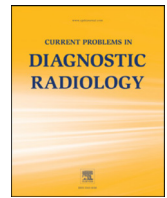




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Nipple Discharge: When is it Worrisome?

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Nipple discharge is the third most common breast related complaint seen in the breast clinics. Although the majority of cases are due to a benign etiology, 5%-12% cases of pathological nipple discharge may be harboring an underlying malignancy. A thorough radiological workup in cases of pathological nipple discharge is thus of utmost importance, with the initial imaging modality depending on the age of the patient. The imaging modalities include mammogram (MG) and ultrasound (US) with addition of breast MRI if the nipple discharge is clinically suspicious and no MG or US correlate is identified. Magnetic Resonance Imaging (MRI) also holds promise in demonstrating the exact extent of a pathology detected on US and thus aids in the planning of further management.

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Introduction

Most radiologists are familiar with imaging of the breast when a female comes with the complaint of a breast lump, which is the most common presentation in clinical practice.¹ Nipple discharge is the 3rd most common complaint in the outpatient department, after lump and mastalgia. The initial workup of this entity begins in the breast clinics, where patients with nipple discharge can be triaged into having physiological discharge, i.e., not needing further imaging; and pathological discharge which warrants further workup with imaging to rule out malignancy. It is of utmost importance to be aware of the various causes of nipple discharge, as in 5%-12% cases it may be the first presentation of a malignancy.² Even in the presence of a benign etiology, the radiologist plays a major role in detecting the cause and in mapping the extent of the disease for surgery. As a high percentage of nipple discharge are due to papillary lesions of the breast, where the radiologist is an integral part of the multidisciplinary team; not only in planning vacuum assisted breast biopsy (VABB) or excision of these lesions, but also in establishing radiological-pathological (rad-path) correlation. The current review highlights the differences between physiological and pathological discharge and discusses the various pathologies causing suspicious nipple discharge with their imaging features. An algorithmic imaging approach for cases of nipple discharge is also presented with a brief note on the management of these cases.

Physiological and Pathological Discharge

The breast consists of multiple acini which are a part of the terminal ductal lobular unit (TDLU), also called the basic functional unit of the breast. Multiple TDLUs merge into minor and major lactiferous ducts. A group of TDLUs form lobules; and lobules form lobes. Ducts from the individual lobes, about 5-9 in number, dilate to form sinuses near the nipple and then open into the nipple. These TDLUs are supported by the stroma of the breast.³

Nipple discharge occurs due to physiological or pathological processes in the TDLUs or mammary ducts which lead to excess secretions or hindrance of drainage.⁴

The work-up of a case of nipple discharge begins with a good history, constituting details such as color and nature, spontaneous or expressed, unilateral or bilateral and single or multiduct. Bilateral expressed or nonspontaneous discharge noticed by the patient on pressing the nipple which is whitish, green, yellowish in color usually constitutes physiological discharge and frequently does not require further evaluation with imaging other than routine screening mammography (MG).^{5,6} Galactorrhea may require further laboratory investigations to rule out hyperprolactinemia in addition to a detailed history of intake of dopamine receptor blocking drugs. However unilateral, spontaneous, serous or serosanguineous discharge which is frequently from a single duct is pathological in nature and is the one which needs thorough imaging (Table 1). Cytology of this discharge, even though frequently done, is neither sensitive nor specific and can be avoided.⁷ In patients with pathological discharge, it has also been observed that higher patient age, presence of palpable abnormalities and recent onset nipple retraction are more likely to harbor malignancies.^{8,9} Nipple discharge in males is always pathological as it may have an underlying malignancy in one-fourth to one-half of the cases.¹⁰

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TABLE 1
Differences between characteristics of physiological and pathological nipple discharge.

Physiological nipple discharge	Pathological nipple discharge
White, greenish, coffee-colored, yellow, brown/black	Serous or serosanguineous, blood stained
Expressed/non-spontaneous	Spontaneous
Multi-duct/Multi-pore	Single duct/Uni-pore

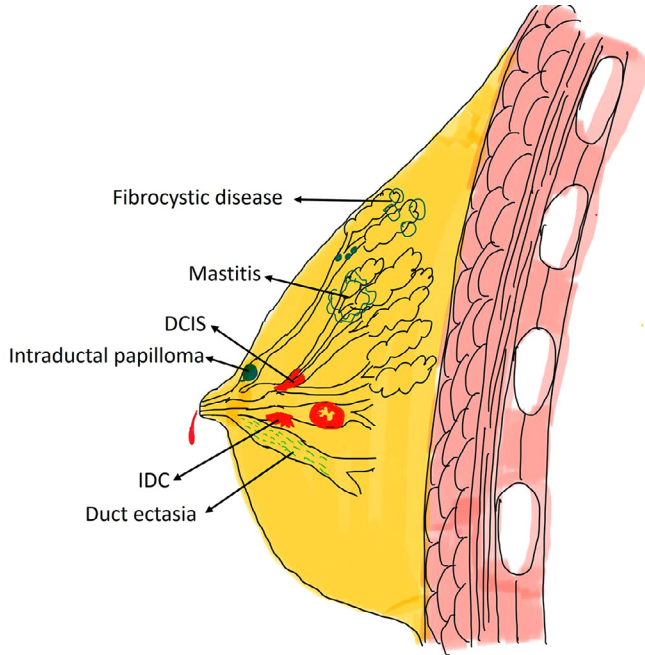


FIG 1. Pathological and physiological causes of discharge.

Fig 1 shows the various causes of nipple discharge.

Imaging Modalities in Evaluation of Pathological Discharge

Retroareolar ultrasound (US) and MG are the primary imaging modalities to evaluate nipple discharge. In younger women <30 years of age, US is primarily performed; with MG being used as a complementary investigation if required; while in women above 30 years of age, mammography should be done as the first modality for diagnostic imaging.⁶

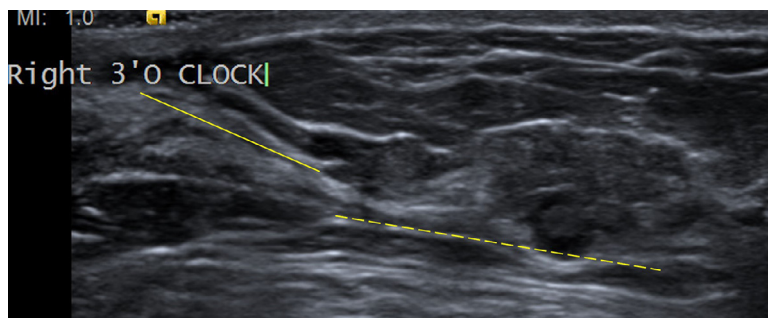


FIG 2. Radial targeted breast ultrasound shows length of duct from nipple base to mass (long solid line) and length of duct segment affected by mass (dotted line). Report of ultrasound examination should include clockface position of intraductal mass and size of intraductal mass in addition to distance of mass from nipple. Ultrasound guided VAB yielded intraductal papilloma.

