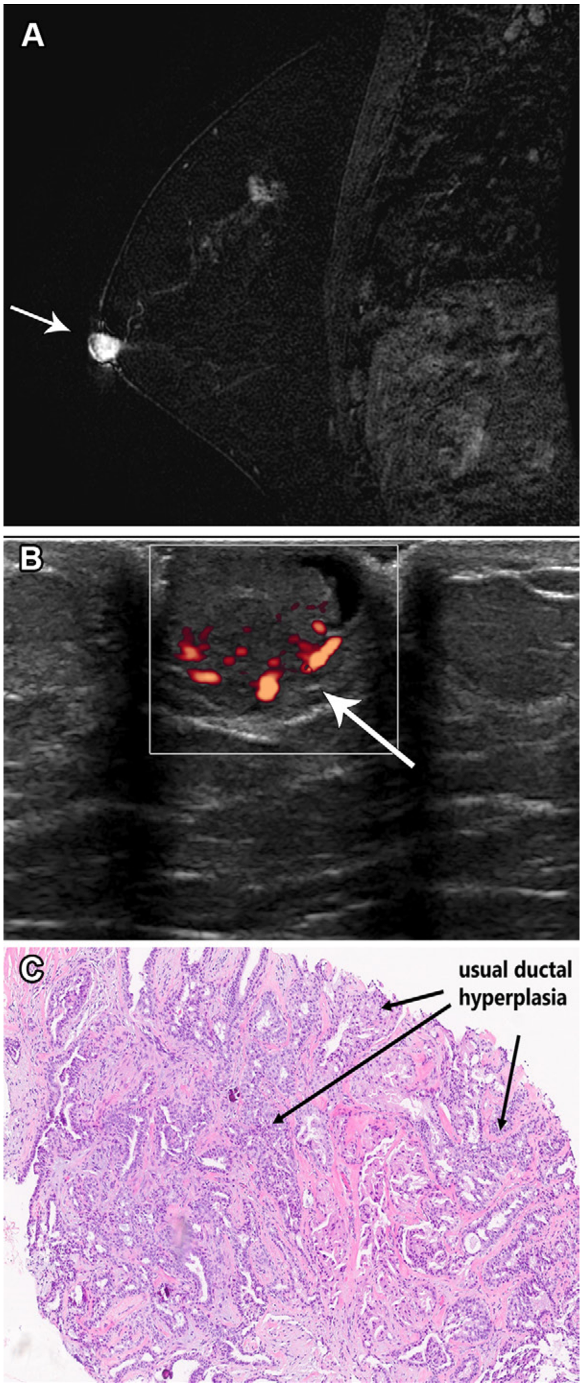


Figure 17. Nipple adenoma in a 61-year-old woman with Li-Fraumeni syndrome who presented for screening breast MRI. **(A)** Sagittal postcontrast T1-weighted subtraction MR image shows an enlarged enhancing right nipple (arrow) with washout kinetics (not shown). **(B)** Longitudinal power Doppler US image shows an isoechoic mass (arrow) within the nipple, with increased vascularity. **(C)** Histopathologic analysis revealed adenosis and usual ductal hyperplasia in a papillary architecture. (Hematoxylin-eosin stain; original magnification, ×4.) The diagnosis after surgical excision was nipple adenoma.

