

Review Article

The conundrum of breast cancer mimics

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A B S T R A C T

The BIRADS lexicon ensures a standard reporting terminology in breast imaging and serves as a means of smooth communication between the radiologist and the referring physician. BIRADS assessment categories 4 and 5 warrant a biopsy to rule out underlying malignancy. However, a substantial number of cases in these categories sometimes turn out to be benign on biopsy. These benign mimics encompass inflammatory, sclerosing, neoplastic and a few other miscellaneous conditions. Awareness of these various mimics of breast cancer can equip the radiologist to handle these apparent cases of radiologic-pathological (rad-path) discordance better, guide overall patient management, avoiding inadvertent excisional biopsies and help alleviate patient anxiety and confusion.

Introduction

With ongoing advancements and easier access to breast imaging in both screening and diagnostic settings, there is a substantial increase in the detection of more breast pathologies, resulting in a steep rise in the number of breast biopsies performed. This has led to increased cancer detection rates and better management of breast cancer, however, more than half of these biopsies ultimately yield benign results.¹ Though an irregular spiculated breast mass with associated architectural distortion usually brings the diagnosis of cancer to mind, it may sometimes surprisingly turn out to be a benign lesion. Breast Imaging-Reporting and Data System (BI-RADS) lexicon is a means of smooth communication between the breast radiologist and the referring physician.² A BIRADS 4 or 5 assessment warrants a biopsy, however, these even these findings have a wide range of probability of being a cancer, which ranges from 2 to greater than 95%. Thus, many findings might ultimately be benign on percutaneous or excisional biopsy. Even the highest assessment category of BI-RADS 5 has upto 5% chances of being benign. This review article will thus discuss the various benign causes of BIRADS 4b, c and 5 lesions and highlight their salient features. Awareness of these mimickers will allow the breast multidisciplinary team to offer better care to patients and manage potential cases of radiological-pathological discordance. This will allay the anxiety caused by an additional repeat or surgical excisional biopsy, and also reduce the health system costs. It, however, should be reiterated here that even in cases having benign biopsy results, biopsy should be repeated if clinico-radiological suspicion of malignancy seems high.

Various pathologies that mimic cancer

Entities that mimic breast cancer can be divided into inflammatory etiologies, tumors, sclerosing lesions and miscellaneous conditions as shown in [Table 1](#).

*Inflammatory etiologies**Idiopathic granulomatous mastitis (IGM)*

This condition is characterized by lobulocentric non-caseating granulomas, and is classically described in pre-menopausal women, particularly having history of lactation in the past 5 years.^{3,4,5} Hyperprolactinemia has also been attributed as an implicating factor.⁶ Patients with IGM usually present with long standing history of pain and lump in the breast and may mimic inflammatory breast cancer.⁷ Long standing cases may develop chronic discharging sinuses and have a waxing and waning course, making the condition highly morbid.⁸

Ultrasound (US) is usually the first modality used in evaluation of these women due to the younger subset of patients. These may appear as heteroechoic non-mass area with angular or irregular margins representing focal mastitis or extensive involvement of the breast, with multiple tracking irregular intercommunicating collections having tubular extensions into the surrounding parenchyma. Dilated ducts with internal contents may also be seen. Associated skin thickening and nipple retraction is frequently present. Multiple discharging sinus tracts are often noted, which is classical for this condition.^{9, 10} Cases presenting as isolated irregular hypoechoic masses with angular margins and surrounding intraductal extension may be difficult to differentiate

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Table 1
Breast cancer mimics.

Inflammatory etiologies	Idiopathic granulomatous mastitis, chronic mastitis, abscess, Diabetic mastopathy
Benign proliferative conditions	Radial scar and complex sclerosing lesion, sclerosing adenosis
Tumors	Granular cell tumor, fibromatosis
Miscellaneous conditions	PASH, Fat necrosis

from malignancy.¹¹ One should also be wary that repeated attempts at aspirating these organized collections/ inflammatory tissue may not yield any material. This condition should also be suspected in cases of repeated sterile cultures from small pockets of collection.

Mammogram shows global or focal asymmetry of fibroglandular tissue, irregular masses, skin thickening, nipple retraction, trabecular thickening, suspicious axillary nodes or may even be normal in select cases (Fig. 1).

Magnetic resonance imaging (MRI), if done, shows masses with conglomerate rim or heterogeneous enhancement, or non-mass

