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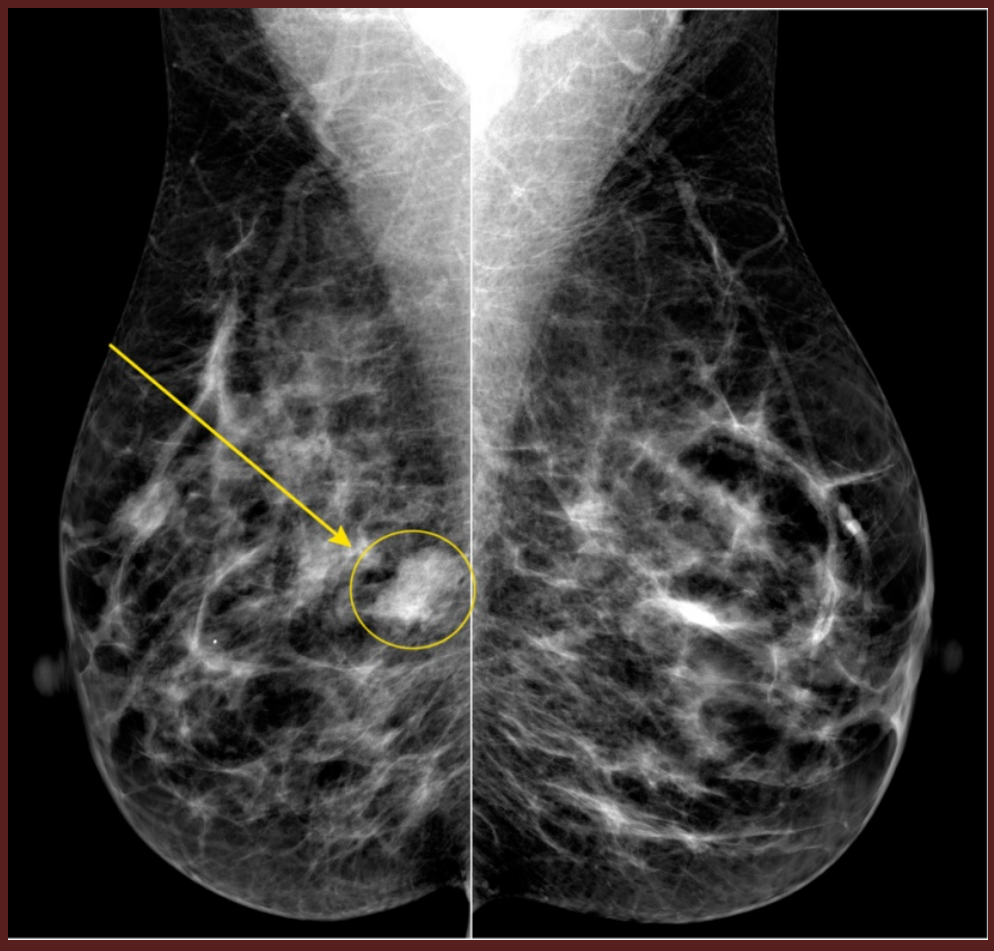
BREAST IMAGING



Guest Editor: Susann E. Schetter, D.O.

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Breast Imaging

Guest Editor: Susann E. Schetter, D.O.

In This Issue

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"At times our own light goes out and is rekindled by a spark from another person.

Each of us has cause to think with deep gratitude of those who have lighted the flame within us."

-Albert Schweitzer

The practice of Medicine is not evolving, but rather changing at a break-neck pace. As Radiology has been the beneficiary of swift technological advances, so have we been challenged by disruptive changes that disconnect us from our referring physicians and patients. It is my strong personal belief that Breast Imaging, and other elements of our specialty, enable us to cross this divide. Connecting personally with patients in consultation, in the ultrasound suite, and during biopsy procedures enables us to put a face on our profession and fashion our own definition of the Radiologist's role in the practice of medicine.

I am honored and thrilled to have the opportunity to serve as the guest editor of this issue of the JAOCR. My great thanks to the authors and contributors, my colleagues in practice, prior Fellow, and current residents, who have offered a variety of topics that I hope you find interesting. The article on breast implants presents readers with the opportunity to review the normal appearance and commonly encountered complications and management. The review of breast density was included at this time due to the increasing exposure in the popular press and legislative actions influencing our practice.

I would like to additionally offer thanks to Dr. William O'Brien for his interest, enthusiasm, and exceptional talents that launched this publication and sustain its continuing success, and to the AOCR staff, particularly Ms. Jessica Roberts, for their knowledgeable support.

Medicine is a challenging career, a commitment to life-long learning, and an opportunity to change a life, every day. Maintaining our expertise in imaging, and continually learning about trends in medical diagnosis, treatment, and research enable us to be the partner in patient care that our referring physicians value most. The environment of change before us offers a unique opportunity to take a step back, reassess our position, and reclaim the relationships that may have been diminished in the last decades. Let's start this year with a reaffirmation of our choice and a renewed understanding of the privilege of our work.

Imaging of Breast Implants and Their Associated Complications

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INTRODUCTION

Breast implant procedures have been performed since the late 19th century for augmentation, correction of congenital abnormalities, and post-mastectomy reconstruction. Over the years, the surgical options and types of implants available have evolved. As a result, the augmented breast can have a widely variable appearance, and the practicing radiologist must recognize the numerous variations in implant construction that are encountered clinically.

Magnetic resonance imaging is the most accurate method for evaluating breast implants and their complications due to the high sensitivity and specificity (sensitivity 89% and specificity 97%), inherent high soft tissue contrast, and lack of ionizing radiation.[1-5] For these reasons, breast MRI has been increasingly used to both screen and diagnose complications in patients with implants. The usefulness of MRI derives from its ability to selectively suppress or emphasize the signal of water, fat, or especially silicone. The high spatial and soft tissue resolution makes MRI ideal for the characterization of breast implants.[6]

This article reviews the normal appearance, as well as early, late, and rare complications associated with different types of breast implants.

NORMAL APPEARANCE

Proper diagnosis of implant complications requires a thorough understanding of the imaging characteristics of normal implants. Single lumen silicone and saline implants, which consist of a single polymer shell filled with silicone or saline, are the most frequently used devices for breast augmentation/reconstruction. Saline implants have a valve to allow volume adjustment, which helps identify them on MRI.

The classic double lumen implant contains an outer saline shell with silicone on the inside, while reverse double lumen implants have an adjustable inner saline shell and outer silicone shell.[2,4,5] MRI sequences that are selective for silicone and fluid help differentiate the implant type.

Saline implants follow fluid signal on all sequences. Silicone implants can have variable signal on T1 and T2 weighted sequences, but display high signal intensity on silicone selective sequence. Each type of silicone gel filled implant has slightly different imaging findings related to the manufacturing process and viscosity of the silicone gel.[2]

Implants may be placed in a prepectoral or retropectoral location. The benefits of placing implants behind the pectoralis muscle include decreased incidence of capsular contracture and improved visibility of the breast tissue on mammography.[7,8] Locating the position of the muscle on MRI using the sagittal images can help differentiate the implant position (**Fig. 1**).

Normal implants are triangular in shape. They may have numerous and/or complex radial folds on MR imaging which should not be confused with rupture (**Fig. 2**). Implants placed for congenital abnormalities such as Poland syndrome or pectus deformity may have an atypical or asymmetric appearance which should not be confused with malpositioning. Clinical history can help determine whether the implant is truly malpositioned.

Breast implants are categorized into five implant generations reflecting product development over time. The recent generations of silicone gel implants have a cohesive viscous silicone gel, and as a result, these implants will rarely have a totally collapsed implant shell with rupture, differing from the older generations (**Fig. 3**). Most of these demonstrate gel leakage and silicone migration.[2] The third and fourth implant generations offered models of breast implants with textured or uniformly smooth surfaces.