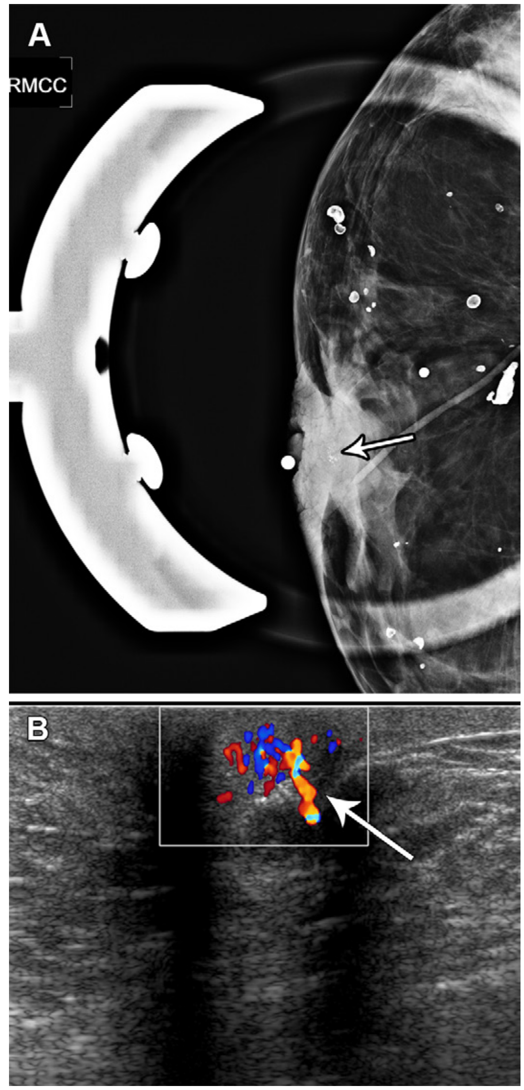


Figure 18. Syringomatous tumor of the nipple in a 77-year-old woman with a history of breast cancer treated with lumpectomy who was called back for calcifications in her right nipple. **(A)** Right breast craniocaudal magnification-view mammogram shows grouped amorphous calcifications (arrow) in the retroareolar region. **(B)** Longitudinal color Doppler US image shows a nipple mass with increased vascularity (arrow). Biopsy and subsequent surgical excision yielded syringomatous tumor of the nipple associated with DCIS.

Syringomatous Tumor of the Nipple

Syringomatous tumor of the nipple (SyT) arises from the adnexal eccrine gland of the skin. Although benign, SyT mimics cancer because it can locally infiltrate surrounding tissue (38). Histologically, SyT is centered in the dermis of the NAC, often appearing as a solitary firm mass in the subareolar region. Common clinical findings include tenderness and pruritis. Ulceration, nipple inversion, and discharge are less common (39). Mammographic findings are often nonspecific and may include a circumscribed or spiculated subareolar mass with or without microcalcifications (40). US images may show an irregular mass with internal heterogeneous echoes (Fig 18) (39). SyT is histologically challenging to diagnose owing to the overlap of microscopic features with those of other nipple disorders. As a result, the diagnosis is often determined after