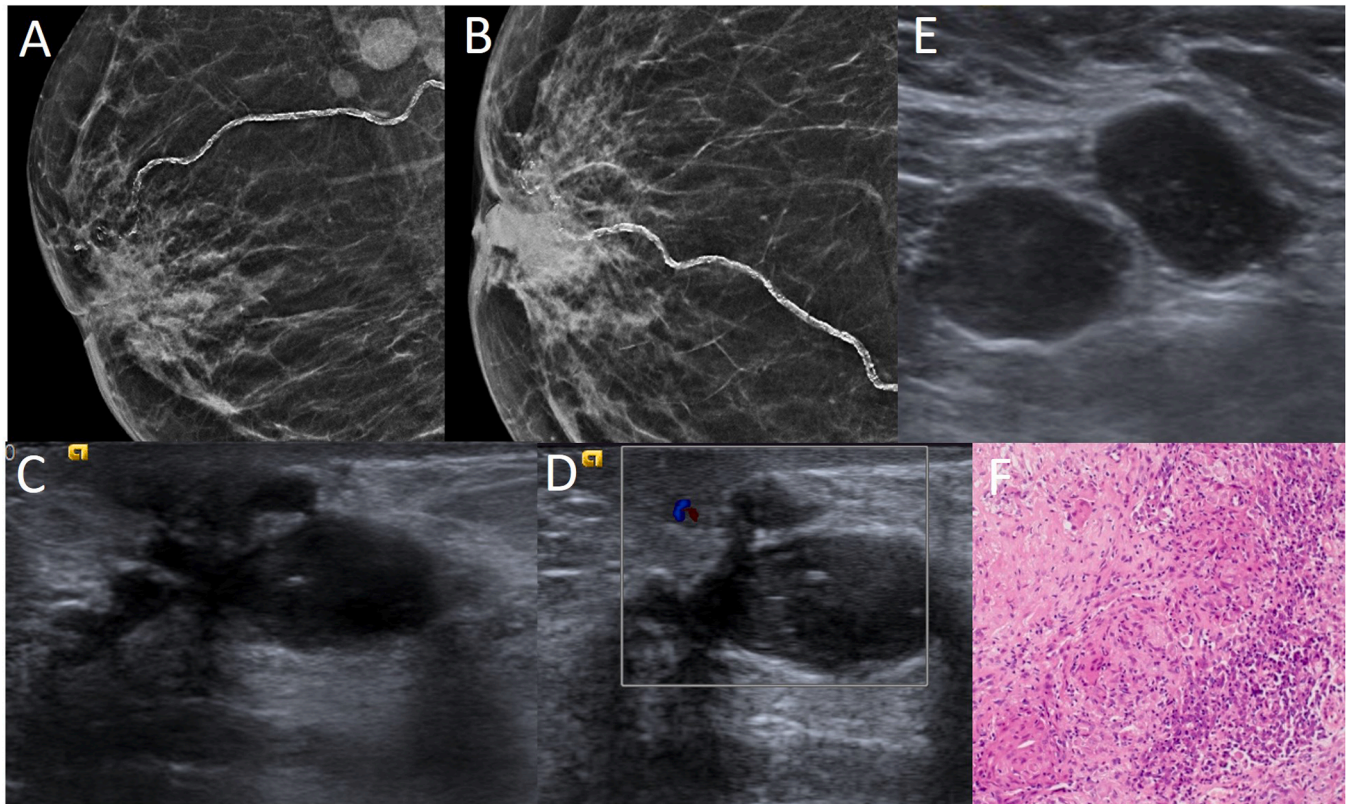


Fig. 1. 61-year-old female presented with recent onset unilateral nipple retraction and pain. Mammogram (A, B) shows an irregular mass with obscured margins and associated architectural distortion in retroareolar region with associated periareolar skin thickening and nipple retraction. Ultrasound (US) revealed a hypoechoic mass with intraductal extension (C, D). Suspicious axillary lymphadenopathy was also present (E). US guided 14 G core biopsy (F) showed features of granulomatous mastitis. A repeat biopsy was done as the female was elderly and had no history of recent lactation or childbirth. Repeated biopsy revealed granulomatous inflammation comprising of epithelioid cell granulomas, multinucleated giant cells, lymphocytes and epithelioid histiocytes with negative stain for acid fast bacilli or fungi, consistent with idiopathic granulomatous mastitis. Of note is that idiopathic granulomatous mastitis may be an uncommon cause of inflammatory pathology of breast in the elderly, being usually seen in women of childbearing age.

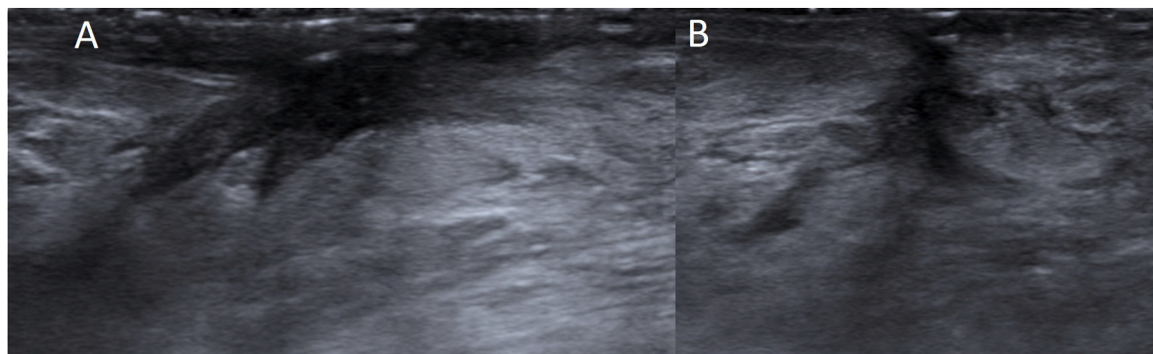


Fig. 2. 33-year-old female came with complaints of pain and lump in left breast for three months. US revealed an irregular hypoechoic mass with angular margins (A, B) which was infiltrating into surrounding parenchyma. Core needle biopsy showed inflammation with mixed cellular infiltrate suggestive of mastitis. Resolution of symptoms and imaging findings was seen on eight weeks follow up after antibiotics.

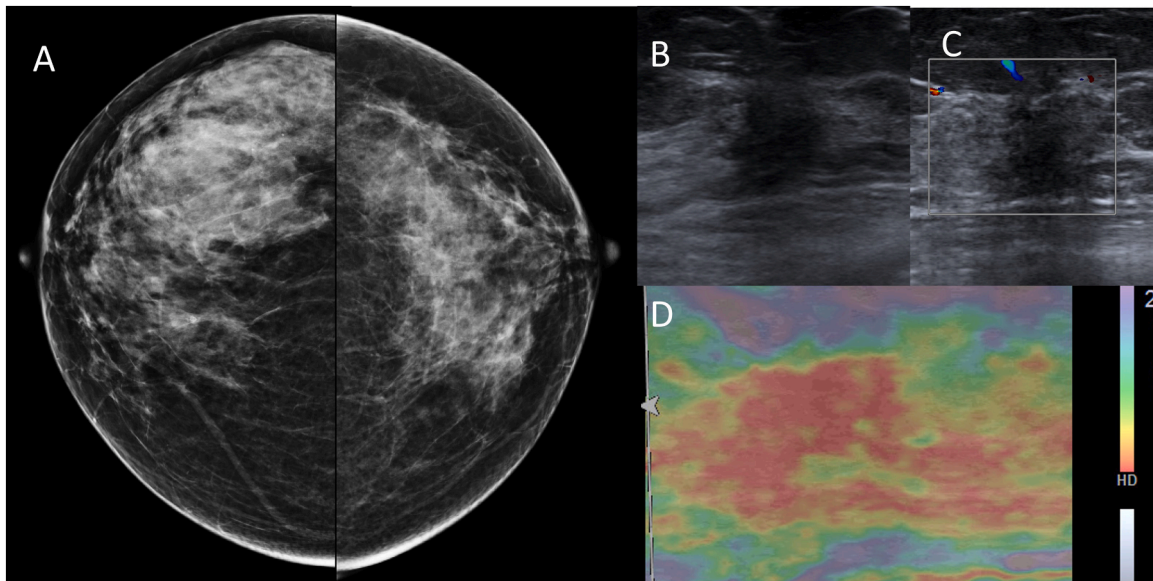


Fig. 3. A 70-year-old diabetic woman reported a firm lump in her right breast persisting for the past year. The mammogram revealed an asymmetry in the outer right breast (A). A correlative ultrasound (B) displayed a hypoechoic irregular nonparallel mass with angular margins and posterior acoustic shadowing. Notably, there was no internal vascularity (C), and the lesion appeared stiff on elastography (D). An ultrasound-guided core biopsy, utilizing a 14 G needle, revealed dense fibrosis and B-cell lymphocytic infiltrate surrounding the ducts, lobules, and vessels. Given the patient’s 25-year history of Type 2 diabetes managed with insulin, the diagnosis was established as diabetic mastopathy.