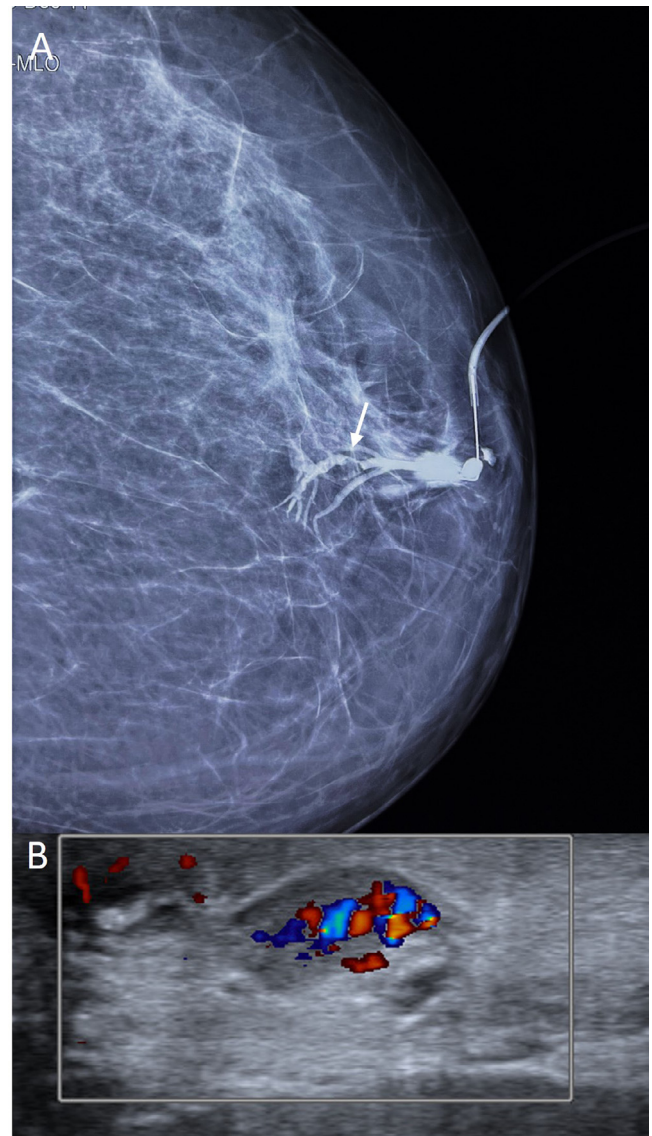


FIG 3. Conventional ductography done with Jabczenski ductogram cannula showing opacification of the affected ductal tree. The retroareolar duct is dilated with one of branches showing an intraductal filling defect (arrow). Correlative ultrasound showed an intraductal echogenic soft tissue suggestive of papilloma.

Mammography (MG)

Other than masses or architectural distortion, MG should be carefully scrutinized for calcifications suspicious for DCIS, as it is the most common malignancy presenting as nipple discharge. Benign rod-like

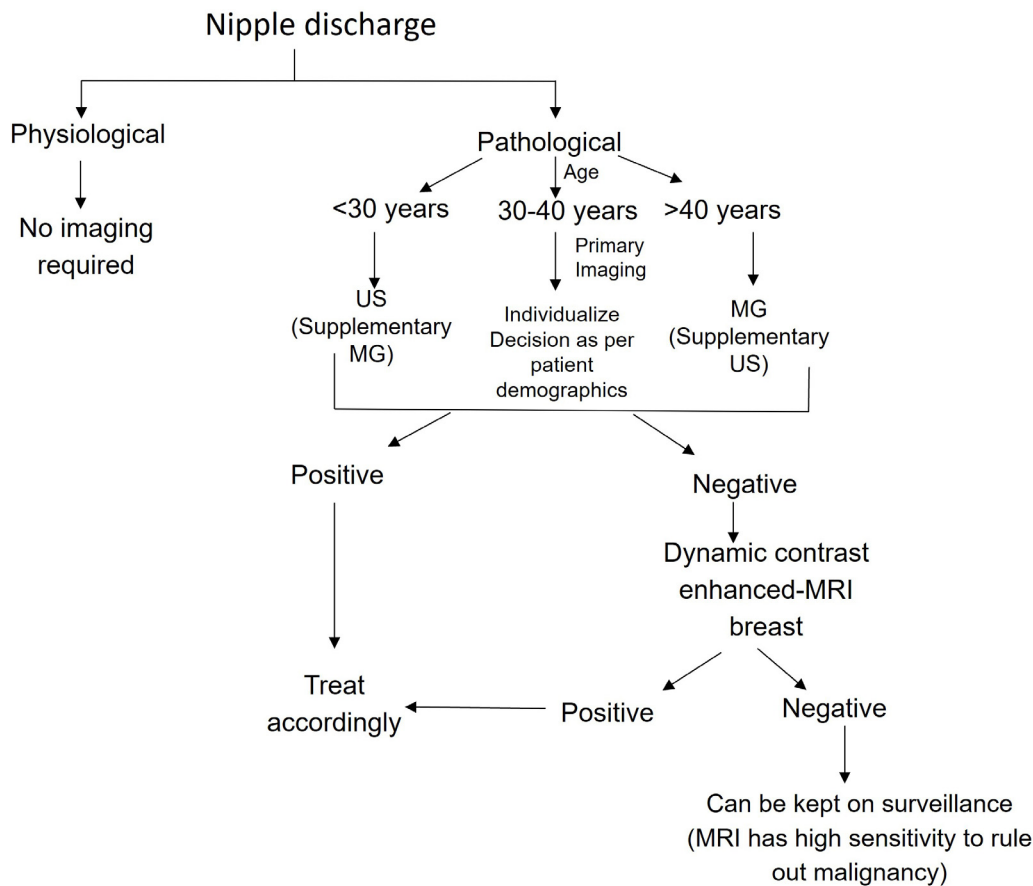


FIG 4. Imaging Algorithm for workup of nipple discharge.

calcifications may be seen in cases of plasma cell mastitis or duct ectasia. Solitary dilated duct, especially if it appears as a new finding on MG, should be carefully evaluated with US. It should be remembered that in many cases, MG has a low yield in evaluation of nipple discharge.^{1,4}

Ultrasound (US)

It is warranted in all cases of pathological nipple discharge as most culprit lesions will be small, noncalcified intraductal masses in the retroareolar region which may not be picked up on MG. Common benign findings may be ductal dilatation with echogenic nonvascular contents signifying ductal ectasia with inspissated secretions. Intraductal soft tissue, irregular duct margins and periductal hypoechoic soft tissue are suspicious findings.¹¹ The US report should clearly state the clockface location, distance of the mass from the nipple base and length of the segment of the duct involved by the intraductal mass (Fig 2). It is not advisable to image the nipple keeping the US probe straight anteriorly, as most of the retroareolar ducts may be obscured due to shadowing. Instead, Stavros described various methods to image the retroareolar region.¹² The "peripheral compression technique" provides a better angle of insonation over the ducts. Retroareolar region can also be assessed by "two hand compression technique" where the ducts at the base of the nipple are imaged between the operator's hand and the angled probe. The "rolled nipple technique" best evaluates the duct within the nipple.^{12,13}