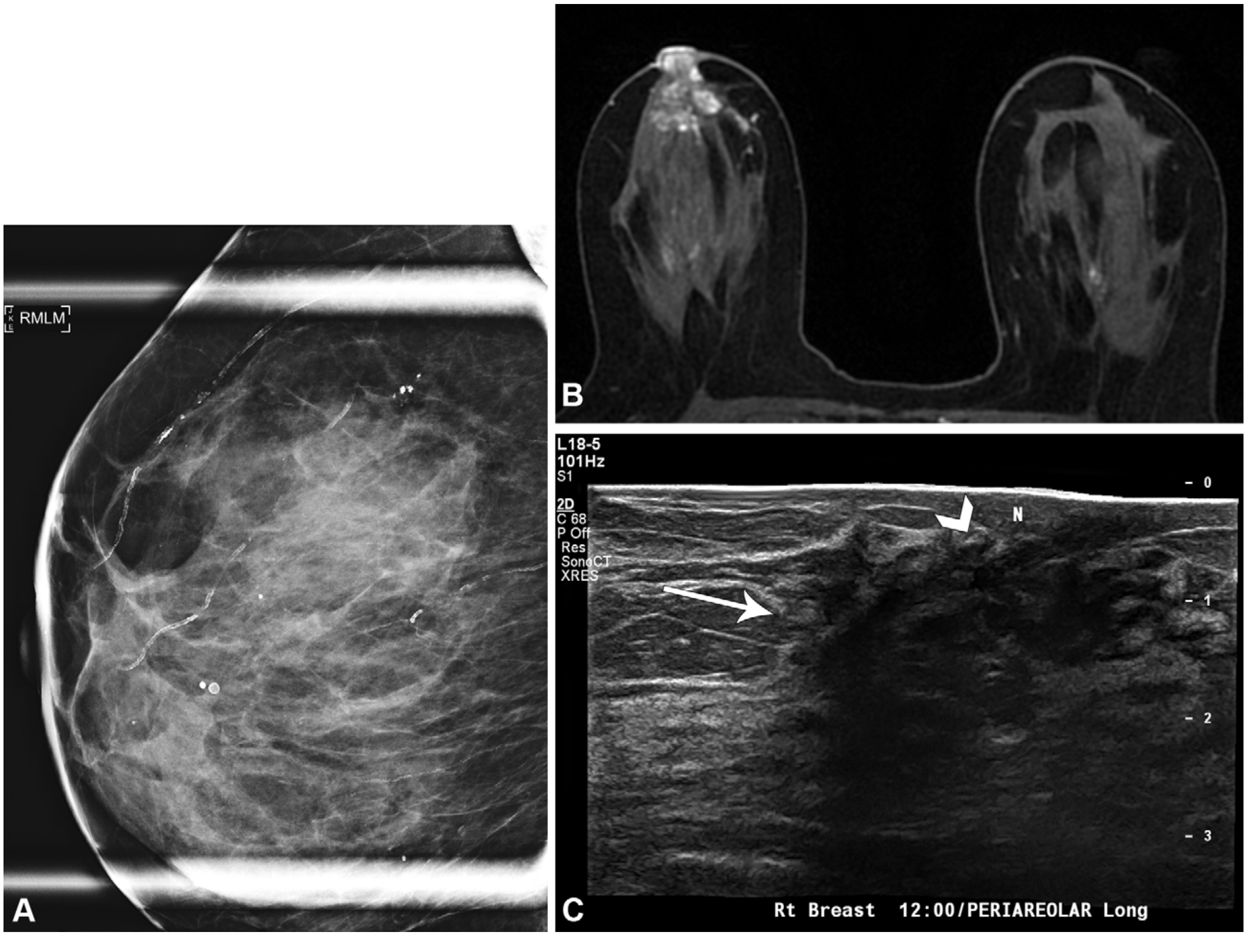


Figure 19. Retroareolar right breast cancer obscured by heterogeneous breast density in a 73-year-old woman with a history of contralateral left breast cancer after breast conservation therapy who presented for surveillance. **(A)** Lateral right breast spot magnification-view mammogram shows benign-appearing calcifications without suspicious findings. Bilateral breast US (not shown) performed for surveillance was negative for suspicious breast findings, but it did show suspicious right axillary adenopathy, which was sampled at biopsy and proved to be metastatic. **(B)** Bilateral breast MR image acquired for further evaluation shows a retroareolar mass involving the right nipple, which was not evident at mammography or US. **(C)** Second-look US shows a suspicious mass (arrow) that extends to the base of the right nipple (arrowhead); this 3-cm mass was not identified at initial US owing to normal nipple *(N)* shadowing.

surgical excision (39,41). Wide local excision with clear margins remains the preferred treatment to reduce recurrence; the reported recurrence rate is up to 45% in cases in which there are no clear surgical margins (42).

Malignant Tumors of the NAC

Breast Cancer

Invasive cancer and DCIS can begin in or spread to the nipple. Invasive ductal carcinoma, the most common breast cancer type, is also the most common malignancy involving the NAC (20). About 10% of breast cancers arise within the central ducts, less than 2 cm from the nipple (10). Subareolar cancers are challenging to identify because they can be mistaken for normal nipple structures at mammography or may be obscured by retroareolar shadowing at US (Fig 19).

Nipple-sparing mastectomy (NSM) has become more prevalent because it provides superior cosmetic results (43). The primary oncologic concern with NSM is the potential for residual tumor cells in the NAC, which may lead to recurrence. The prevalence of NAC involvement in breast cancer ranges between 9% and 14% (43,44). High-grade tumors, human epidermal growth factor receptor 2–positive central tumors, tumors larger than 5 cm, multifocal tumors, and nodal involvement are risk factors for NAC involvement (43,44).

Mammography and US are insufficient for assessing NAC invasion. Preoperative breast MRI is useful in determining the lesion-to-nipple distance and recognizing worrisome enhancement between the nipple and the known malignancy (45). Earlier studies showed that a lesion-to-nipple distance greater than 2 cm was unlikely to be associated with NAC invasion (46). In more recent studies, this cutoff has been reduced to 1 cm (47). When predicting NAC involvement, a combination of any tumor-nipple enhancement (during the early or delayed phase) with the lesion-to-nipple distance enables the best prediction of NAC involvement by breast cancer (Fig 20) (45). The high negative predictive value (94.8%) of breast MRI aids in the selection of NSM candidates (48). Despite this, intraoperative subnipple biopsy should still be performed to detect occult nipple invasion, allowing excision of the NAC at

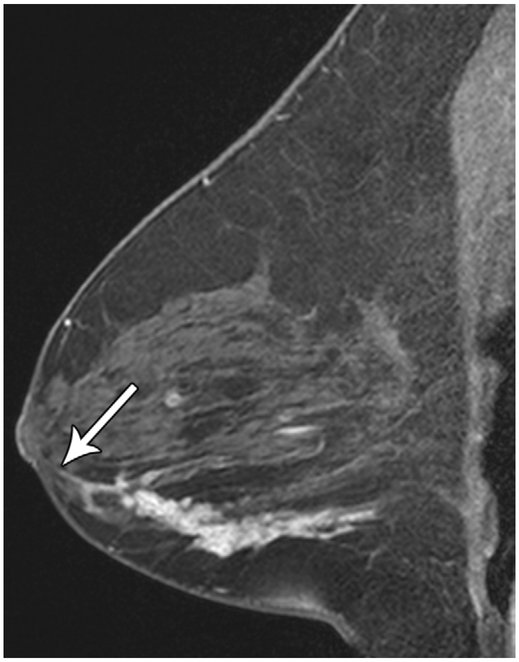


Figure 20. Preoperative MRI evaluation of the NAC in a 55-year-old woman with right breast invasive ductal carcinoma and DCIS. Preoperative breast MRI was performed to evaluate the disease extent. Sagittal postcontrast T1-weighted breast MR image shows a distance of greater than 1 cm between the nipple base and the anterior aspect of the known malignancy (arrow). The patient underwent breast nipple–sparing mastectomy successfully. The surgical margins and results of intraoperative biopsy of the nipple base were negative for malignancy.