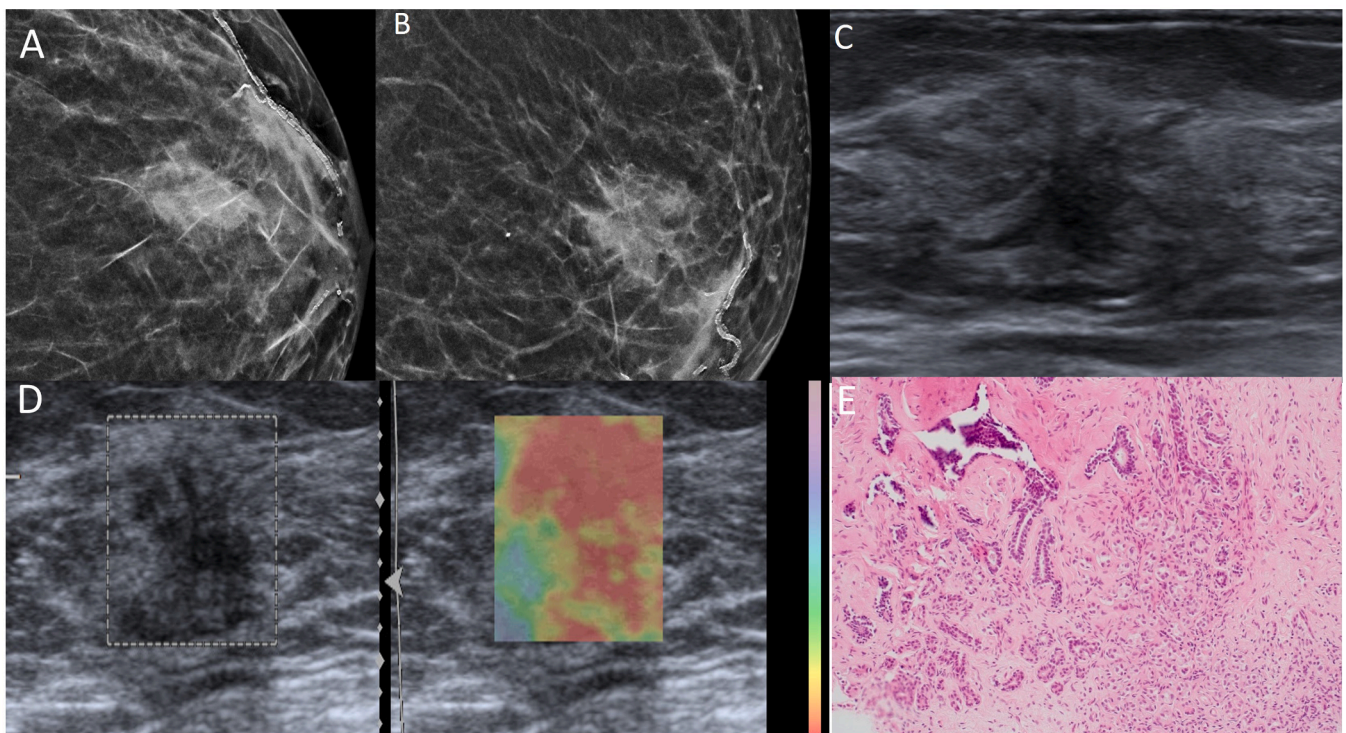


Fig. 4. 45-year-old female with positive family history for carcinoma breast in her mother came for a screening mammogram. An area of focal symmetry was seen on the mammogram (A, B). On US (C), it correlated with an irregular mass having spiculated margins which was hard on elastography (D). US guided biopsy of this mass (E) revealed features of sclerosing adenosis showing florid epithelial hyperplasia with apocrine change and adjacent dense sclerosis with no loss of myoepithelial layer.

enhancement in segmental or regional distribution, with skin thickening and reactive axillary lymphadenopathy. Confluent T2 bright signal and rim enhancement likely represent micro abscesses and are considered hallmarks for granulomatous mastitis (Fig. 1).¹²

Treatment options include corticosteroids or other

immunosuppressants such as methotrexate.¹³ Local excision or mastectomy may be done in cases not responding to medical management.¹⁴ Spontaneous resolution has been documented in mild cases.