Conventional Ductography

Initially conventional ductography used to be performed for evaluation of nipple discharge in cases with negative MG and US. In this, the suspected duct was cannulated with a narrow gauge cannula (like Jabczynski cannula) and 0.2-0.3 mL iodinated contrast was instilled slowly and carefully, avoiding instillation of air bubbles, followed by a standard 2-view mammographic exposure.^{11,14} Positive findings included irregularity of the ducts, intraductal filling defects or abrupt cut-off in the duct (Fig 3).¹⁵ Due to its invasive nature, failure to recognize or cannulate the culprit duct, inability to directly visualize the pathology and low specificity of the procedure, this technique is infrequently resorted to nowadays.^{16,17} Due to its low sensitivity and specificity and added patient discomfort, this procedure has almost been replaced by MRI.¹⁶

Magnetic Resonance Imaging (MRI)

Due to the high sensitivity of MRI in the range of 93%-100%, it is a promising modality in the evaluation of pathological nipple discharge, especially in cases with negative US and MG evaluation.¹⁸ Pathological findings include enhancing intraductal masses, or linear or segmental nonmass enhancement which could represent neoplastic or inflammatory etiology.^{11,18} There may be intrinsic intraductal T1 hyperintensity due to hemorrhage or proteinaceous debris. Subtracted contrast enhanced sequences can pick small foci of enhancement within these T1 hyperintense areas, which can represent papillomas or foci of ductal carcinoma in situ (DCIS).¹ Studies have shown that a

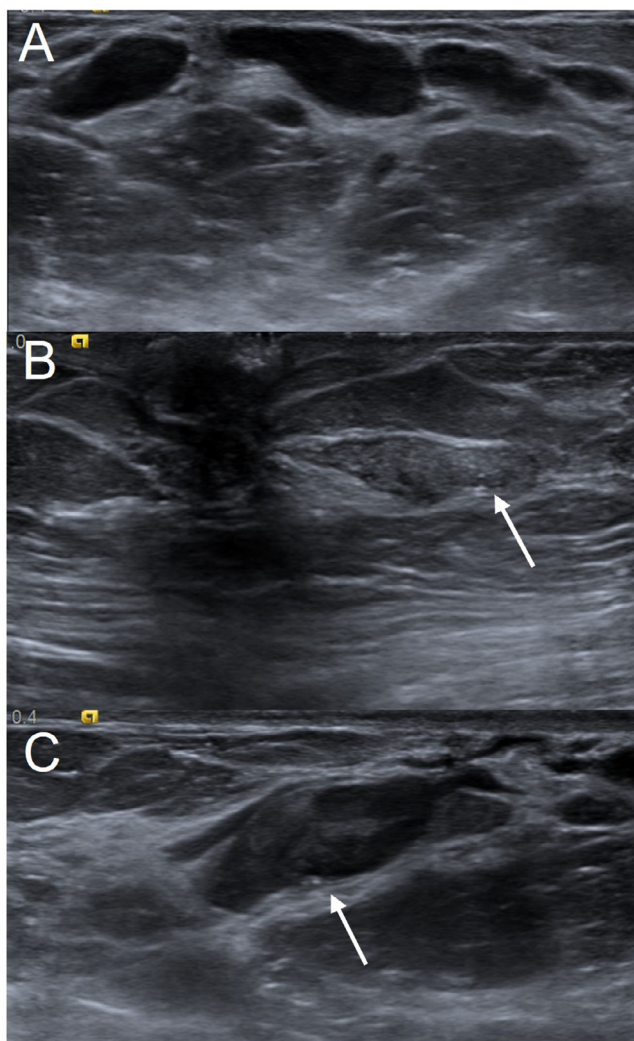


FIG 5. Duct ectasia in a premenopausal lady who complained of having greenish nipple discharge for 2 years. Ultrasound (US) images show dilated ducts (caliber >3mm) (A), extending beyond the central breast. Internal non-vascular echogenic contents (B,C) are seen, suggesting inspissated secretions.

negative MRI has a high sensitivity for ruling out malignancy and can avoid a central duct excision.¹⁹ Even the small proportion of cancers missed by MRI were eventually found to be grade 1 DCIS.²⁰ It also can localize peripheral lesions that are missed by a central duct excision. MRI also helps to map the exact disease extent and helps in the surgical plan. In cases of rad-path or clinicopathological discordance, MRI plays a role in giving an overview of the disease process and MRI guided biopsy of most suspicious area can be planned. Also, US at times may not be able to characterize intraductal contents as secretions or soft tissue due to the absence of demonstrable vascularity. MRI helps in such cases by depicting the enhancing intraductal component, and hence serves as a problem-solving tool.

Indirect MR ductography constitutes noncontrast sequences which are heavily T2 weighted and demonstrate dilated ducts well. Intraductal soft tissue is seen as a filling defect. Direct MR ductography can also be done by instilling gadolinium-based contrast agent into the ducts at the nipple like conventional ductography, followed by T1 weighted imaging.

Fig 4 describes the imaging algorithm in cases of pathological nipple discharge.

Pathological Nipple Discharge

Pathological nipple discharge can be present as a result of various etiologies which range from harmless benign causes to extensive malignancies. The following sections discuss the benign and malignant etiologies which may present as, or have accompanying pathological nipple discharge. (Duct ectasia is a cause of physiological nipple discharge, however discussed here due to its common occurrence).

Benign

Ductal Ectasia

This is defined as dilatation of mammary ducts to >3mm in diameter with or without inspissated secretions within.¹¹ Frequently seen in perimenopausal women as a part of normal involution, and in smokers, it usually presents with expressed thick cheesy nipple discharge. However, it may be asymptomatic in up to 50% cases, where it is incidentally detected on US.²¹ On imaging, dilated tubular structures conforming to ducts are seen on MG and US. These ducts might be anechoic on US or may have echogenic nonvascular content within, signifying secretions (Fig 5). Associated inflammation may be seen in the form of periductal thickening, increased echogenicity of surrounding fat and fibroglandular parenchyma or even microabscesses. Duct ectasia is a benign diagnosis and usually requires no treatment.

Fibrocystic Disease

This is a common pathology encountered in day-to-day practice due to which patients frequently present with mastalgia. Some patients may also complain of yellow or serous nipple discharge.²² MG if done, can show small circumscribed equal density masses in the background of dense parenchyma, which correspond to multiple cysts on US. Diffuse scattered punctate calcifications may also be seen. US shows multiple small simple cysts scattered in the breast. Few complicated cysts showing internal echoes and thin septae may be seen additionally. Treatment is conservative and involves symptomatic relief. US-guided aspiration of large, tense cysts can be done for pain relief.