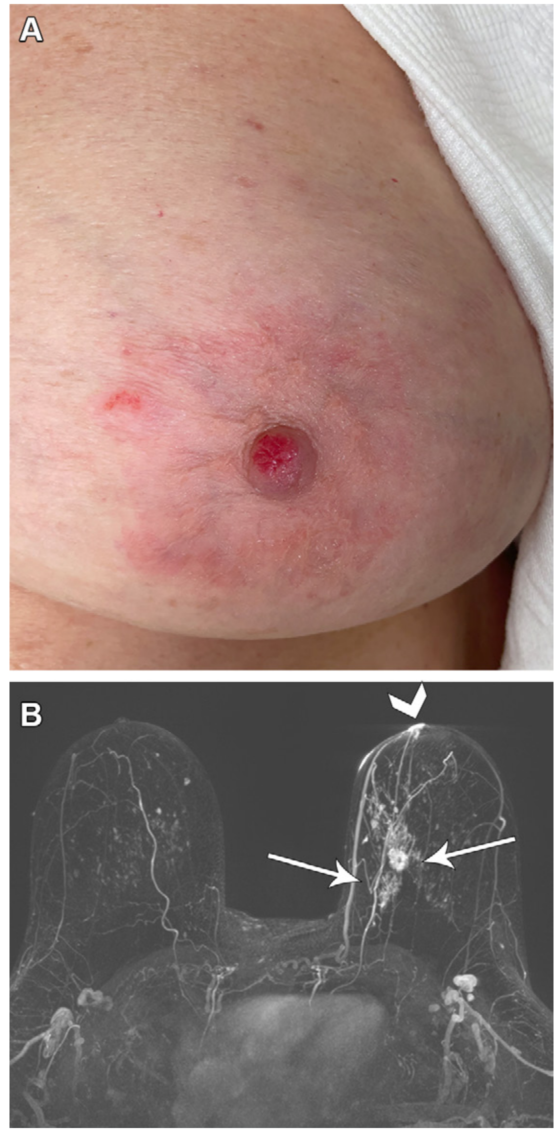


Figure 21. PD of the breast in a 68-year-old woman with left nipple pain, excoriation, and bloody nipple discharge. **(A)** Photograph of the left breast shows erythema and inflammation of the left NAC. **(B)** Maximum intensity projection breast MR image shows abnormal enhancement of the left nipple (arrowhead) and an irregular breast mass with irregular margins and associated clumped segmental nonmass enhancement in the medial breast (arrows). The patient was diagnosed with PD of the nipple with invasive ductal carcinoma and DCIS (positive for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor) of the left breast.

the time of surgery if it is involved (48). Breast MRI is sensitive for the detection of NAC involvement by a known malignancy. The cutoff lesion-to-nipple distance is 1 cm.

PD of the Breast

PD of the breast is a rare cancer that accounts for 0.5%–5.0% of all breast cancers (49). It is characterized by the presence of tumor cells within the epidermis of the NAC. The pathogenesis is controversial. The epidermotropic theory speculates that ductal cells migrate to the nipple epidermis from an underlying breast cancer, while the transformation theory speculates that Paget cells result from keratinocytic malignant transformation (49).

PD of the breast is most common among women between the ages of 50 and 60 years (49). The clinical characteristics of PD of the breast are eczematoid changes that can progress to nipple ulceration and NAC destruction. Given the eczematoid symptoms (Fig 21A), PD of the breast can be mistaken for benign skin conditions, leading to possible delays in the diagnosis if temporary relief occurs with steroid treatment (50). Unlike PD of the breast, NAC eczema typically involves both nipples (51).