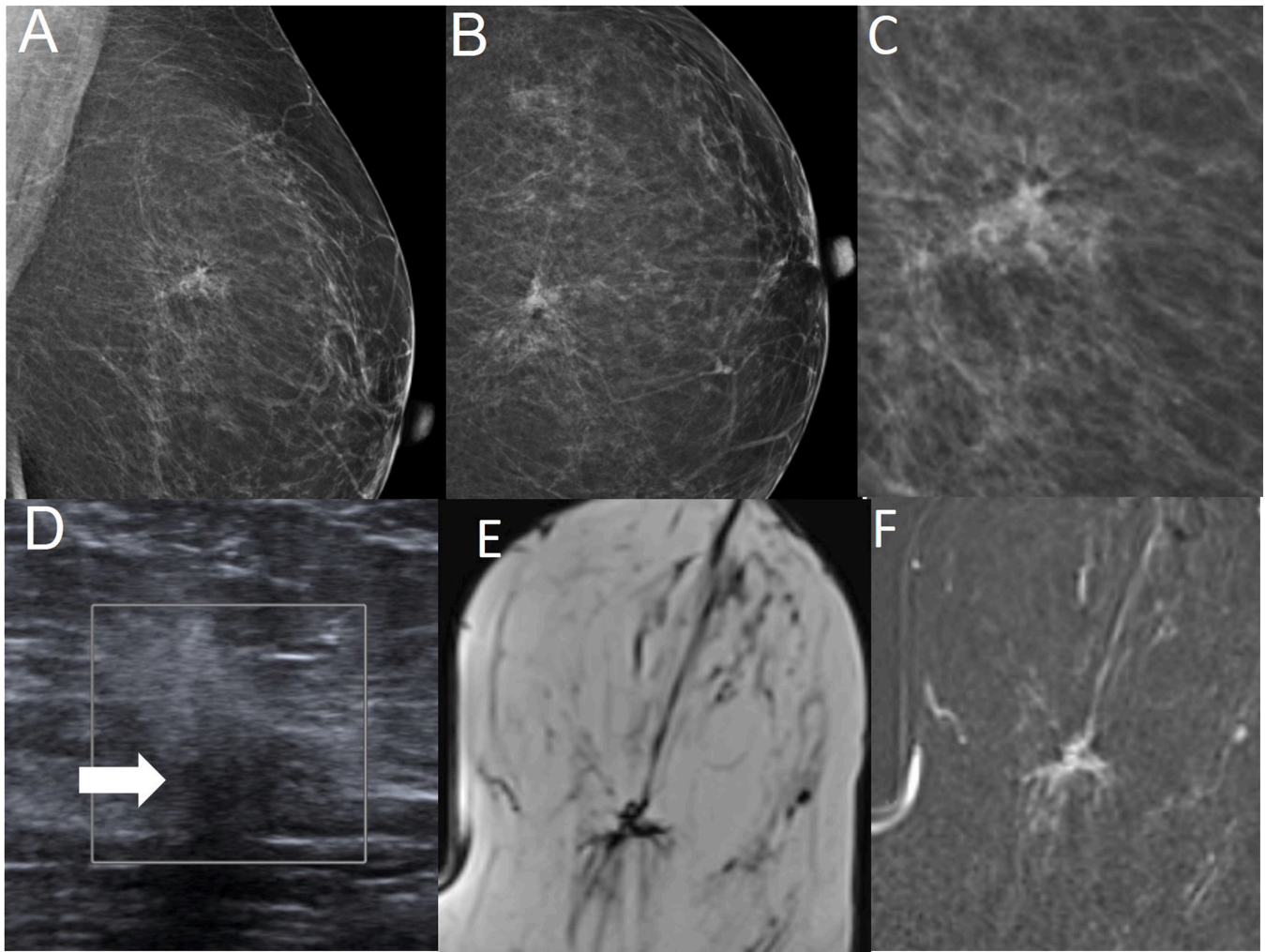


Fig. 5. 51-year-old female with a screen detected architectural distortion with long gracile spicules in the upper central breast (A, B), which is seen better on digital magnification (C). Correlative US (D) shows an irregular mass (arrow) with indistinct margins, posterior shadowing, surrounding architectural distortion and no internal vascularity. MRI breast (E, F) revealed a homogeneously enhancing small irregular mass with spiculated margins with associated architectural distortion. US guided vacuum assisted biopsy was done which revealed a radial scar. The findings were stable after a follow up of 5 years.

Chronic mastitis

Acute mastitis presenting with local signs of inflammation and painful tender breast is a common puerperal condition affecting the breast which is diagnosed clinically. Chronic non-puerperal mastitis may have non-specific presentations such as pain, palpable lump and nipple discharge. Mammogram can show focal or global asymmetry and skin thickening with reactive axillary lymphadenopathy. On ultrasound, irregular hypoechoic masses are typically observed in the absence of any drainable collection (see Fig. 2). This appearance may raise suspicion for malignancy, and in such cases, the diagnosis can be confirmed through a core needle biopsy.¹⁵

It's crucial to differentiate between mastitis, abscess, and inflammatory breast carcinoma. In cases of non-resolving, non-puerperal mastitis in an elderly female with no drainable collections, diffuse involvement rather than focal disease, suspicious axillary nodes with displaced hilum, and eccentric cortical thickening instead of reactive lymph nodes, the breast radiologist should promptly consider sampling the breast without delay, as these features are indicative of potential inflammatory breast carcinoma.¹⁶

Lymphocytic mastopathy

Lymphocytic mastopathy is a rare pathology affecting the breast in patients with diabetes, autoimmune disorders or might be idiopathic. It

is characterized by perivascular and peri lobular inflammation due to lymphocytic infiltration.¹⁷ Seen in cases of long-standing, uncontrolled type 1 or type 2 insulin dependent diabetes mellitus, it may be due to matrix proliferation due to an autoimmune response to hyperglycemia.¹⁸ They frequently present with hard painless lump in breast, often at multiple locations. Mammographically, it may be occult or present as a mass or focal asymmetry. On ultrasound, the mass appears as an irregular hypoechoic mass with posterior acoustic shadowing, making it indistinguishable from malignancy (see Fig. 3). These masses are usually self-limiting and surgical excision is not needed.¹⁹

Benign proliferative breast conditions

Sclerosing adenosis

Sclerosing adenosis is usually seen in perimenopausal women, with most cases being detected incidentally. It is a benign, lobulocentric proliferative process in which lobules are enlarged and increased in number, in addition to an increased number of glands within each lobule in a background of disordered acinar, myoepithelial and connective tissue elements.²⁰ Although not a premalignant condition, breast cancer is associated nearly twice as commonly with these lesions.²¹ Sclerosing adenosis can also coexist with various benign proliferative diseases of the breast. Mammography findings can vary from a normal appearance

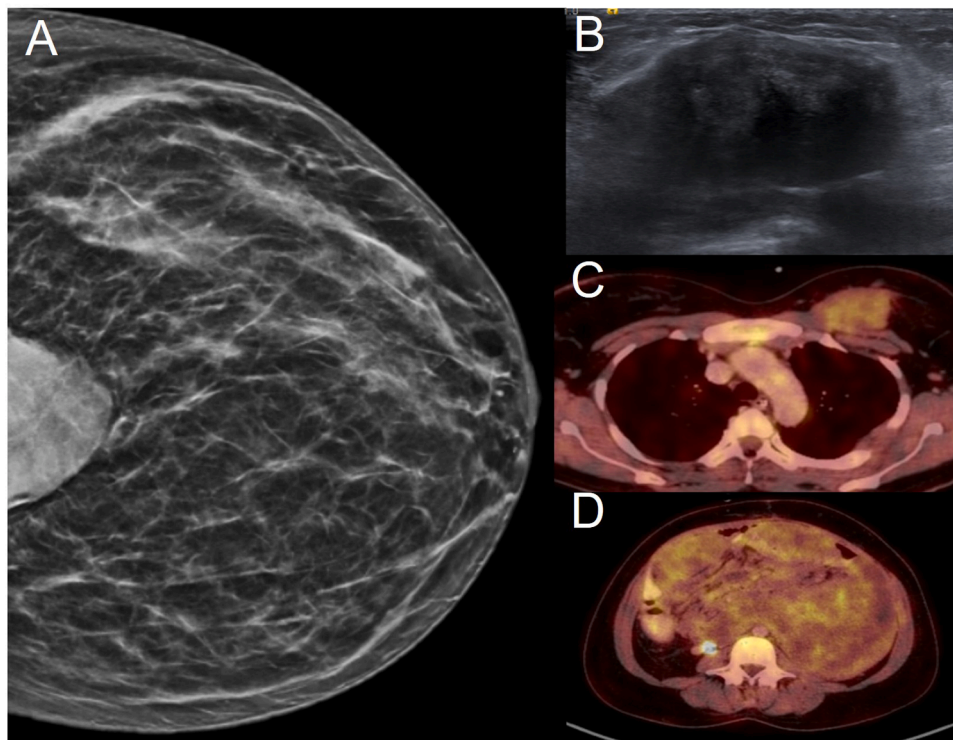


Fig. 6. 38-year-old female, diagnosed case of Gardner syndrome, presented with a lump in left breast. Mammogram (A) revealed a high density circumscribed mass located at posterior depth in the breast. US (B) showed a hypoechoic circumscribed parallel mass which was categorized as BIRADS 4b. Mass showed PET uptake (C) along with sheet like soft tissue diffusely infiltrating the mesentery showing PET avidity (D). US guided biopsy revealed features of fibromatosis.