Intraductal Papilloma

This is by far the most common cause of bloody nipple discharge, however, can also present with spontaneous serous discharge.²³ These are papillary lesions which grow from ductal epithelium into the lumen and can be present in central or peripheral ducts. Central papillomas are usually solitary and more commonly present with nipple discharge. Peripheral papillomas are mostly multiple, present with a palpable lump, nipple discharge or as an incidental lesion, and are more likely to harbor malignant foci. MG might be normal in some cases or may show a solitary dilated duct. US should always be done to evaluate cases of pathological nipple discharge as MG may be less sensitive in detecting papillomas. A dedicated US of the retroareolar region is a must to look for dilated ducts with internal soft tissue. Intraductal polypoidal soft tissue with vascular core on doppler denotes presence of papillomas which might be single or multiple (Figs 6, 7). Too much pressure while doing US might obliterate the vascularity in the lesion. Also, power doppler is more sensitive in detecting intramass vascularity. Papillomas may harbor foci of atypia or even DCIS and have variable upgrade rate on excision ranging between 21%–38% (Figs 8, 9).²⁴ The usual treatment of symptomatic central papillomas is central duct excision or microdochectomy. Management of asymptomatic papillomas not showing any atypia varies from center to center, with some surgeons preferring to follow them up if radiology and pathology are concordant.²⁵

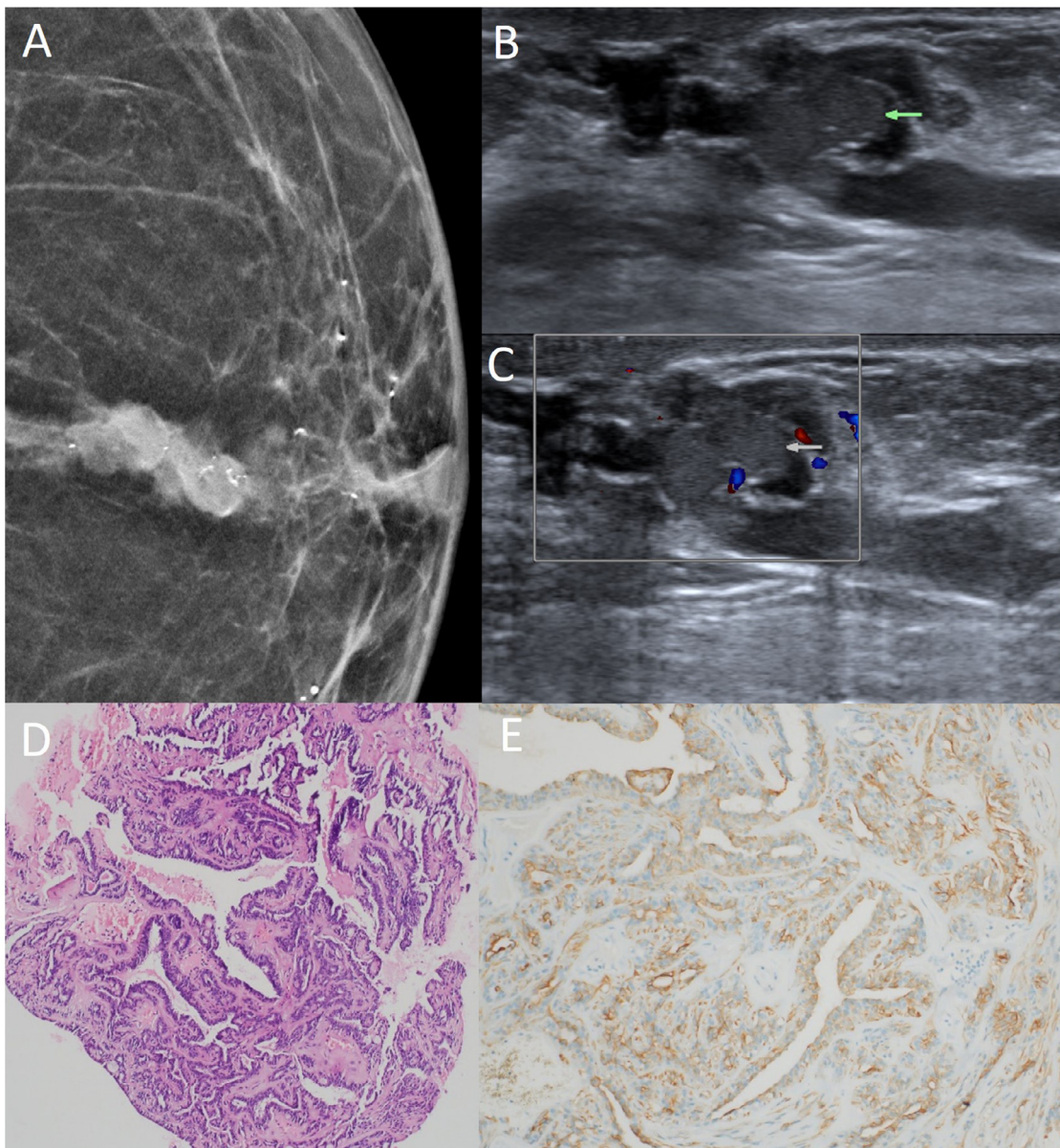


FIG 6. Solitary dilated duct on mammogram (A) with benign round and rod like calcifications within and elsewhere in the breast. US showed a dilated duct (B) in the retroareolar region with intraductal vascular soft tissue showing vascularity (C). US guided 9-gauge (G) VABB in this patient with serous nipple discharge was done (D, E) which showed cystically dilated duct filled with papillae having hyalinized fibrovascular core covered with epithelial and myoepithelial layer, consistent with benign papilloma. There was no atypia.

Mastitis

Mastitis is localized inflammation involving breast parenchyma and may be seen in the puerperal or nonpuerperal setting. Patient mostly presents with localized breast pain, tenderness and local signs of inflammation. A small proportion, up to 1%-2%, of these patients may also have associated nipple discharge; particularly in the setting of duct ectasia with periductal mastitis.^{26,27} These cases are usually managed by the surgeon or the physician and imaging is required in nonresolving cases or when suspicion of a breast abscess exists. MG is usually not tolerated by patients due to pain and tenderness, however if done, shows global or focal asymmetry with trabecular and skin thickening. US appearances vary from ill-defined areas of increased echogenicity signifying inflammation; to irregular heteroechoic intercommunicating areas with or without drainable collections. In periductal mastitis, these heteroechoic areas are seen in the

parenchyma adjacent to the dilated ducts. Management is by antibiotics and anti-inflammatory drugs. Drainage of any liquified abscess can be done under image guidance or by surgery.