Before implant insertion, especially in oncoloplastic breast reconstruction, a tissue expander is usually placed into the mastectomy site to stretch the remaining skin in preparation for the placement of a

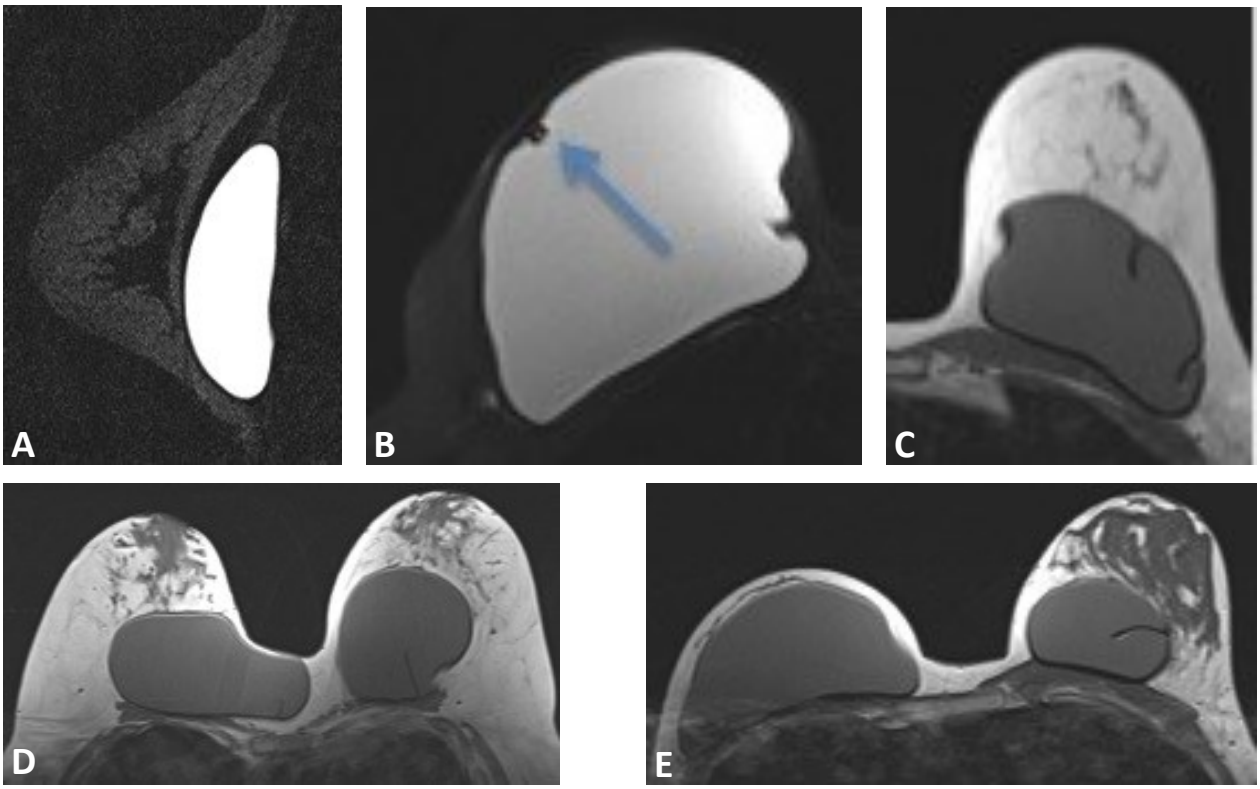


Figure 1. Normal Implant Appearance in Different Patients. Sagittal silicone selective image of the left breast (**A**) demonstrates a normal single lumen silicone implant. Note the high signal, normal triangular shape of the implant, and retropectoral position. Axial T2 weighted image of the right breast (**B**) shows a normal single lumen saline implant. Note the normal triangular shape and the valve (arrow) indicating it is a saline implant. Axial T1 weighted image of the left breast (**C**) demonstrates a normal single lumen silicone implant in the prepectoral position with pectoralis posterior to the implant. Normal radial folds are present. Axial T1 weighted image (**D**) demonstrates bilateral prepectoral silicone implants placed for pectus deformity. Although the right implant appears displaced medially, this was the desired position for cosmesis. Axial T1 weighted image (**E**) demonstrates bilateral prepectoral silicone implants placed for cosmesis in a patient with Poland syndrome. Note that absence of the right breast tissue and chest wall musculature.

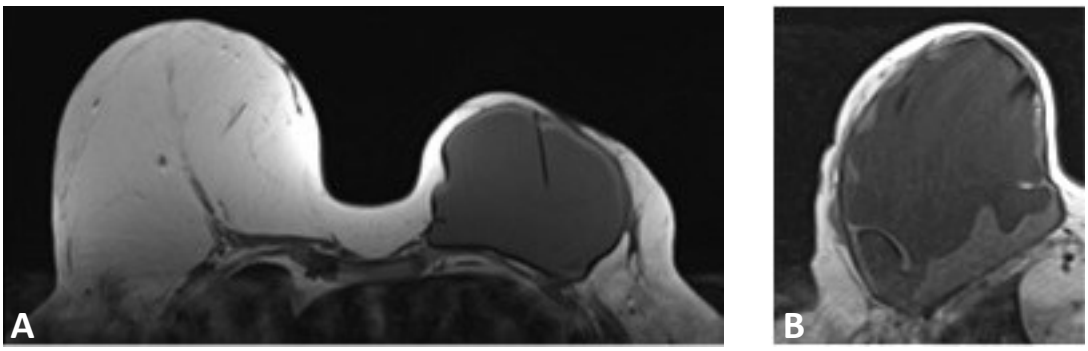


Figure 2. Radial Folds. Axial T1 weighted image (**A**) demonstrates normal findings in a patient with a history of right breast cancer status post TRAM flap reconstruction. The patient has a left single lumen silicone implant which shows a normal radial fold. This was placed for cosmesis after right reconstruction. Axial T1 weighted image of a right double lumen implant (**B**) demonstrates extensive normal radial folds. The implant was intact without rupture. Note that folds may be multiple and complex.

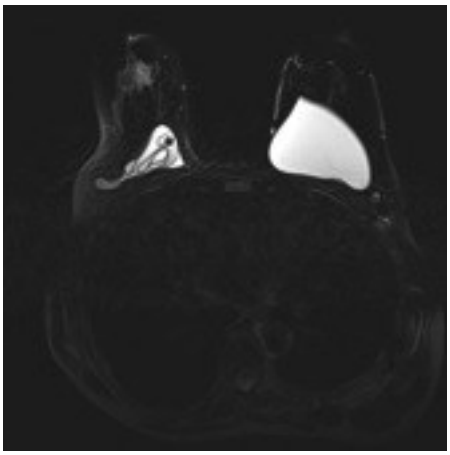
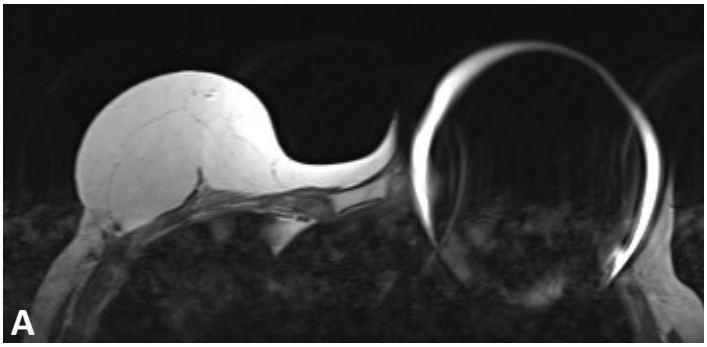


Figure 3.
Breast implant collapse. Axial T2 FS image of the breasts from an MRI in a patient with a clinically apparent change in the shape of the right breast demonstrates complete collapse of the right implant.



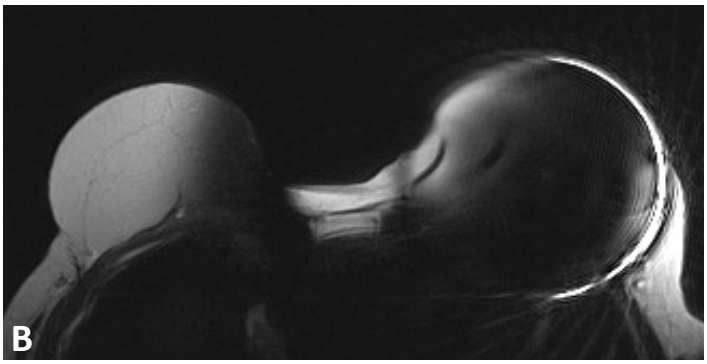


Figure 4.
Tissue expander artifact. T1 (A) and T2 (B) weighted axial images of the breasts demonstrate significant metal artifact from a left breast expander which had been filled to 200 cc with sterile injectable saline. This patient underwent breast MRI scan as she was unaware that she had a breast expander in place and assumed she had a breast implant.

permanent implant.[2] The expander is placed in its collapsed form and fluid is introduced into the tissue expander to slowly inflate it. This process may continue for several weeks or months until the tissue expander is filled to an optimal volume for permanent breast implant placement. Some breast tissue expanders should be considered a contraindication to MRI because of the magnetic marker of the filling valve (**Fig. 4**). Expander manufacturers list possible consequences such as overheating, possible expander displacement, and possible reduction of magnetization of the marker.