Full-thickness nipple punch biopsy is diagnostic for PD of the breast. Nipple exfoliative cytology also can be helpful. The presence of pale Paget cells with increased cytoplasm is the histologic signature of PD of the breast (52). PD of the breast is associated with a high histologic grade, lymph node involvement, absence of estrogen and progesterone receptors, and overexpression of human epidermal growth factor receptor 2 (53). An underlying invasive cancer or DCIS is present in up to 90% of cases (52). Multicentricity is reported in 32%–41% of cases (54,55). Mammographic findings of PD of the breast include NAC thickening, retraction, flattening, and microcalcifications (20). In as many as 50% of cases, mammography is negative (56). Dilated ducts, masses, and calcifications are

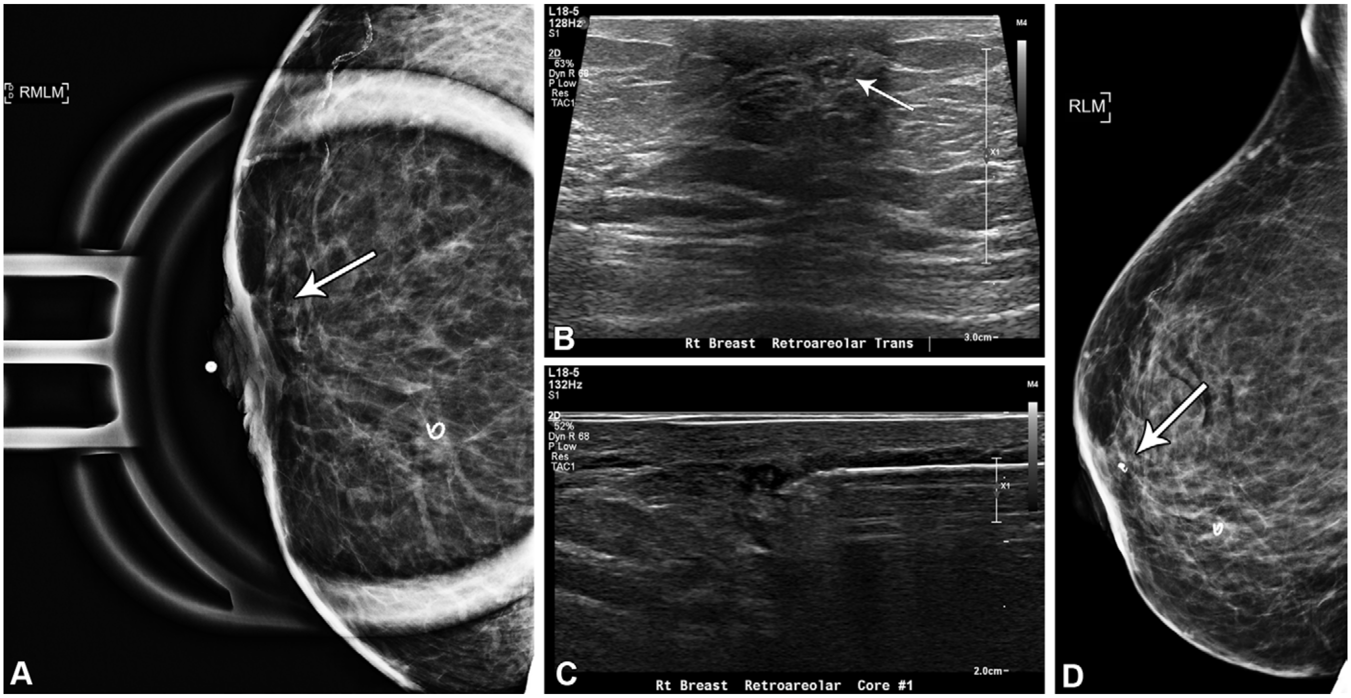


Figure 22. US-guided biopsy of retroareolar calcifications performed in lieu of stereotactic biopsy in a 66-year-old woman. The patient was called back after screening for right breast calcifications. **(A)** Lateromedial magnification-view right breast mammogram shows grouped suspicious retroareolar calcifications (arrow). **(B)** Transverse US image shows a correlating mass (arrow) with echogenic foci. **(C)** US image was obtained during US-guided biopsy. Analysis of the biopsy specimen (not shown) confirmed the presence of calcifications. **(D)** Lateromedial postprocedural mammogram findings confirmed removal of the calcifications and the appropriate clip position (arrow). Pathologic analysis demonstrated an atypical papillary lesion.

the most common US findings (2). Breast MRI should be performed to identify an underlying malignancy if none is seen at conventional imaging (Fig 21B). MRI features include flattening or asymmetric enhancement of the nipple, nonmass enhancement, and enhancing masses (57).

Mastectomy is the standard treatment of PD of the breast. However, breast-conserving surgery with central lumpectomy and whole-breast radiation may be a less invasive option with similar survival rates (58). When PD of the breast is associated with an invasive malignancy, the prognosis is worse than that for PD that is associated with DCIS alone or PD that is confined to the NAC (59).