Malignant

Ductal Carcinoma In Situ (DCIS)

It is the most common malignant lesion to present as bloody or serous nipple discharge. It is classically detected on screening MG as suspicious pleomorphic segmental or fine linear calcifications; and nipple discharge is a much rare presentation. It may also present as a mass on imaging. Usually, it is amenable to US guided core biopsy or can be sampled under stereotactic guidance.²⁸ In a small proportion, sonomammogram might be negative with lesion only detected on MRI as nonmass enhancement (Fig 10).²⁹

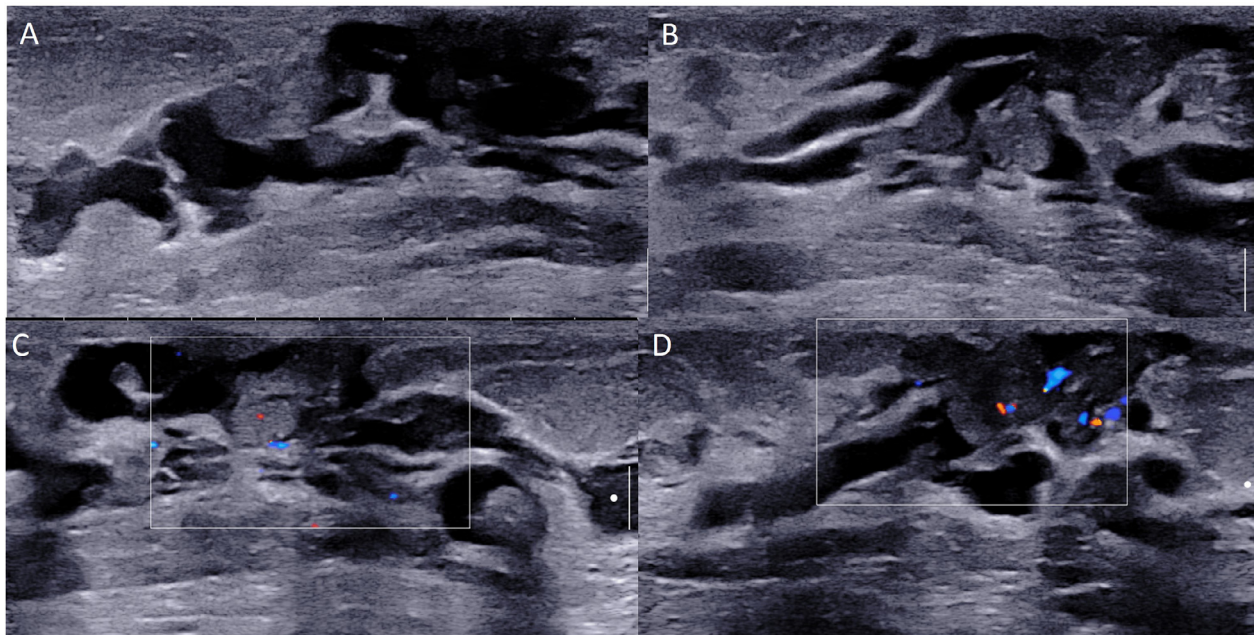


FIG 7. A 38-year-old female presented with right breast serous nipple discharge. Ultrasound (A-D) showed dilated central and peripheral ducts with multiple (>5) intraductal echogenic masses projecting into the duct lumen, with few showing vascular core, consistent with multiple papillomas (papillomatosis).

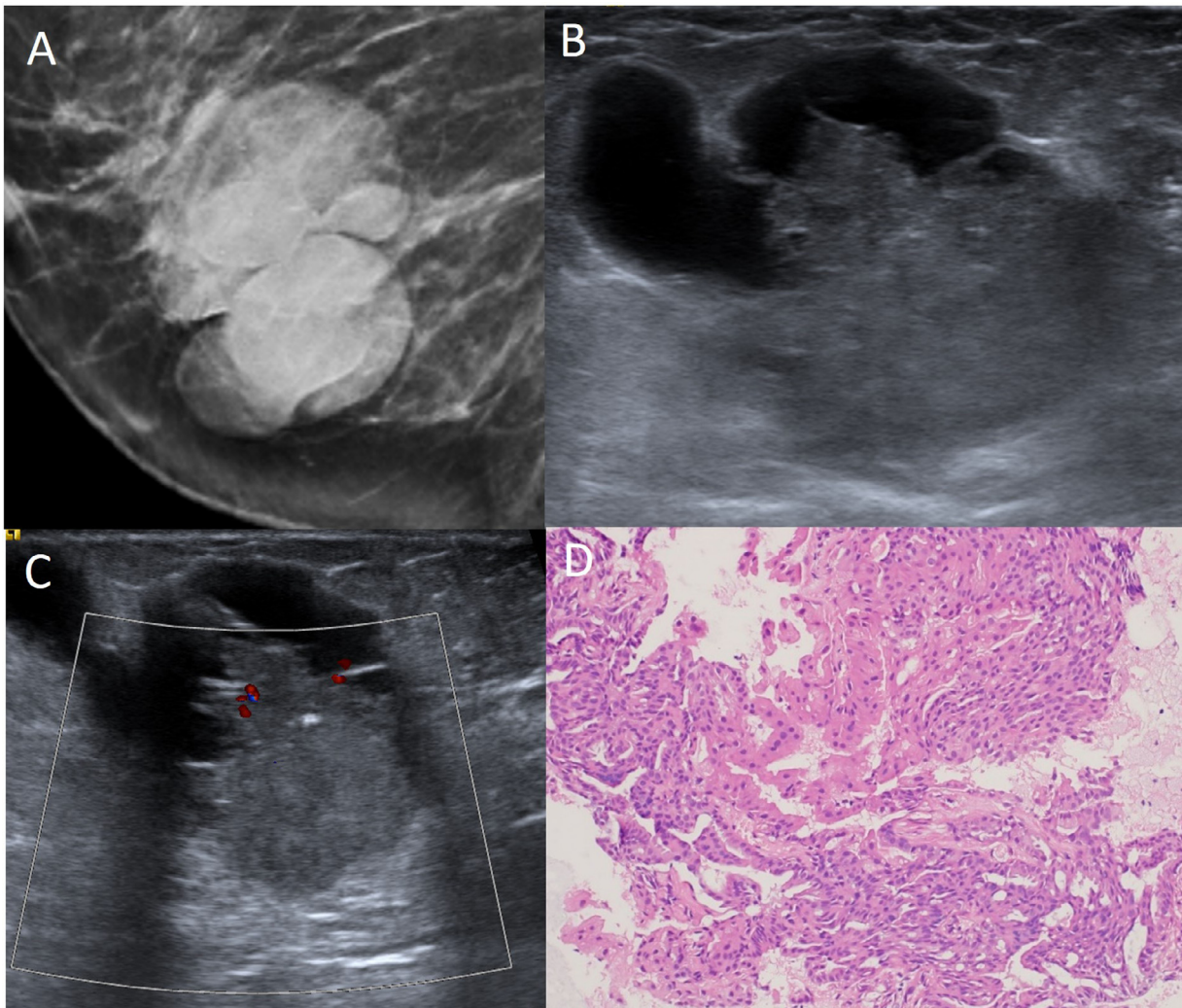


FIG 8. In this 60-year-old female with lump and bloody nipple discharge, mammogram (A) showed a large irregular lobulated mass without any calcifications. On US (B, C), it corresponded to a complex mixed solid cystic mass with internal vascularity. Core needle biopsy from the solid component showed features of intraductal papilloma. Due to large size, palpability and suspicious US features of the lesion, it was excised and was upgraded to intraductal papilloma with atypia (D), with area of atypia up to 3mm.