EARLY COMPLICATIONS

Implant complications that occur in the immediate post-surgical period include the development of collections around the implant and infection.

Peri-implant Collections.

Small seromas or peri-implant fluid collections are considered normal and are favorable. They are felt to be reactive and related to inflammatory response to the implant. Small seromas present as T2 hyperintense fluid collections around the implant on MRI (**Fig. 5a**). This fluid may be beneficial as it may prevent capsular contracture and implant damage from minor trauma.[4] Large or rapidly growing seromas, however, are problematic (**Figs. 5a and b**). They can be painful, cause deformity, and increase the risk of infection. Therapeutic aspiration or percutaneous drainage of fluid can be performed when large seromas become symptomatic. Older implants made of polyurethane (no longer used in the United States) can undergo chemical breakdown, inciting an inflammatory response that could lead to the development of complex seromas.[5,9] However, such fluid collections are usually a late complication of breast implants.

Infection.

Infection is reported to be the leading cause of morbidity associated with breast implants, seen in 2.0-2.5% of patients. The majority of cases are peri-operative and may be related to contamination of the skin, implant, or surgical instruments. Delayed infections are less common and are generally related to systemic infections.[10] Symptoms of implant-associated infection include redness, swelling, discharge, fever, and pain. The presence of large peri-implant collections increases the risk for infection. MRI findings suggestive of implant infection include the presence of complex fluid collections around the implant, skin thickening, and edema. (**Fig. 5c**)

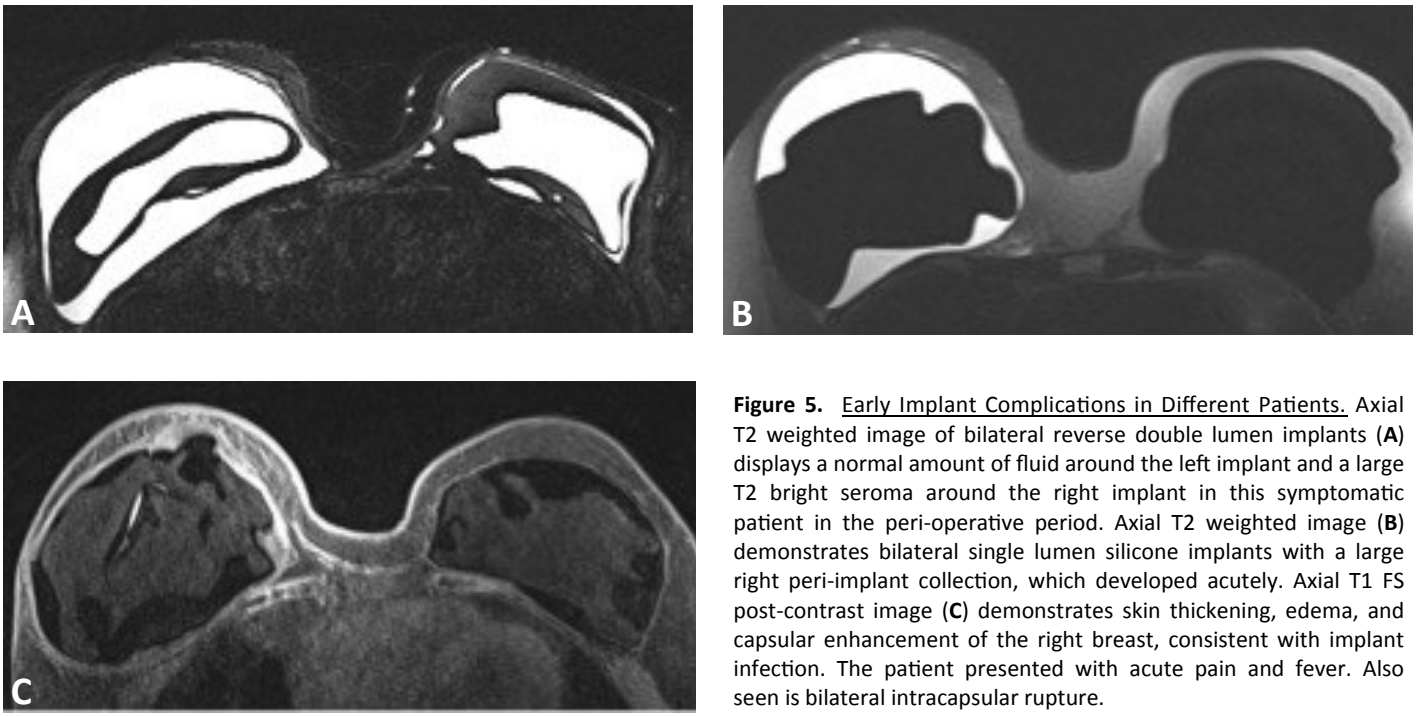


Figure 5. Early Implant Complications in Different Patients. Axial T2 weighted image of bilateral reverse double lumen implants (**A**) displays a normal amount of fluid around the left implant and a large T2 bright seroma around the right implant in this symptomatic patient in the peri-operative period. Axial T2 weighted image (**B**) demonstrates bilateral single lumen silicone implants with a large right peri-implant collection, which developed acutely. Axial T1 FS post-contrast image (**C**) demonstrates skin thickening, edema, and capsular enhancement of the right breast, consistent with implant infection. The patient presented with acute pain and fever. Also seen is bilateral intracapsular rupture.

DELAYED COMPLICATIONS

Delayed complications seen in breast implants include the development of contractures, implant rupture, and gel bleed.

Contractures.

Capsular contractures are the most common delayed complication noted in implants. They are caused by excessive scaring around the implant, which leads to deformity and unsatisfactory cosmesis. When contractures are present, the implant can become rounded in shape, losing its normal triangular configuration on MRI.[1-5,10] Radial folds are frequently observed in patients with capsular contracture.[2] Occasionally, the capsule tears, allowing part of the implant to herniate into adjacent parenchyma. The capsule sometimes calcifies, and rigid calcium deposits may be palpated immediately adjacent to the implant.[2,7]

Rupture.

Implant rupture is the most common delayed implant complication discussed in the imaging literature. It most often occurs 10-15 years after implant placement. Implant rupture can have various causes, although most ruptures have no obvious traumatic origin and sometimes occur in asymptomatic patients. The incidence of rupture increases with implant age. The average incidence is approximately two implant ruptures per 100 implant-years with an estimated probability of being intact after 5 and 10 years of implantation of 98% and 83-85% respectively.[1,11,12]

Saline implant ruptures are readily detected clinically as the implant will significantly decrease in size with extrusion of the fluid. Rupture of silicone implants, however, can be more difficult to recognize. Clinical diagnosis is based solely on nonspecific findings such as palpable nodules, asymmetry, or tenderness.[13] Patients usually present with pain, contour change or deformity of the implant or palpable mass.[3] Clinical evaluation may fail to detect breast implant rupture that occurs over time without loss of breast volume and misshapenness. Breast pain on the clinical examination of implants is a strong predictor of rupture, but the absence of pain does not exclude rupture.[2,14]

There are two types of silicone implant rupture. The more common intracapsular rupture occurs when there is disruption of the implant shell without

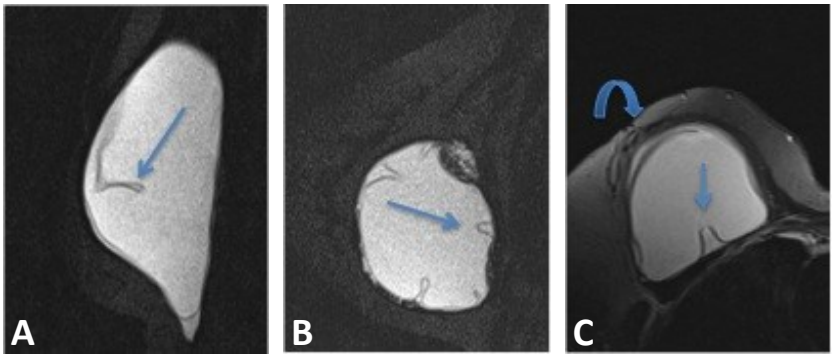


Figure 6. Early Signs of Implant Rupture in Different Patients. Sagittal silicone selective image of the right breast (**A**) demonstrates a "tear drop" sign (arrow), consistent with intracapsular rupture. Sagittal silicone selective image of the right breast (**B**) reveals a "keyhole" sign (arrow), consistent with intracapsular rupture. There is also extracapsular free silicone. Axial T2 image of the right breast (**C**) demonstrates a "keyhole" sign (arrow) and "intracapsular line"(curved arrow) sign, consistent with intracapsular rupture.