Biopsy Techniques

US-guided Biopsy

Nipple calcifications and masses are uncommon but can pose a management challenge for radiologists when they are detected (60). Calcifications of the NAC are commonly benign; however, a malignant cause is possible and must be excluded. Therefore, suspicious NAC calcifications, similar to calcifications elsewhere in the breast, require biopsy. For the initial attempt to sample nipple calcifications, US guidance should be used. With meticulous US scanning, a sonographic correlate for mammographic calcifications may be identified. US-guided biopsy can then be a more feasible alternative to stereotactic biopsy (Fig 22).

Performing US-guided biopsy of a nipple mass or nipple calcifications is challenging but feasible; it requires patience and planning. The nipple is a sensitive structure with many nerve endings, so ample local anesthetic should be administered. Additional measures to alleviate discomfort include using buffered lidocaine with sodium bicarbonate or lidocaine with epinephrine and allowing time for the lidocaine to take effect before the biopsy. The patient should be made aware of the possibility of pain and bloody nipple discharge following the procedure.

US-guided fine-needle aspiration (FNA) is the easiest method used to sample nipple masses or calcifications. Nonthrow core-needle biopsy (CNB) also can be performed if FNA results are negative or inconclusive. Although quite effective, the use of FNA can be limited or nondiagnostic for some benign or high-risk breast lesions, in which case CNB is more likely to be diagnostic (61). A throw device or vacuum-assisted biopsy can be used if the calcifications or the mass extend posteriorly into the retroareolar region (Fig 23). If the imaging target is calcifications, a radiograph of the specimen is suggested to document calcification retrieval (60). If biopsy of a nipple mass or calcifications with US guidance is not feasible, wedge excision and skin punch biopsy of the nipple are surgical alternatives, but they may lead to nipple deformity (60).

Stereotactic Biopsy

Stereotactic biopsy of the NAC is challenging because of the superficial location and the thin compression of the target, which make it difficult to stabilize during biopsy (60). In addition, the biopsy incision should not penetrate the areola,

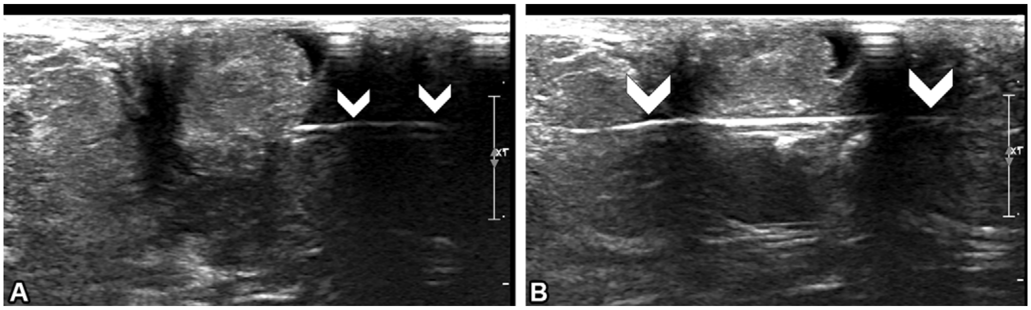


Figure 23. US-guided biopsy of a retroareolar-nipple mass in a 61-year-old woman. Images at US-guided core-needle biopsy before **(A)** and after **(B)** the biopsy gun was fired show the biopsy needle (arrowheads) successfully targeting the portion of the retroareolar mass within the breast. Ample local anesthetic was administered to ensure that the nipple was adequately anesthetized. The diagnosis was nipple adenoma. (See Fig 17 for the diagnostic workup in this patient.)