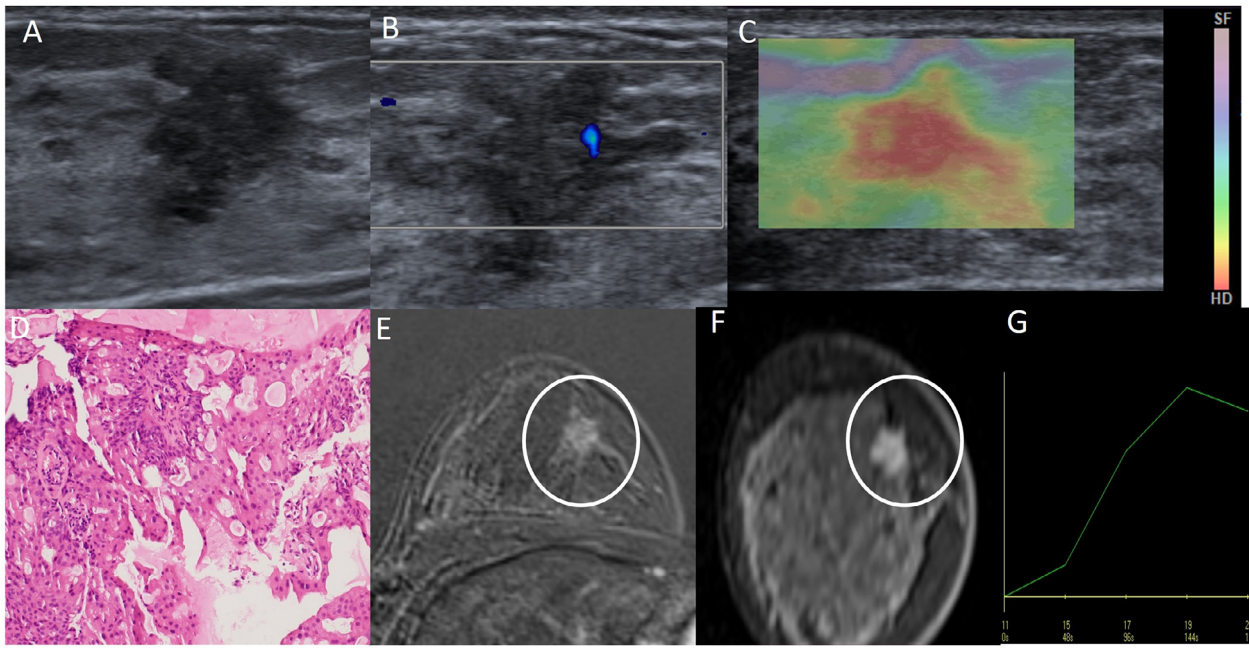


FIG 9. An 18-year-old female came with breast lump and bloody nipple discharge for the past 3 months, which is a rare symptom in teenagers. Ultrasound was done as the first imaging investigation, which showed an irregular hypoechoic mass with antiparallel orientation having angular margins and few adjacent prominent ducts (A). The mass showed internal vascularity (B) and was hard on elastography (C). US guided 14 G core biopsy (D) revealed an intraductal papilloma with DCIS with tumor arranged in papillary configuration. On immunohistochemistry (IHC), areas with solid and cribriform pattern with diffuse estrogen receptor (ER) positivity were present. Dynamic contrast enhanced MRI was done to rule out any multicentricity or multifocality. Subtracted axial post contrast (E), and coronal post contrast MPR (F) showed an irregular mass with homogeneous enhancement and plateau (Type 2) kinetics (G). No other mass or area of nonmass enhancement was seen in both breasts.

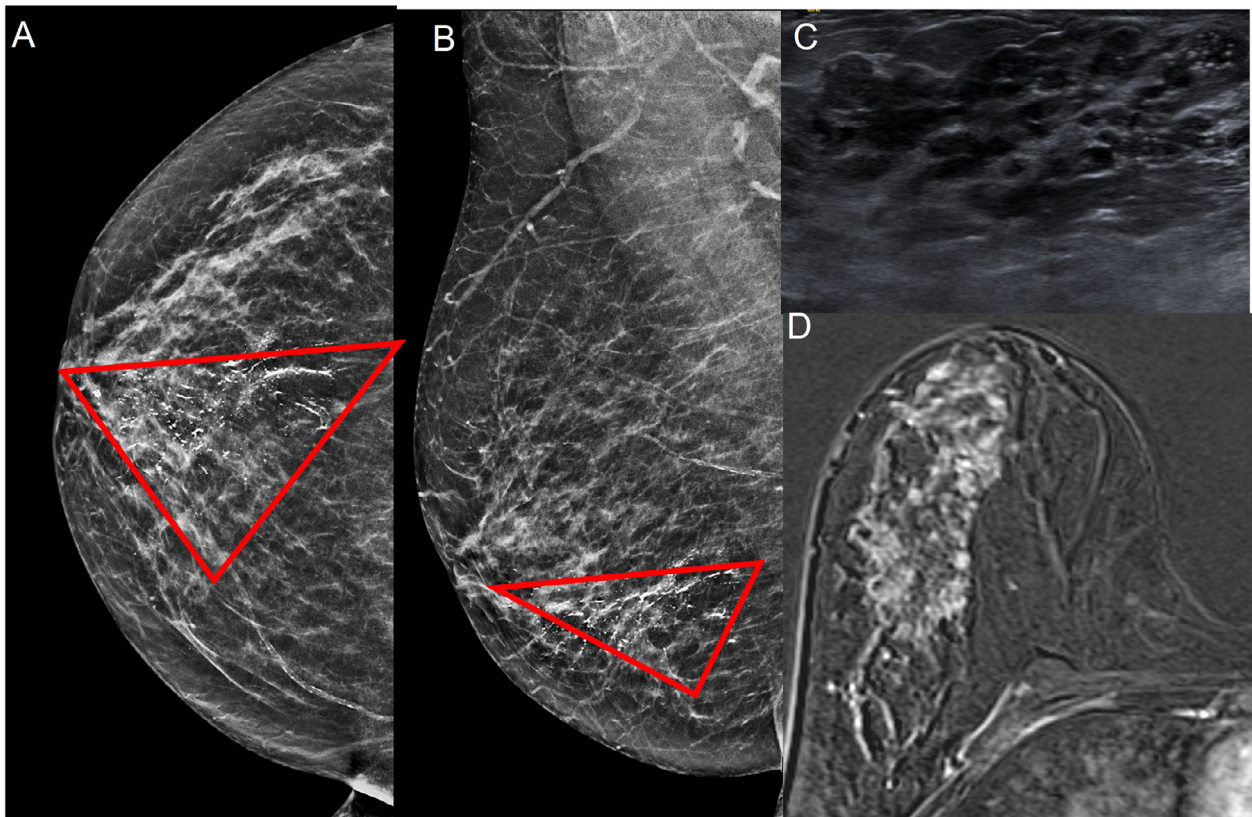


FIG 10. A 40-year-old female presented with bloody right nipple discharge for 2 months. Mammogram (A,B) shows pleomorphic and linear calcifications in segmental distribution in lower inner breast (red triangle), with apex of the triangle pointing towards the nipple. Correlative US (C) depicted intraductal soft tissue in dilated ducts with multiple intraductal calcific foci. US guided 14 G core biopsy revealed DCIS. At times, non-calcified DCIS may only be visible on MRI as segmental non-mass enhancement (D)(different patient).