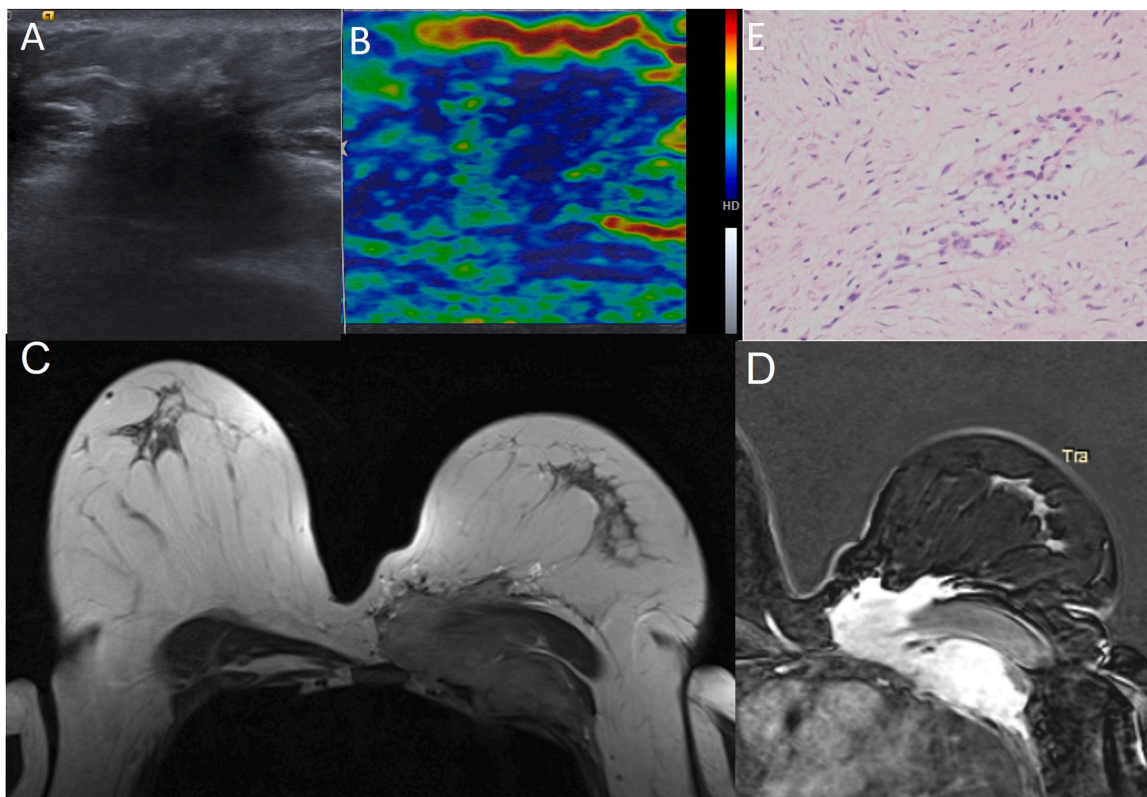


Fig. 7. Another case of fibromatosis breast in a 27-year-old female. The US revealed a hypoechoic spiculated irregular mass with posterior shadowing abutting the pectoralis (A), which was hard on elastography (B) and classified as BIRADS 4c. MRI (C, D) helped better depict the posterior location of the mass and invasion of the pectoralis and chest wall. US guided 14 G core biopsy was done which showed spindle cells arranged in long and short fascicles with minimal nuclear atypia, having elongated wavy nuclei, bland chromatin and pale eosinophilic cytoplasm, consistent with fibromatosis (E).

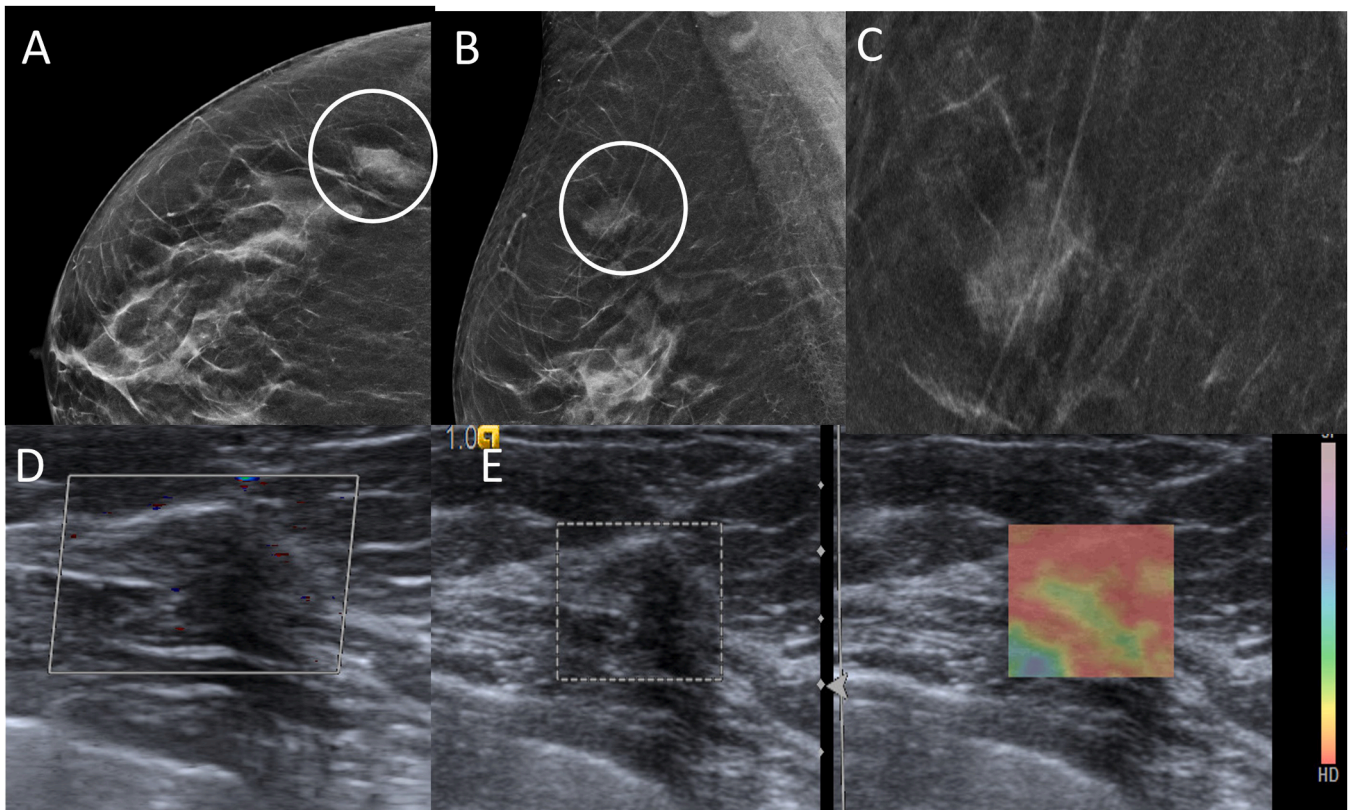


Fig. 8. 47-year-old female presented with a lump in right breast for 5 months with associated pain. Mammogram (A, B, C) showed an equal density irregular mass with indistinct margins in the upper outer quadrant. US revealed a circumscribed heterogeneous, nonparallel mass which was classified as BIRADS 4b. US guided 14 g core biopsy revealed features of granular cell tumor.