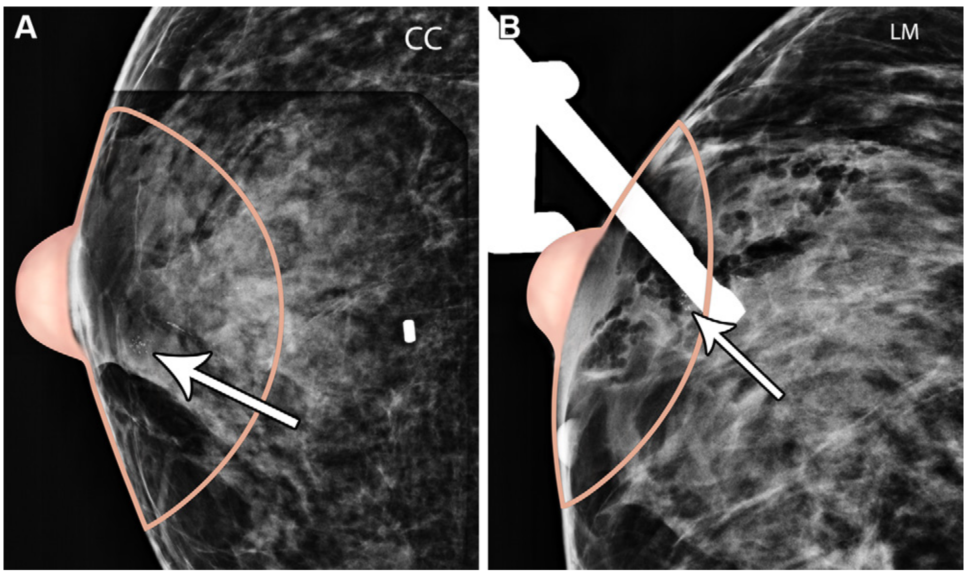


Figure 24. Stereotactic biopsy techniques for retroareolar targets in a 56-year-old woman with a family history of breast cancer who was called back after screening that revealed suspicious retroareolar calcifications. **(A)** Craniocaudal stereotactic scout view left breast mammogram shows pleomorphic calcifications (arrow) overlapping with the areola. **(B)** Lateromedial stereotactic scout view left breast mammogram shows that targeting on the lateromedial view resulted in a better window, with the calcifications (arrow) seen closer to the margin of the areola. Targeting was performed posterior to the areola to avoid the areolar skin. Directional sampling was then performed, with targeting toward the nipple. Specimen radiography findings (not shown) confirmed that the calcifications were sampled. Pathologic analysis revealed DCIS.

as an areolar incision may extend to the nipple, causing a laceration that necessitates the use of absorbable sutures for closure (62). Despite the challenges, there are a few techniques that can be used to safely perform stereotactic biopsy of retroareolar calcifications. As the size of the areola is variable, changing the approach to one that involves a different imaging projection may help to avoid the areola. Also, targeting posteriorly to the calcifications of interest, followed by directional sampling whereby the operator directs the trough of the needle toward the nipple, may be necessary (Fig 24). Because the nipple is thinner than the rest of the breast, a breast sling or hammock that builds up the breast can be created by pressing a towel or saline solution bag against the imaging plate (63).

Nipple-rolling Technique.—Additional maneuvers to facilitate stereotactic biopsy of retroareolar calcifications include rolling the nipple away from the needle entry site (Fig 25). This allows the radiologist to access an entry site outside of the areolar skin (Fig 26). During stereotactic biopsy of a retroareolar lesion, positioning the breast with the nipple rolled away may open a safe window for biopsy that avoids the areola.

Nipple Compression Technique.—Attention should be paid to the method used to compress the nipple and retroareolar region for stereotactic biopsy. If the nipple is compressed in the middle of the compression aperture, which is ideal for other targets, the retroareolar tissue can easily roll and will be unstable during biopsy (Fig 27). The retroareolar tissue becomes thinner with compression than the immediately adjacent posterior breast tissue. Positioning the anterior edge of the plate just posterior to the nipple makes the compression more uniform and stabilizes the breast because only the thin part of the breast is compressed between the plates (Fig 27B).

Lateral Arm Approach.—The lateral arm stereotactic biopsy technique allows the needle to enter the breast parallel to the compression paddle and detector plate. Using this approach may make sampling of retroareolar targets more feasible because an areolar incision is avoided.

Conclusion

The NAC requires meticulous multimodality imaging. Several benign and malignant disease processes, such as papilloma and breast cancer, can involve or arise in the NAC. Significant

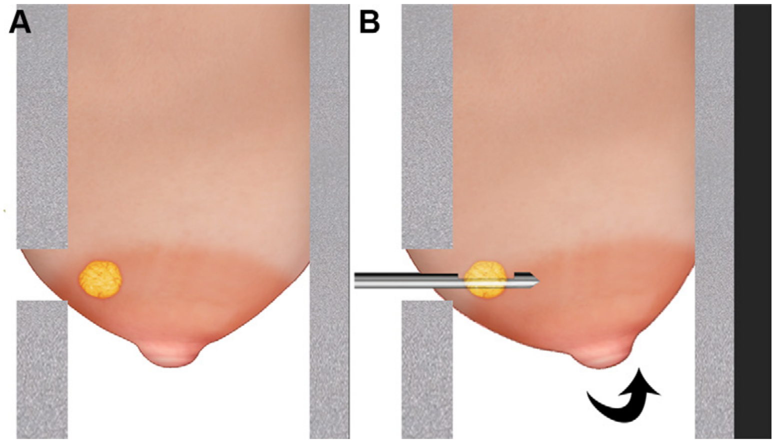


Figure 25. Nipple-rolling technique for stereotactic biopsy. **(A)** Illustration depicts the retroareolar biopsy target overlapping with the areolar region. **(B)** Illustration depicts rolling of the nipple away from the direction of the needle entry site (arrow), which creates an entry site that is away from the areolar skin.