Figure 7. Extracapsular Implant Rupture. Sagittal silicone selective image of the right breast demonstrates hyperintense signal in the axilla (arrow), consistent with free silicone, indicating extracapsular implant rupture.

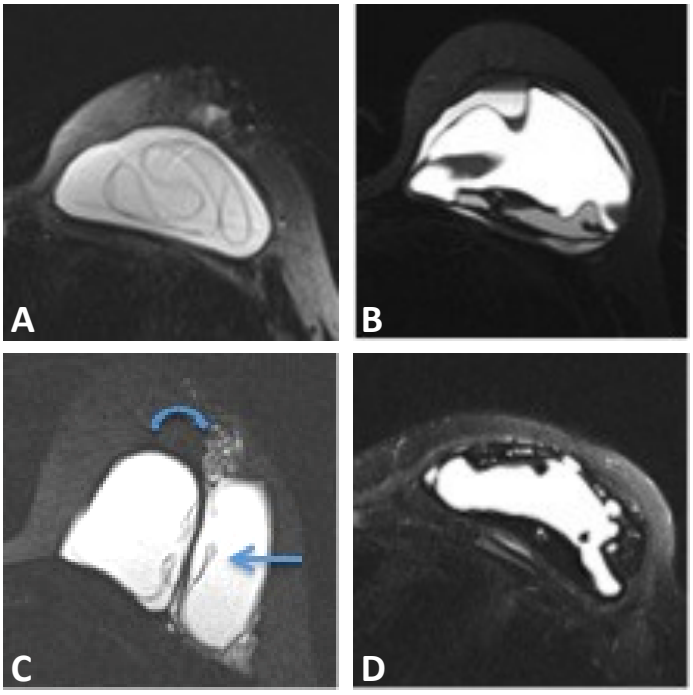


Figure 8.
Examples of Intracapsular and Extracapsular Implant Rupture in Different Patients. Axial T2 weighted image of the left breast (**A**) demonstrates the "linguini sign" consistent with collapsed intracapsular rupture. Axial T2 weighted image of the left breast (**B**) shows a reverse double lumen implant with intermixing of the saline and silicone, consistent with intracapsular rupture. Note the complex fluid-fluid levels. Axial silicone selective image of the left breast (**C**) demonstrates hyperintense signal in the breast parenchyma outside the fibrous capsule (curved arrow), as well as the "tear drop sign" (arrow), indicating both intracapsular and extracapsular rupture. Axial T2 weighted image of the left breast (**D**) demonstrates a reverse double lumen implant with locules of saline within the outer silicone lumen, consistent with intracapsular rupture.

macroscopic silicone extending within the fibrous capsule.[1] If rupture occurs and the implant collapses, the "linguini sign" (multiple curvilinear low signal intensity lines within the T2 bright silicone) will be evident on MRI. An earlier sign of rupture where the shell has not completely collapsed produces the "subcapsular line," "keyhole," "noose," and "tear drop" signs on MRI (**Fig. 6**). The key to distinguishing these signs from a radial fold is identifying silicone on both sides of the implant shell. This can be challenging and multiplanar imaging is helpful, particularly using a combination of both axial and sagittal images.

Extracapsular rupture, defined as macroscopic silicone extending beyond the fibrous capsule of the implant, occurs less commonly. On MRI examination, macroscopic silicone is visualized as high signal intensity deposits (on silicone selective sequences) within the breast tissue, intramammary nodes, internal mammary nodes, and axillary nodes (**Figs. 7 and 8**).[1-5,15]

Gel Bleed.

Gel bleed is a term referring to the microscopic leakage of silicone through an intact implant shell (**Fig. 9**). On MRI, gel bleed can produce subtle high signal intensity on both sides of the implant shell on silicone selective sequences.[5]

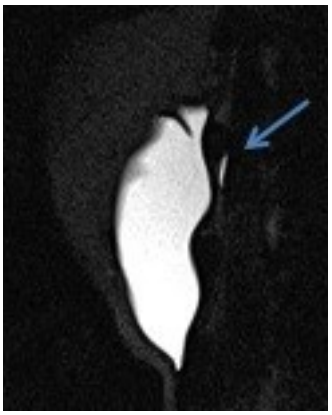


Figure 9.
Gel Bleed. Sagittal silicone selective image of the right breast demonstrates a curvilinear area of high signal posterior to the silicone implant, compatible with gel bleed (arrow). The patient was asymptomatic and no treatment was recommended by her plastic surgeon.

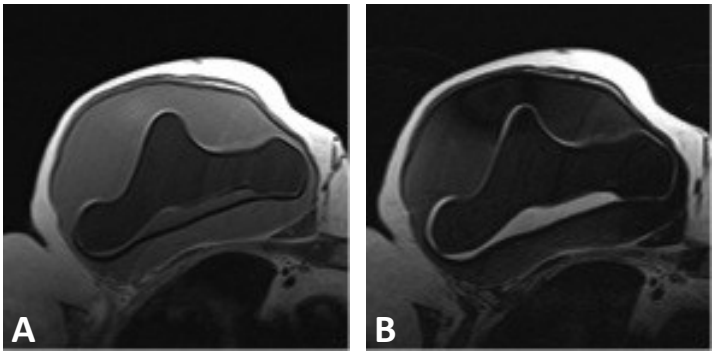


Figure 10.
Hematoma. Axial T1 (**A**) and T2 (**B**) post-contrast images of the right breast demonstrate a large non-simple fluid collection around a double lumen implant. On exploration, this was a large delayed onset hematoma.

RARE COMPLICATIONS

Rare complications of implant placement include the development of new or recurrent breast cancer and post-operative or delayed hematomas. Anaplastic large cell lymphoma is exceedingly rare, but should be considered in any patient with persistent fluid collections around the implant.

Hematoma.

Hematomas are commonly seen in the peri-operative period. They can be large, painful, and require drainage. Delayed hematomas are rare, caused by trauma, coagulopathy, capsular tear, recurrent cancer, or infection.[16] On MRI, hematomas appear as complex fluid collections (**Fig. 10**).

New or Recurrent Carcinoma.

Implants do not increase the risk for breast cancer; however, they can make detection of breast cancer by mammography and US more challenging.[2,7] MRI is an imaging technique to evaluate the entire breast and chest wall. MRI evaluation using dynamically enhanced T1 FS MRI sequences allow identification of suspicious enhancing masses and non-mass like enhancement (**Figs. 11 and 12**). These suspicious findings should be further evaluated with biopsy, as in patients without implants.

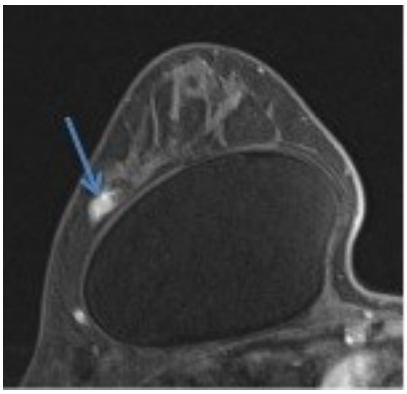


Figure 11.
Recurrent breast carcinoma. Axial T1 FS post-contrast image of the right breast from a screening MRI demonstrates an irregular enhancing mass (arrow) with irregular margins within 2 mm of the implant capsule. Infiltrating ductal carcinoma was diagnosed at biopsy in this BRCA 1 positive patient.

Anaplastic Large Cell Lymphoma (ALCL).