to architectural distortion, a mass with indistinct margins, asymmetry (see Fig. 4a, b), or grouped microcalcifications. Consequently, these findings may closely resemble breast cancer in many cases. On ultrasound, the appearance ranges from a circumscribed hypoechoic mass to an irregular mass or even ill-defined areas with posterior acoustic shadowing (see Fig. 4c, d).^{22,23} No additional management is necessary if radiopathological findings are consistent with sclerosing adenosis (see Fig. 4e).²⁴

Radial scar (RS) and complex sclerosing lesions (CSL)

Radial scars and complex sclerosing lesions are part of the spectrum of sclerosing breast lesions, with radial scars measuring less than 1 cm and complex sclerosing lesions exceeding 1 cm in size.²⁵ They are unrelated to prior surgery or trauma and are, in fact, not scars. The proposed mechanism involves idiopathic inflammation leading to vascular insufficiency.²⁶

These lesions can be incidentally detected during histopathological analysis performed for suspicious architectural distortions on screening mammograms, occurring in about 0.1–2 per 1000 screening exams. They are considered high-risk lesions, with associated malignancy observed in 4–9 % of cases.²⁷

On mammography, radial scars exhibit a variable appearance in different views, lacking a solid dense central nidus. Imaging shows architectural distortion with a stellate configuration having very long and thin spicules and the characteristic "black star" appearance due to a radiolucent center, in contrast to the "white star" appearance of malignancy.²⁸ Characteristically, they lack skin thickening or retraction, are usually asymptomatic clinically, but have a striking mammographic appearance.²⁸ Calcifications if present and are often part of the coexisting benign or malignant disease (Fig. 5a-c). This appearance reflects the histopathological features, displaying distorted ducts and lobules around a central fibro-elastotic core, in a peripheral radiating pattern.

The epithelial component can show varying degrees of hyperplasia and may harbor ductal carcinoma in situ (DCIS) or invasive ductal carcinoma (IDC).²⁹ Immunohistochemical positive staining for myoepithelial cells helps differentiate them from malignancy.³⁰

The advent of digital breast tomosynthesis (DBT) has increased detection of these lesions due to higher sensitivity in detecting architectural distortions not visible on 2D mammograms.^{30, 31} Ultrasound (US) may or may not show a correlate of the mammographically detected lesion, with probability of malignancy being higher with the presence of an ultrasound correlate. When visible on US, they typically appear as hypoechoic masses with indistinct margins and posterior acoustic shadowing or as a discrete area of altered echogenicity (Fig. 5d). MRI may depict them as an enhancing irregular mass or non-mass enhancement, and their variable kinetics may make them indistinguishable from malignancy (Fig. 5e,f).³²

Radial scars per se are not premalignant lesions. During sampling, caution is advised to biopsy the periphery of radial scars/complex sclerosing lesions, as these areas may harbor malignancy. Predictors of upgrade to malignancy include large size (>10 mm), elderly patients, presence of calcifications, and histology showing atypia. Management recommendations suggest removal if there is associated atypia. However, follow-up is acceptable in the absence of atypia on sampling with vacuum-assisted biopsy (VAB), or for lesions less than a centimeter in size, with some centers advocating vacuum-assisted excision (VAE).³³

Benign tumors

Fibromatosis

Also called extra abdominal or mammary desmoid tumor, fibromatosis is a rare locally aggressive non-metastasizing spindle cell tumor of the breast. High rates of local recurrence are reported due to its locally aggressive nature.³⁴ It presents as a painless hard mass, usually fixed to