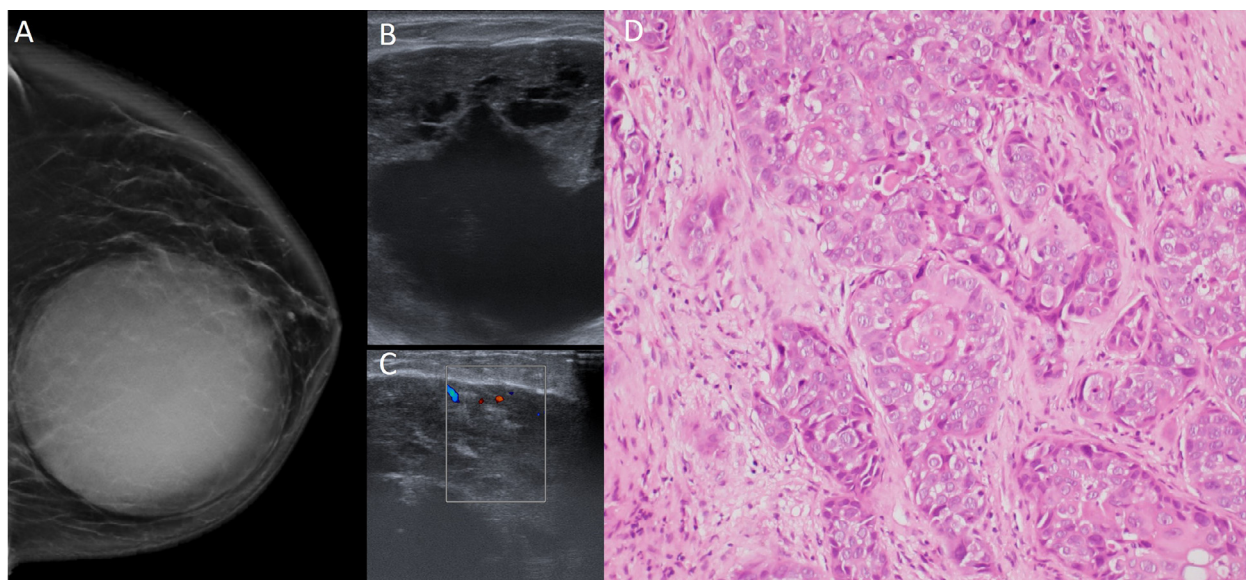


FIG 11. Case of high-grade IDC presenting with lump and serous nipple discharge. Mammogram showed a high density, round, circumscribed mass (A), which on ultrasound corresponded to a large complex cystic mass with internal echoes and presence of a thick, irregular wall (B). The thickened shaggy walls showed vascularity (C). Biopsy from the wall revealed Invasive ductal carcinoma, grade 3.

Invasive Ductal Carcinoma (IDC)

This arises from the ductal epithelium and invades the basement membrane. Common presentation is as a palpable mass, however, rarely they may present only with pathological nipple discharge. They appear classically as irregular masses with spiculated margins, with or without intramass calcifications. US shows similar findings, with intraductal extension of mass, which is characteristic (Fig 11).^{11,29} Of special mention is invasive papillary carcinoma breast which presents with a lump and is frequently associated serous/sanguineous nipple discharge. It has a better prognosis than invasive ductal carcinoma not otherwise specified (IDC-NOS) with lesser frequency of associated nodal disease. Mammography usually reveals circumscribed single or multiple masses in elderly women. On US, circumscribed or irregular solid cystic masses are seen, with solid component showing vascularity (Fig 12).³⁰

Paget's Disease of the Breast

It presents with eczema type rash with nipple destruction with or without serous or sanguineous nipple discharge.¹¹ Diagnosis is established by performing a punch biopsy of the nipple which reveals features of infiltration of nipple epidermis by adenocarcinoma cells. Breast imaging is done to look for underlying features of IDC or DCIS in the breast parenchyma which may be present in nearly 90% cases (Fig 13). However, in a small proportion of cases, no malignancy may be found in the breast. Most patients are managed with mastectomy.³¹

Surgical Management

In case of high clinical suspicion and negative imaging workup, central ductal excision was previously the standard of care to exclude malignancy.³² Studies show that the risk of finding a malignancy in such cases is quite low if US, MG and MRI are negative. This surgery can lead to loss of sensation in the nipple areola or necrosis of the nipple due to neurovascular compromise. Hence, recent data supports that, patients with negative US, MG and MRI can be followed up for 2 years, every 6 months until the discharge disappears; which

is seen in a significant proportion of patients.^{33,34} This statement is based on the evidence that MRI has a negative predictive value (NPV) of 98.2% for ruling out malignancy.³⁵ However, discharge which is massive, debilitating to the patient and persisting for longer, should be a consideration for surgery. Conventionally, methylene blue is used to mark the pathological duct prior to the excision. In this procedure, intraoperative methylene blue dye is injected into the discharging duct through the orifice, which facilitates the opacification of the involved ductal system. This allows precise surgical excision.³⁶ Recently, ductoscopy using small endoscopes of 0.9 and 1.1mm can directly visualize the intraductal pathology and perform more precise microdochectomy. It is an outpatient procedure performed under local anesthesia in which all major ducts and their branches are inspected to the possible depth, which may be limited by the length and the outer diameter of the endoscope. A negative or normal ductoscopy examination has a high negative predictive value to rule out malignancy. However, it is generally limited by nonavailability of the hardware and expertise at most places.³⁷

The Role of Radiologist Beyond Diagnostics

The radiologist is an integral part of the multidisciplinary team involved in the management of a patient with pathological nipple discharge by offering the appropriate imaging modality according to the age and level of suspicion in the patient. Also, image-guided core biopsies using 14-gauge needles or VABB using 9-11 gauge needles are performed in the Radiology suite. As many intraductal lesions may not be visible after the first sample on core biopsy due to collapse of the distended duct or leakage of the fluid component in a solid cystic lesion, VABB offers the best possible sampling technique. In addition, vacuum assisted excision (VAE) can be offered for benign solitary papillary lesions, avoiding a surgical procedure altogether.^{38,39} In many centers, certain pathologies like asymptomatic solitary small central papilloma without atypia, proven by VABB, may be followed up on US by the radiologist to document stability. Other etiologies like duct ectasia and fibrocystic disease may also be kept on regular surveillance.³⁹