Anaplastic large cell lymphoma (**Fig. 13**) is a type of T-cell lymphoma (non-Hodgkin lymphoma) that is extremely rare, diagnosed in 1:500,000 women in the United States each year.[17] Breast involvement is even more rare with a reported incidence of 3 cases per 100 million women per year in the United States.[18] Two main types have been described: tumors expressing the protein anaplastic lymphoma kinase (ALK-positive) and tumors which do not express the protein (ALK-negative). Some associations have been reported between ALK-negative ALCL and breast implants (both silicone and saline). The FDA describes at least 60 case reports of such an association in the literature, which, although it is a low number, is higher than would be expected from existing epidemiology data.[17]

The FDA performed a formal analysis of the published scientific literature on implant associated ALCL. In their review, the median time from implant placement to the diagnosis of ALCL was 8 years (range

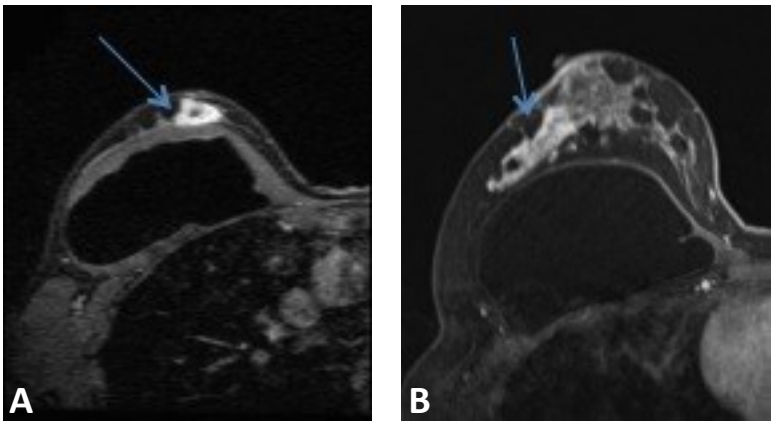
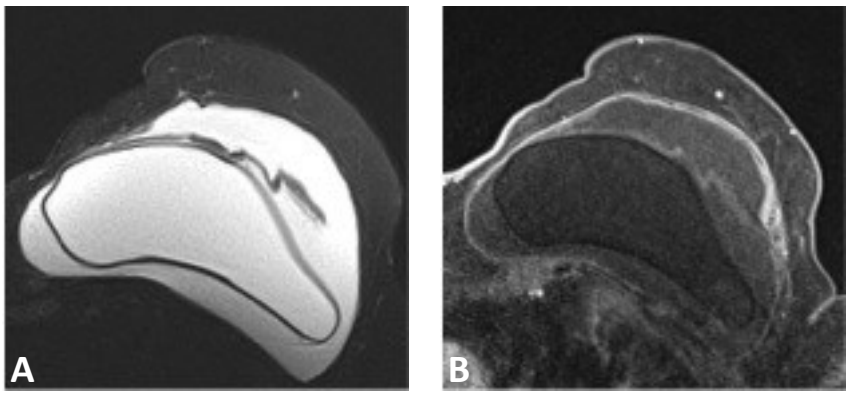


Figure 12.
Newly Diagnosed Breast Carcinoma. Axial T1 FS post-contrast image of the right breast from a screening MRI (**A**) demonstrates an irregular enhancing mass (arrow) with irregular margins. Infiltrating ductal carcinoma was diagnosed following biopsy in this patient. Axial T1 FS post-contrast image of the right breast (**B**) in a different, asymptomatic, screening patient demonstrates segmental non-masslike enhancement (arrow) in the lateral breast at 9 o'clock. DCIS was diagnosed at biopsy.

Figure 13.
Anaplastic Large Cell Lymphoma (ALCL). Axial T2 (**A**) and T1 (**B**) FS post-contrast images of the left breast show a large T2 bright fluid collection around the single lumen saline implant. There is mild enhancement of the capsule on the post-contrast image. This patient had prior capsulectomy for persistent pain. This is a case of biopsy proven ALCL associated with an implant.



1-23 years). Most patients were diagnosed after seeking treatment for symptoms related to their implants (intractable seromas, fibrous capsule, peri-implant mass, etc.), the most common being persistent peri-implant seroma. In most cases the lymphomatous involvement was confined to the capsule. All tumors were ALK-negative.[17]

Current recommendations for management of patients with possible implant associated ALCL include pathologic testing of fresh seroma fluid and representative sections of the capsule, including cytologic evaluation of the fluid with Wright Giemsa stained smears and cell block immunohistochemistry testing for cluster of differentiations and the presence or absence of anaplastic lymphoma kinase (ALK positive or negative).[17]

Until there is more data regarding the development of ALCL in patients with implants, the FDA has requested that all confirmed cases be reported to the FDA.[17]

Summary

In conclusion, MRI is the best tool for imaging evaluation of acute and delayed breast implant complications. Normal implants are triangular in shape and may have numerous or complex radial folds, which should not be confused with implant rupture. Understanding and recognizing potential complications of breast implants and their significance helps facilitate prompt and appropriate management. The most common complications include contractures and implant rupture. Characteristic imaging findings of intracapsular implant rupture include the "linguini," "subcapsular line," "keyhole," "noose," and "tear drop" signs on MRI. Small peri-implant fluid collections are normal and may reduce trauma to the implant. Large, complex collections, on the other hand, particularly when delayed and persistent, may be representative of infectious or rarely neoplastic implant complications.

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Breast Density as an Independent Risk Factor for Cancer

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Introduction

In 2009, Connecticut introduced the first state law mandating that women be informed of their breast density when they receive the lay letter results of their screening mammogram. Since then, another 12 states have legislated similar requirements with variable budget support for the increased costs of supplemental screening exams. The impetus behind these legislative changes is the understanding that increased breast density is associated with decreased mammographic sensitivity for the detection of breast cancer. Epidemiologic studies of early screening performance showed that increased breast density had a negative effect on mammographic sensitivity, termed masking bias.[1] For this reason, vocal advocacy groups have pushed the agenda politically.

Although a masking bias *does* exist in women with dense breasts,[2] there is substantial evidence that increased parenchymal breast density (PBD) is one of the strongest predictors of breast cancer risk. Women with the highest breast density have a risk 2 to 6 times those with lowest breast density.[3] As many as 30% of postmenopausal women have dense breasts, which makes increased breast density the most frequently encountered risk factor for development of breast cancer. Further, it is apparent that PBD can be altered with intervention.[4-6]

This article reviews historical literature and summarizes recent data addressing breast density and the relationship to breast cancer risk. An overview of biochemical and genetic contributions to cancer development and increased PBD, as well as the contributions of hormones and aging is provided. Understanding the known risks conferred by increased breast density will enhance our ability to educate both patients and clinical colleagues when the inevitable questions arise concerning breast density and breast cancer screening.

Historical Use of Breast Density and Mammographic Reporting

Radiologists are accustomed to observing and describing the appearance of the breast tissue on mammograms. In 1976, prior to the acceptance of widespread mammographic screening, John Wolfe published a seminal article in the *American Journal of Roentgenology* describing four breast parenchymal patterns: N1, P1, P2, DY (least to most dense). He determined that the cancer rate in the DY population to be 37 times that of the N1 group, and made recommendations for consideration of prophylactic mastectomy for women with a DY assessment.[7] Forty percent of the cancers identified in his cohort were prevalent cancers (cancers present in the first screening round) due to the lack of routine screening available. Subsequently, it was apparent that the use of the Wolfe patterns was widely variable with poor inter- and intra-observer agreement. Fortunately, his conclusions were eventually shown to over-estimate the importance of breast density as a risk factor for breast cancer. Nevertheless, a positive relationship of breast density to the incidence of cancer was established.

The American College of Radiology (ACR) Breast Imaging Reporting and Data System (BIRADS) categories for breast density (primarily fatty, scattered fibroglandular, heterogeneously dense, and extremely dense) were in part developed to address the issue of masking bias associated with increased PBD (**Fig. 1**).[8] The Mammography Quality Standards Act (MQSA) adopted the ACR BIRADS definition and mandated the categorization of breast density into one of these 4 categories. Moderate inter-observer agreement has been measured, with kappa coefficients of 0.43 – 0.59; these k values are higher for BIRADS 1 and 4 assessments, which are more straightforward than the BIRADS 2 and 3 categories. Although there is known decreasing sensitivity of mammograms as one