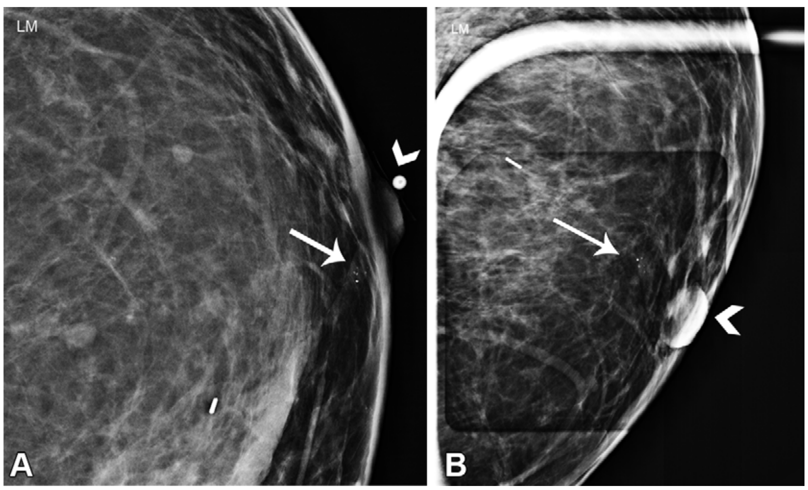


Figure 26. Nipple-rolling technique for stereotactic biopsy performed in a 64-year-old woman with suspicious retroareolar calcifications who presented for stereotactic biopsy. **(A)** Lateromedial magnification-view mammogram shows the calcifications (arrow) at the base of the nipple (arrowhead), without a safe window for biopsy outside of the areola. **(B)** Lateromedial scout view mammogram shows the nipple (arrowhead) rolled medially, away from the direction of the needle entry. This created a window for the needle to enter the breast posterior to the areolar skin. The retroareolar calcifications (arrow) were targeted by using a lateral-to-medial approach.

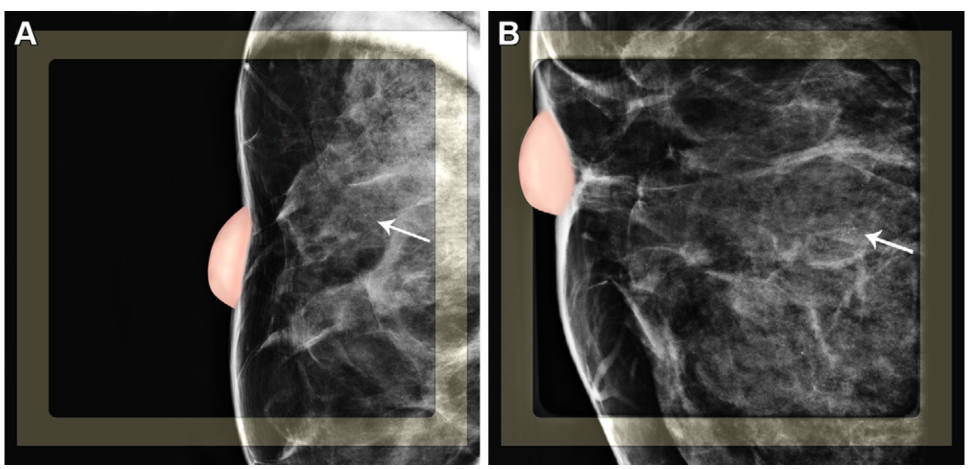


Figure 27. Nipple compression technique for stereotactic biopsy. **(A)** Lateromedial stereotactic scout view mammogram in a 53-year-old woman undergoing stereotactic biopsy shows how the nipple and calcifications (arrow in **A** and **B**) are positioned in the center of the paddle aperture. Although this is the standard approach for stereotactic biopsy, it is not ideal in this scenario. The retroareolar tissue becomes thinner with compression than the immediately adjacent breast tissue, causing the nipple and retroareolar tissue to easily roll inward and become unstable during the biopsy. **(B)** Another lateromedial stereotactic scout view mammogram, with the patient positioned differently, shows how ideally, the plate should be positioned with the anterior edge of the paddle just posterior to the nipple. This will create pressure on a larger surface of the breast, stabilizing the breast and the retroareolar tissue by keeping the retroareolar tissue stretched and allowing the radiologist to complete the biopsy successfully.

overlap of imaging findings and clinical presentations among benign and malignant NAC diseases makes assessing this region challenging. Furthermore, performing image-guided biopsy of tissue in this region is difficult and poses further diagnostic and management challenges. Breast MRI is the preferred imaging modality for assessing NAC involvement by breast cancer. Currently, a 1-cm or greater tumor-to-nipple distance on breast MR images indicates suitability for nipple-sparing mastectomy. Further research is needed to evaluate the accuracy of breast MRI when the tumor-to-nipple distance is less than 1 cm.

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