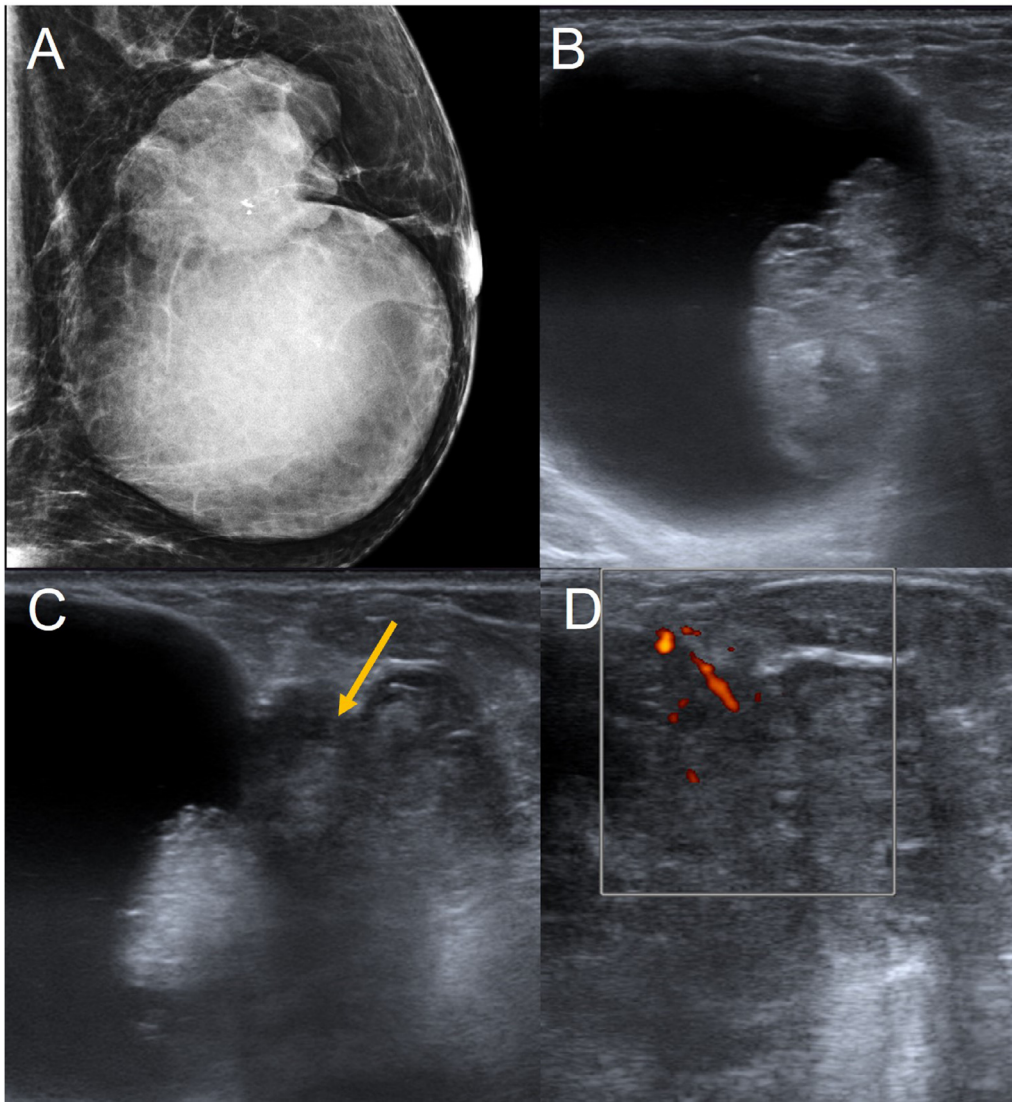


FIG 12. A 69-year-old female came with a gradually increasing lump and bloody nipple discharge. Mammogram (A) shows an irregular, circumscribed, high density mass with foci of calcification. Ultrasound (B) better revealed the internal character of the mass and depicted a complex solid cystic mass with vascular solid component extending into the adjacent breast (C, D). Biopsy taken from the solid component extending into the breast (arrow in C) showed features of invasive papillary carcinoma with absent myoepithelial cells in the papillae and periphery.

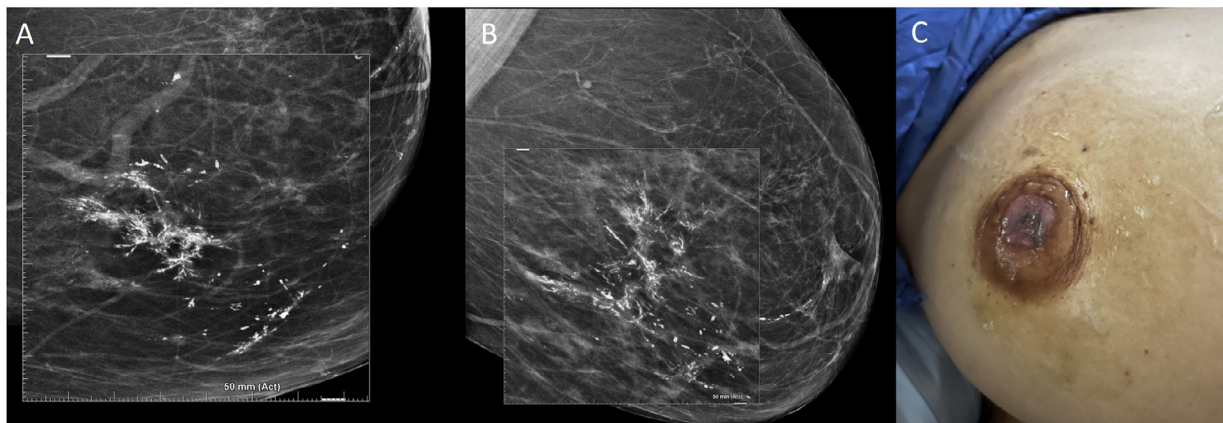


FIG 13. A 44-year-old female with bloody nipple discharge and excoriation of nipple. Mammogram craniocaudal and mediolateral oblique views (A, B) very well demonstrating the fine linear and fine linear branching calcifications of DCIS in this case, proven to be Paget's disease of the breast (C).

Rad-path correlation is also a very important component in the management algorithm due to the particularly small size of these lesions, making them more prone to sampling errors. Breast imagers should be aware of the features of papillary lesions associated with upgradation at surgery, which include size > 1cm, Breast imaging reporting & data system (BIRADS) category >4b, cases of rad-path discordance and presence of palpable mass or associated microcalcifications.⁴⁰

Conclusion

Nipple discharge is a common complaint seen in the breast clinic, with most causes being benign in nature. Due to the association of malignancy in a small proportion of cases of pathological nipple discharge, it is important to thoroughly image these patients. Mammogram and ultrasound are the initial imaging modalities. MRI has proven to be a promising modality to evaluate nipple discharge as it has a very high sensitivity to rule out malignancy. The risk of underlying malignancy falls to very low in patients having negative imaging, and thus changes the previous notion of a central duct excision in all these patients. Image guided biopsy, and particularly vacuum assisted breast biopsy, play an important role in deciding the further management.

Acknowledgment

NIL

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