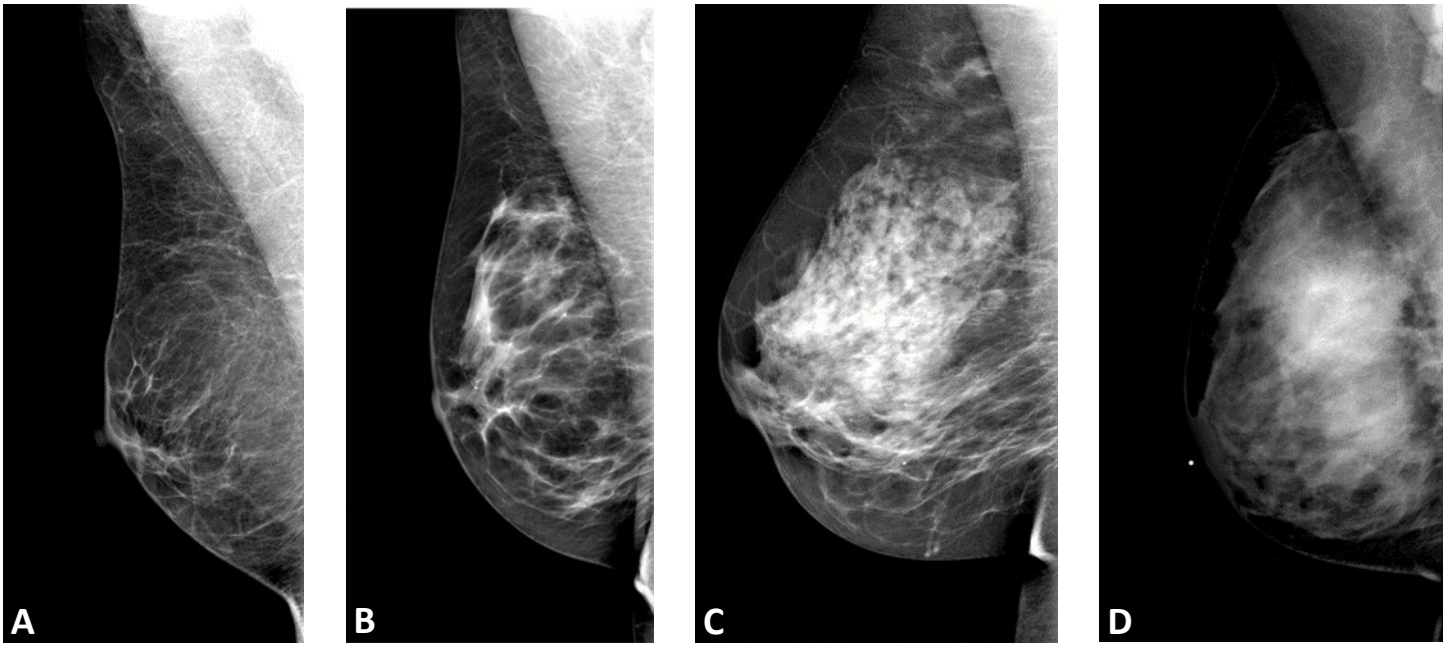

Figure 1. Categories of Breast Density. From left to right, MLO images show almost entirely fat (**A**), scattered fibroglandular densities (**B**), heterogeneously dense (**C**), and extremely dense (**D**) breast density.

proceeds from BIRADS 1 to BIRADS 4, there is no inherent relevance to breast cancer risk conferred by this assessment.[9]

Certainly, high breast density decreases the conspicuity of breast lesions, and delay in the diagnosis of breast cancer remains in the top five errors in radiology malpractice claims. In fact, nearly 70% of these claims refer to women less than 50 years of age, accounting for 78% of all indemnity paid. In contrast, more than 75% of all typical infiltrating ductal carcinoma is seen in women *over* 50 years of age,[10] paradoxically rising in a population with decreasing breast density and raising questions regarding the process of involution and extracellular factors that contribute to carcinogenesis. Yet, data support mammography as the best, albeit imperfect, screening modality, with a resultant decrease in mortality in all age brackets.

Calculations of Breast Density and Breast Cancer Risk

In 1995, two articles were published in the *Journal of the National Cancer Institute* (JNCI) addressing the importance of breast density as a risk factor for the development of breast cancer. Boyd, et al. published the first computer-assisted, threshold measurement of breast density (Cumulus method), developed at Sunnybrook, Toronto, Ontario, Canada.[3] This method includes the digitization of film/screen mammograms which are then presented for evaluation on a high resolution workstation. The observers select the outline of the breast as the first threshold to separate the structure of the breast from the background, and a second threshold is established by the observer to delineate the dense tissue from the non-dense breast tissue. The breast density was calculated as a percentage of "dense" pixels of the total area of the breast (**Fig. 2**) .[3] Boyd, et al.'s study excluded all prevalent cancers and all women who developed cancer within one year of entry into the study. The researchers found a statistically significant increase in the number of cancers developed in the women with the greatest breast density. This positive correlation was seen in all age groups, and a calculated increased relative risk of 5 – 6 fold was similar for both Radiologist-observed and quantitative threshold determination of the percent breast density.

Using screening and follow-up information from the Breast Cancer Detection Demonstration Project, Byrne, et al. determined a similar positive relationship

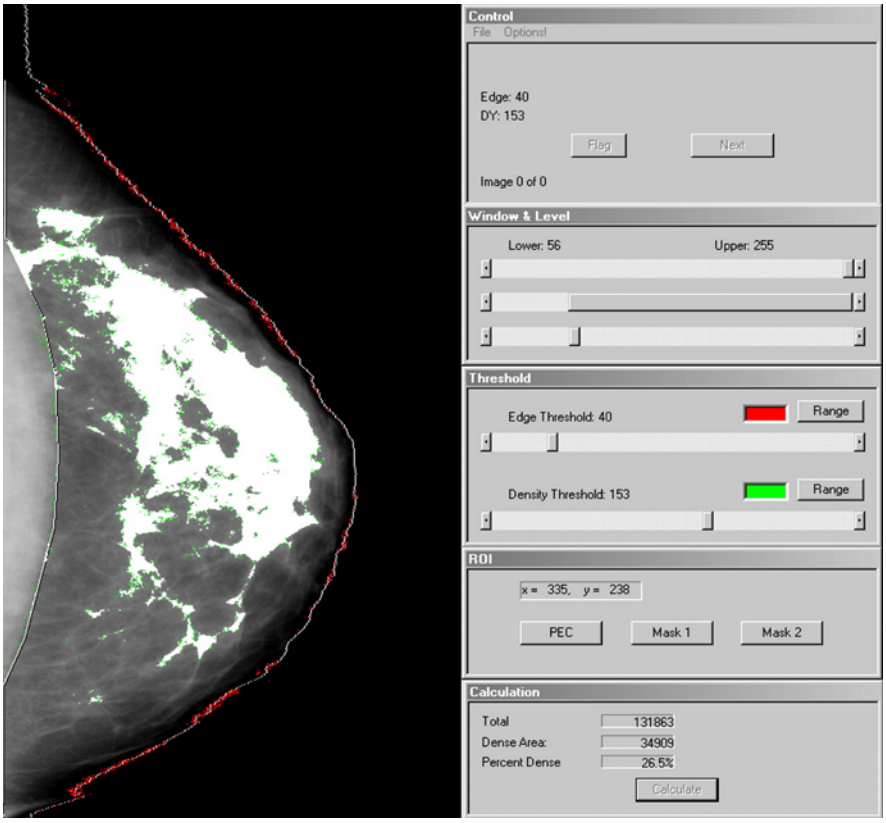

Figure 2.
Computerized Breast Density Measurement. Unilateral breast image demonstrates computerized threshold method of measuring breast density (Cumulus method). Image courtesy of Martin Yaffe, PhD, Sunnybrook Research Institute, Canada.

between high PBD and breast cancer risk that was independent of age and menopausal status. Baseline density evaluations of 1880 case subjects and 2152 control subjects were recorded by observers using the Wolfe classifications. Patients were followed for 16 years, decisively eliminating the masking bias and allowing for determination of the risk conveyed by breast density 10 years beyond the baseline assessment. Both studies show a 4 – 5 fold increase in breast cancer risk for women with >75% breast density, adjusting for BMI and family history.[9]

Subsequently, quantitative evaluations of larger data sets were published, to advance the understanding of these relationships. Harvey, et al. reviewed twelve breast density studies that used the computerized threshold method.[11] An increased cancer risk was associated with increased breast density in every study, outcomes unaffected by masking bias. Incident breast cancer cases showed no dramatic change in breast density over the course of 2 – 8 years, proving that baseline density was as important as density at the time of diagnosis.

A systematic review of aggregate data representing greater than 14,000 cases and 226,000 non-cases explored sources of conflicting data in 42 articles due to the use of different qualitative and quantitative methods of breast density assessment and variable patient age ranges. A meta-analysis of this data was published by McCormack and Silva in 2006.[12] Breast density was confirmed as the strongest risk for breast cancer, independent of masking effect and not restricted to any particular age bracket. Although both screen detected and interval cancers are more numerous in the women with high PBD, there is no correlation between increased breast density and prognosis at the time of breast cancer diagnosis.[13]

A positive correlation between high PBD and the Gail model was established by Palomeres, et al.[14] The Gail model is a commonly utilized tool for breast cancer risk assessment, stratifying risk with well-understood factors related to personal hormonal and familial cancer histories. The model assigns a percent chance of cancer development at 5 years and over a lifetime. Higher PBD was found in women with greater than 15% lifetime risk compared to those with less

than 15% lifetime risk. Interestingly, the women in the higher risk group had twice the breast density of those with lower risk.[14]

Current published guidelines for women with a 20% lifetime risk recommend supplemental cancer screening with MRI; however, for those whose risk ranges from 15 – 20%, there are no clear recommendations.[15]

Contributions to Breast Density

Intrinsic factors contributing to breast density include age, genetics, serum and tissue hormone levels, and body mass index (BMI). Extrinsic factors include hormone supplements or replacement, diet, exercise, alcohol, and environmental factors.