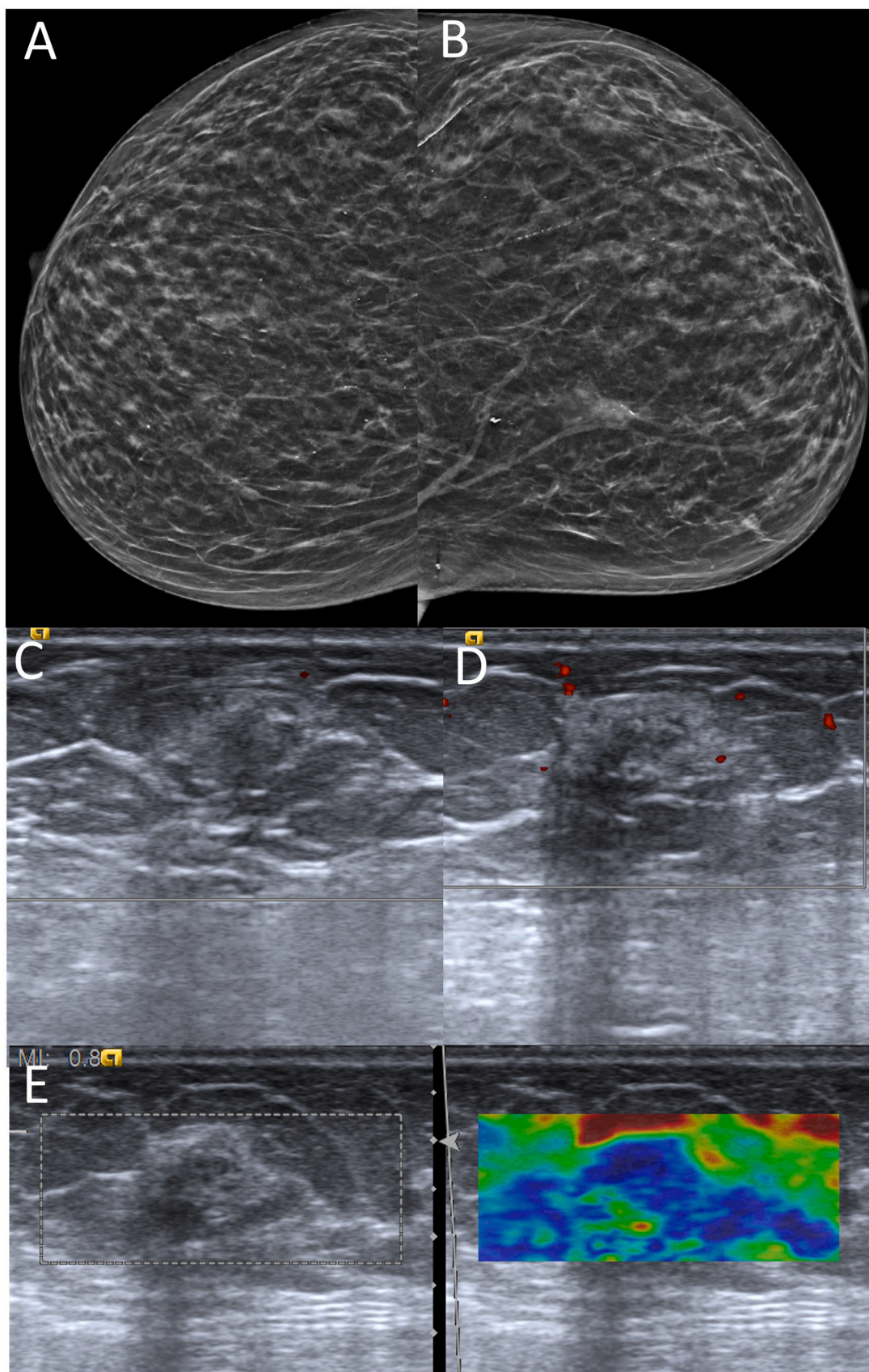


Fig. 9. Screening mammogram (bilateral craniocaudal views shown) (A,B) of a 40-year-old high-risk female revealed focal asymmetry in left inner breast. Targeted US (C, D) revealed an irregular, heterogeneous mass with indistinct margins and mixed posterior features. It revealed hard areas on strain elastography (D). As the woman was in high-risk category, it was reported as BIRADS 4b and a US guided 14 G core biopsy was done, which showed features of pseudoangiomatous stromal hyperplasia (PASH). On retrospective review of the gray scale US images, few slit like cystic spaces could be appreciated within the mass.

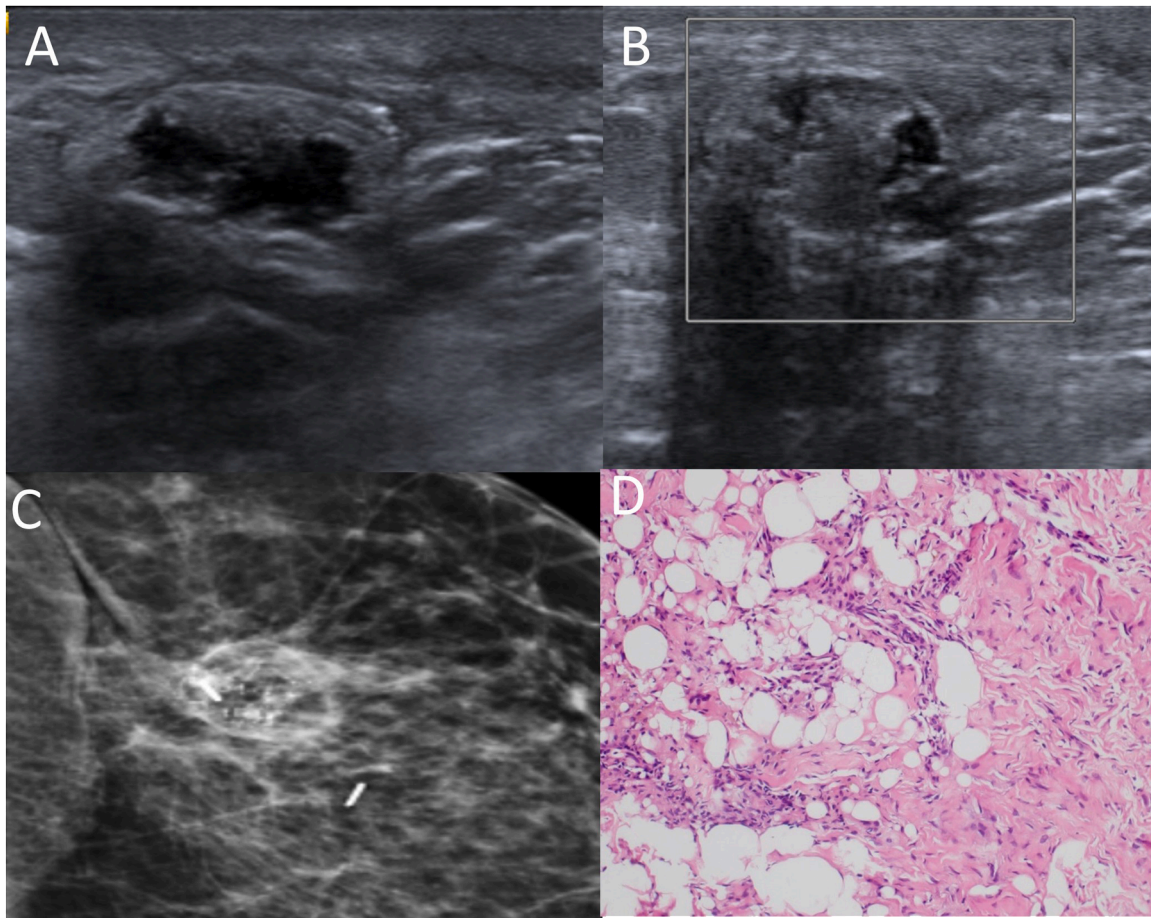


Fig. 10. In a 36-year-old woman who underwent a breast oncoplastic procedure for the removal of a breast carcinoma, the surgeon detected a hard mass at the scar site. Subsequently, a non-image-guided biopsy was performed. An ultrasound (A, B) was requested, which showed a complex suspicious heterogeneous mass at the surgical site without any vascularity. A mammogram (C) done subsequently 3 days later showed areas of fat and dystrophic calcification within the mass suggesting fat necrosis, which was confirmed by the pathology result (D).

the underlying pectoralis muscles. It is hypothesized to arise from the prepectoral fascia, and thus, is classically seen in the deep breast, although it may arise anywhere in the breast. It is most commonly reported in females of reproductive age. While most cases are sporadic, a notable association exists with patients who have familial adenomatous polyposis coli (APC) and Gardner's syndrome.³⁵ Prior trauma or local surgery, exogenous hormone use, and implants have also been implicated in sporadic cases.³⁶

On imaging, it is indistinguishable from primary breast malignancy and appears as a high-density irregular mass with spiculated margins (Fig. 6a). However classical location along to the pectoralis with its invasion or extension into chest wall may be clues.^{37,38,39} Calcifications are uncommon. These masses may not be included in the mammogram due to their deep location. US findings vary from circumscribed heteroechoic mass to irregular spiculated mass with dense posterior shadowing (Figs. 6b, 7a, b). MRI is reserved for assessment of muscular invasion. Enhancement within the pectoralis muscle, indicative of tumor infiltration, should be differentiated from chest wall invasion in which enhancement is seen within intercostal, serratus anterior, or latissimus muscles. These tumors appear isointense on T1 and hyperintense on T2 with enhancement of post contrast scans showing variable kinetics (Fig. 7c, d).