Hormones.

The effect of hormones and aging on breast density has been extensively studied. At mid-menstrual cycle, ovulation is accompanied by a strong luteinizing hormone (LH) peak and concurrent rises in estradiol and follicle-stimulating hormone (FSH) (**Fig. 3**). Although progesterone levels begin to increase at this time, they peak later in the luteal phase with continued elevation of estradiol. This premenstrual elevation of progesterone and estrogens is responsible for retention of water within the breast tissue and increased cellular proliferation, resulting in higher tissue volumes. Breast imaging studies are ideally performed in the follicular phase of the cycle (week 2), when these effects are least influential.[16] Timing of examinations to the follicular phase decreases discomfort of mammograms and may increase compliance with mammographic screening. The specificity of ultrasound and MRI also increases in the follicular phase. Accuracy of interpretation can improve when timing is optimized as the parenchymal appearance is dramatically altered in some patients. A recent study in *Radiology* showed variation in the levels of enhancement of normal breast parenchyma and benign lesions in week 2 vs. week 4 of the cycle, favoring imaging in week 2. This effect did not apply to the malignant lesions.[17]

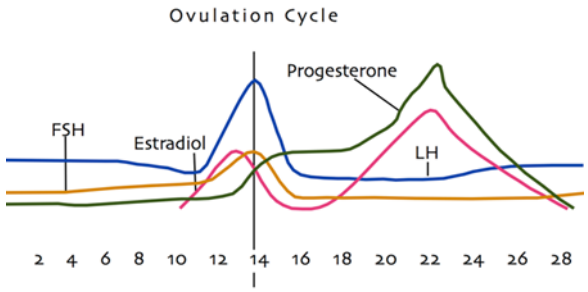

Figure 3. Changes in Relative Hormone Levels Related to Menstrual Cycle.

Hormonal influences contribute to higher breast density and higher levels of breast cancer in nulliparous women, as well as in those who have fewer children and at later ages. For women with larger areas of fibroglandular tissue and increased breast density, perimenopausal hormone effects can be dramatic. These effects arise from shortening of the follicular phase of the cycle and higher pre-ovulatory estradiol levels contributing to increasing size and number of breast cysts. It is reasonable to assume that these changes in breast density are related to proliferative effects of endogenous hormones.

Histologic evaluations have shown that morphologic changes in the tissue received from surgical and core biopsy specimens matched with the phase of the menstrual cycle.[18] Specimens from women in menstrual days 6 – 15 showed clear distinction between epithelial and myoepithelial layers of the acini and an absence of stromal edema. Mitosis and apoptotic bodies were not present. In contrast, at days 25 – 28, epithelial cells showed prominent nuclei, large nucleoli, frequent mitotic figures, and increased apoptosis. Also present in the immediate pre-menstrual phase were increased inflammatory cells and extensive stromal edema.[18] These histologic data support the recommendations for timing of imaging studies with the menstrual cycle.

Postmenopausal status and increasing age usually contribute to a progressive decrease in breast density. Unfortunately, this is a general trend that does not uniformly apply to all women.[19]

Age.

The common decrease in breast density and corresponding histologic change that occurs with age is described as involution.[19,20] Sixty-five percent of women in their 20's have greater than 50% breast density. This drops to 50% of women in their 40's. For postmenopausal women, approximately 30% of women have greater than 50% density, and this proportion persists into the 70's. In contrast, 34% of postmenopausal women have predominantly fatty tissue.[11]

The incidence of breast cancer increases with age. The decrease in PBD with age has been attributed to involution of breast tissue. This paradox contributes to some confusion as to the importance of breast density as a risk factor for malignancy. Involution of breast tissue occurs first peripherally, with progressive radiolucent changes on the mammogram. There may be some protective effect of involution, although the exact mechanism is unknown. It is clear, however, that postmenopausal women with higher breast density are more likely to develop cancer than those with lower breast density.[9,19]

Genetics.

Hormone status, parity, and BMI influence mammographic density, but genetics may play the largest role in the determination of an individual's PBD. Twin studies of sisters in North America and Australia proved a positive correlation for similarity in breast density among monozygotic twins that was twice that of the dizygotic twin group, measuring 60 – 67% when adjusted for age and other covariates.[21]

Mammographic differences exist across racial lines. In a retrospective review of 15,292 patients, the breast density was greatest for Asian women. There was little difference otherwise among whites, African Americans, or other ethnic groups when adjusted for BMI and age.[22]

Exogenous Hormones.

The Women's Health Initiative randomized 16,608 women to combined hormone replacement therapy (HRT), estrogen plus progestin, or placebo. Seventy-five percent of women receiving the hormone therapy showed a mean increase of 6% in breast density after one year, compared to the placebo group who charted a 0.9% decrease in baseline PBD. Baseline variables evaluated included race and ethnicity, socioeconomic status and education, full hormonal history, duration and use of oral contraception, physical activity, and use of tobacco and alcohol. The effects of HRT on breast density persisted for the 2-year duration of the study.[4] Additional studies have shown an increase in breast density over controls in the cohort receiving HRT; however, there is no evidence that there is a direct relationship to cancer development.[5,23] Both ER positive and ER negative cancers have an increased incidence in women with increased breast density.[4]

BMI.

Higher BMI correlates with a lower quantitative measurement of breast density and perceived density on mammographic interpretation. In contrast, one observes an increase in apparent mammographic breast density when patients experience significant weight loss, as in individuals following bariatric surgery. Obesity is related to increased cancer incidence in postmenopausal women, creating a paradoxical increase in cancer with decreased breast density. The exact mechanism is unknown but is attributed to an increase in local estradiol levels in breast fat secondary to local adipocyte aromatase activity.[24]

In the investigation of the influence of the non-dense tissue on the development of breast cancer, Lokate, et al. conducted a nested case-control study within a cohort of EPIC-NL, the Dutch contribution to the European Prospective Investigation into Cancer and Nutrition. Models including BMI, dense area and non-dense area, showed statistically significant independent positive correlation with breast cancer risk of the non-dense, or fatty breast.[24] Aromatase activity is found in fatty breast tissue, and larger areas of body fat serve as a source of estrogens. In postmenopausal women, cancer incidence is independent of serum estrogen levels, suggesting that higher local tissue estrogen levels may be more important in cancer development.[25]

An alternative consideration is that adipocytokines secreted in the breast fat, leptin, and adiponectin, may

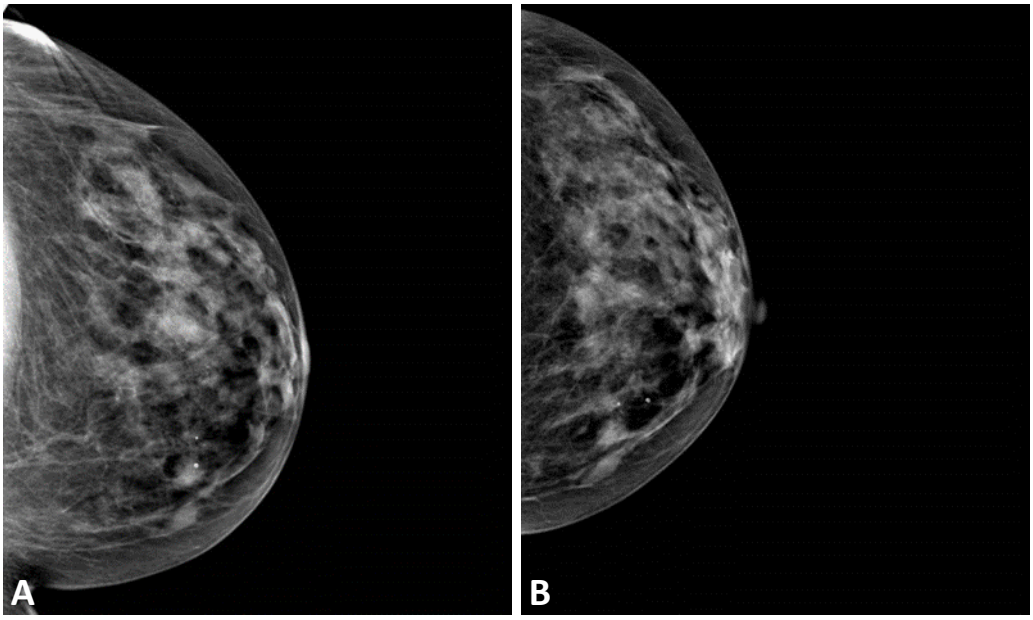

Figure 4.
Effect of Patient Positioning on Breast Density. Two CC views of the same patient, same day (**A and B**), illustrate variations in breast density dependent on positioning.

play a role in cancer risk. Leptin promotes proliferation and enhances cancer cell growth, and adiponectin enhances apoptosis, decreases cell proliferation, and also enables the use of insulin. In obesity, leptin levels are elevated and adiponectin levels are low, possibly explaining the association of higher cancer incidence in this population.[26]

An unanswered question is whether cancers preferentially occur in sites of greater PBD. DCIS has been associated with mammographically dense tissue,[27] but there is little evidence that this is true for invasive cancers. Most invasive cancers occur in the upper outer quadrant of the breast, the location of the greatest concentration of breast parenchyma.[28] Vachon, et al. studied the location of tumors relative to breast density in 372 incident breast cancer cases and 713 matched controls, and determined that increased breast density represented a "general marker of breast cancer risk, not specific to breast side or location of the eventual cancer."[29] Some of the problems with this and other studies of its kind have been the application of rather crude estimations of regional breast density, lack of correlation with volumetric data, as well as other factors that contribute to radiographic breast density such as compression thickness, exposure factors, beam energy, and breast positioning.