Histopathology shows spindle cell proliferations with rare or no mitosis or nuclear pleomorphism with varying degrees of collagen (Fig. 7e). Abnormal β -catenin nuclear positivity and absence of CD34 and cytokeratin staining are hallmarks.³⁹ Management of fibromatosis usually includes wide excision; however, surveillance or medical

management with tyrosine kinase inhibitors may be appropriate in some circumstances based on tumor location.⁴⁰ MRI can also be used to monitor treatment response or detect recurrent/residual disease.⁴¹

Granular cell tumor (GCT)

Granular cell tumor is a rare tumor in the breast, hypothesized to be of Schwann cell origin.⁴² It was first described by Abrikossoff in 1926 and is sometimes referred to as Abrikossoff's tumor.

The majority of cases are benign, with only 1–2 % reported as malignant. It typically manifests as a palpable, painless lump in the breast, often found in the upper inner quadrant. While it commonly appears superficial, described along the cutaneous branches of the supraclavicular nerve, lesions can present in any quadrant or depth.

Usually, these lesions exhibit slow growth, stabilizing at a size of around 3 cm.⁴³ Imaging findings are indistinguishable from malignant breast masses (see Fig. 8) and may indicate associated skin or nipple retraction due to desmoplasia.⁴⁴ Diagnosis is suggested through pathological analysis, revealing large polygonal cells with abundant eosinophilic granular cytoplasm. These cells have small, round to oval eccentrically located nuclei with inconspicuous nucleoli, and mitosis is rare. Strong positive staining for the S-100 protein is characteristic.⁴⁵

Management typically involves a wide local excision of the mass, with an excellent prognosis. Malignant GCT, although very rare, should be considered in cases of tumors exceeding 5 cm, the presence of local invasion, or associated axillary lymphadenopathy.⁴⁶

Table 2
Summary of salient imaging and pathology features of breast cancer mimics.

	Imaging	Histopathology
Idiopathic granulomatous mastitis	On mammogram, focal or global asymmetry, with skin thickening and nipple retraction. On US, irregular hypoechoic masses with tubular extensions in adjacent breast, communicating with each other	Non-caseating granulomas centered on lobules, in a background of inflammation. It is a diagnosis of exclusion and other granulomatous etiologies like tuberculosis, sarcoidosis, polyangiitis, etc. need to be ruled out
Chronic mastitis	Irregular hypoechoic masses with angular margin on US, with or without drainable collections	Inflammation with mixed cellular infiltrate of histiocytes, lymphocytes, eosinophils
Radial scar and CSL	Architectural distortion with thin long spicules, mostly incidentally detected	Fibroelastotic core with entrapped ducts and epithelium
Sclerosing adenosis	Irregular mass, architectural distortion or focal asymmetry appearing as circumscribed or spiculated mass on US	Lobules are enlarged and increased in number in addition to an increased number of glands within each lobule in a background of disordered acinar, myoepithelial and connective tissue elements
Granular cell tumor	On mammogram, small, irregular, ill circumscribed mass. On US, heteroechoic, irregular, nonparallel mass, classically in upper inner quadrant of superficial breast, along the cutaneous territory of supraclavicular nerve	May be near small nerve bundles. Bland polygonal cells with abundant granular cytoplasm and prominent nucleoli. S-100 positivity
Fibromatosis	Background of APC* and Gardner's syndrome, with posteriorly placed, irregular, hypoechoic, spiculated, non-calcified mass near pectoralis	Spindle cells with no nuclear pleomorphism or mitosis infiltrating adjacent lobules and ducts. Lymphocyte aggregates at periphery
Fat necrosis	Post operative, post traumatic or post radiation setting, appears as a complex mass on US. On mammogram, an irregular, spiculated mass with or without visible fat density. It develops calcification over time which has a peripheral curvilinear appearance	Disruption of fat cells with vacuole formation, surrounded by lipid laden histiocytes with foreign body type giant cells with variable amount of fibrosis and collagen. It is a benign inflammatory process

* APC-Adenomatous Polyposis Coli

Miscellaneous conditions

Pseudoangiomatous stromal hyperplasia (PASH)

It is a benign disease of the breast characterized by a complex network of slit-like spaces lined by slender spindle cells within a background of stromal hyperplasia.⁴⁷ These slit-like spaces can be confused as vascular spaces, and hence the name. It is thought to be a proliferative response of myofibroblasts, probably to hormonal stimuli, seen in pre- and perimenopausal age group, or in women with a history of hormone replacement therapy. On mammogram, they appear as circumscribed, non-calcified masses (Fig. 9a, b), or focal asymmetry. US may show a circumscribed hypoechoic mass indistinguishable from a fibroadenoma or may show a mixed echogenicity mass (Fig. 9c, d). US and MRI may reveal these cystic slit-like spaces.⁴⁸ PASH may exist in tumoral and non-tumoral forms and are known to grow in size.⁴⁹

Fat necrosis

Fat necrosis in the breast is a great mimicker of cancer due to its

varied imaging appearance. It is characterized by non-suppurative inflammation, and may occur after accidental trauma, or more commonly following breast surgery or radiation therapy.⁵⁰ Its imaging appearance can range from typical benign oil cysts, to suspicious looking spiculated masses giving posterior shadowing, depending on the amount of associated fibrosis.⁵¹ Mammogram always scores over US in diagnosing this entity by demonstrating fat density within. Cases seen early in the course of the fat saponification only reveal ill-defined hyper-echogenicity or oil cyst on US and do not have any overlap with features of malignancy. However, in cases with associated significant fibrosis, appearances on particularly US may be bizarre, like spiculated hypoechoic masses with dense shadowing, cysts with echogenic nodules with posterior enhancement or shadowing, which may seem alarming (Fig. 10a, b). Mammogram findings may show oil cysts or benign rim or punctate or coarse calcifications (Fig. 10c). In most instances fat can be demonstrated on mammogram. Suspicious findings include malignant pattern of linear or linear branching calcification, focal asymmetry, or dense masses, where the reparative fibrosis has completely replaced the fat component.^{52,53} Biopsy may be necessary in such cases to rule out malignant etiology. MRI, if done, can show lesions isointense to fat as in other regions of breast and demonstrate the characteristic T1 hypointense signal on fat saturated images. Imaging mirrors the histology, consisting of fat spherules with adjacent histiocytes, and hemosiderin deposition, fibrosis and calcifications (Fig. 10d). Fat necrosis may regress, remain stable and even progress with time.

Table 2 summarizes the imaging and pathology findings of various breast cancer mimics.

Conclusion

Due to the current increase in breast imaging in both screening and diagnostic settings, there is higher detection of breast lesions. A substantial proportion of breast biopsies of suspicious findings ultimately return benign histopathological results, which may confuse the treating team as well as the patient. Thus, it is imperative for the breast radiologists, surgeons and referring physicians to be aware of these benign mimickers of breast cancer to manage these cases of radiological-pathological discordance appropriately, and to offer best care to the patient.

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Declaration of competing interest

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