Increasing the Accuracy of Quantitative Measurement

Measurements of breast density have historically been achieved either by visual inspection, or the application of a computer-assisted threshold method, in which the operator determines the distinction between dense and non-dense areas as described above. Although there has been considerably high intra-observer and inter-observer concordance reported, visual setting of a threshold is quite subjective. The two dimensional measurements cannot account for the non-uniform thickness of the periphery of the compressed breast, the 3-D non-uniformity of glandular tissue distribution, and the fact that quantification will always be subject to breast positioning (**Fig. 4**). In addition, published reports use a variety of measures including absolute and percent area density. Newer volumetric methods incorporate the Digital Imaging and Communications in Medicine (DICOM) data from the full field digital mammography (FFDM) image to quantify the amount of breast tissue, using both absolute and percent (relative) density by volume. These methods incorporate the effect of beam energy for the different target-filter combinations, half-value layer (HVL), kVp, and mAs, as well as compression thickness and degree of compression,[30] and are highly reproducible for the data set of each image. Few studies are currently

published to validate this volumetric approach. One comparison of threshold and volumetric methods showed no clear advantage in showing correlation with known breast cancer risk factors in a cohort of 370 screening cases,[31] but a larger body of work is emerging.

Reducing Risk Through Modification of Breast Density

Spurring interest in the quantification of breast density is research aimed at the potential to modify a woman's risk of breast cancer by altering (decreasing) breast density. Although changes in breast density have not been proven to confer protection or increase risk, the use of breast density as a biomarker for risk remains valid. If histologic changes could be matched to the imaging changes in breast density, the possibility of altering risk and preventing cancers becomes even more compelling.

Other risk reduction strategies have been evaluated with mixed results. Protective effects of physical activity have been proven, with 30 epidemiologic studies showing a 20 – 40% reduction of cancer risk among pre and postmenopausal patients in various geographic locations, despite variations in the techniques used to evaluate this protection. The risk reduction increases with increasing activity.[32] The results of a study evaluating the association of physical activity on breast density found no statistically significant reduction in the percent or absolute breast density at any level of physical activity.[33] A randomized control trial (ALPHA) looked at the influence of aerobic exercise on breast density and found no correlation with breast density reduction, suggesting that the positive effect of exercise operates through another mechanism.[34] Diets lower in fat, higher in fiber, Mediterranean diets, and lower alcohol consumption are associated with lower PBD and decreased overall cancer rates.[35]

Selective estrogen receptor modulators (SERMS) are approved for the adjuvant treatment of breast cancer. The NSABP P-1 trial evaluated the use of tamoxifen, the first widely used SERM, in the adjuvant treatment of ER + breast cancer. Patients were followed for 15 years after a 2 – 5 year course of therapy and showed a 50% reduction in the recurrence and contralateral occurrence of breast cancer that persists for 7 – 12 years.[36] Limiting the widespread use of tamoxifen are undesired side effects of deep venous thrombosis (DVT), stroke, pulmonary embolus, and endometrial cancer. The subsequent NSABP P-2 (STAR) trial proved raloxifene, an effective SERM therapy with far less risk of endometrial cancer and thromboembolic events,

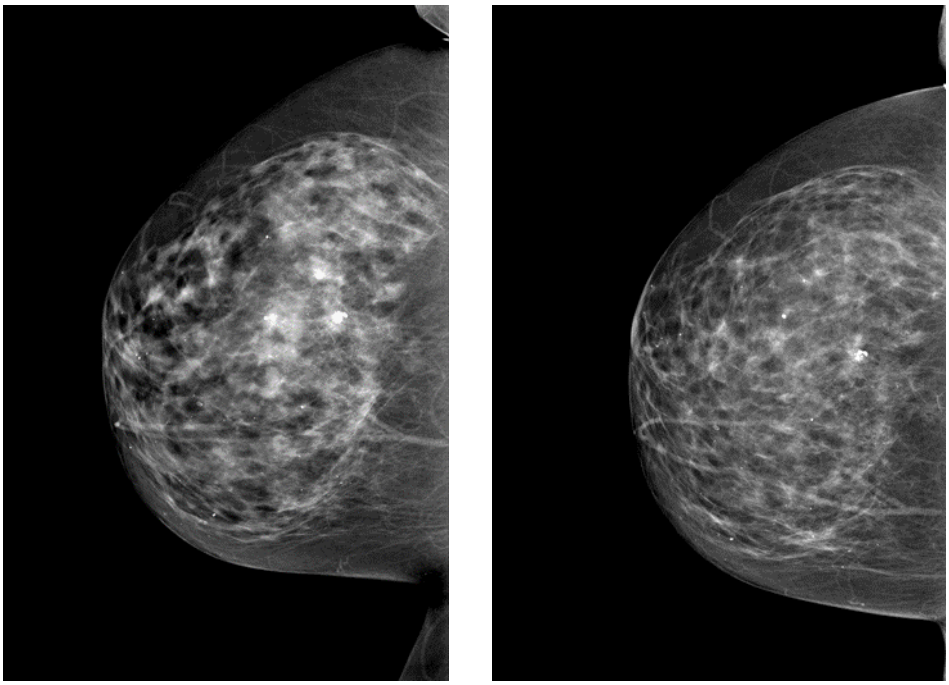

Figure 5.
Selective Estrogen Receptor Modulators' Effect on Breast Density. CC views of the same patient before tamoxifen therapy (**A**) and one year after therapy (**B**) with some reduction in PBD.

provided 78% of the risk reduction of tamoxifen, which equates to a 38% reduction in breast cancer.[37] Tamoxifen has been shown to have a statistically significant decrease in breast density in both premenopausal and postmenopausal women, irrespective of age. Raloxifene has been shown to have a lesser effect on breast density (**Fig. 5**).[37,38]

Eilertsen, et al. employed a fully automated, volumetric breast density assessment method to evaluate changes in breast density following HRT (increased density) and raloxifene therapy (decreased breast density). This confirmed the results of prior studies and offered insights into the potential of this tool to eliminate the subjective nature of human measurements.[38] Volumetric methods have shown high correlation with MRI volumetric quantification of breast density.[39] Positive relationships between dense tissue volumes and breast cancer risk have been proven with 3-D methodology.[40] The mathematical 3-D methods which incorporate bio-physical principles in a reproducible and automated manner should be embraced as a superior method of assessing breast density.

If increased PBD conveys a higher risk for breast cancer, can intervention to diminish breast density be protective? This, in part, depends on defining what contributes to breast density. Ductal and acinar epithelium is the site of breast cancer development, but abundant research suggests that density is not solely related to the presence of greater volumes of epithelium.

Aromatase is an enzyme responsible for converting androgens to estrogens on a local level. Through the study of core biopsy tissue, it has been shown that the stromal cells have higher levels of aromatase immunoreactivity than the epithelial cells in areas of dense breast tissue.[25] As a result, there is enhanced estrogen synthesis and a greater lifetime exposure to locally produced estrogen in the breast, independent of serum estrogen levels.

The contribution of collagen to breast density was studied from random sections of subcutaneous mastectomy specimens at autopsy. Li, et al. measured the radiographic breast density of the tissue samples and correlated this with stained nuclear area of epithelial and non-epithelial cells, collagen, and glandular area. Collagen was responsible for 29% of the density, 4% of the nuclear density, and 7% of the glandular area. Interestingly, the percentage of collagen was decreased with increasing parity and number of live births, commonly cited factors that decrease breast cancer risk.[41]

Microdissection techniques have contributed to the biochemical and genetic understanding of the mechanisms of tumorigenic conversion of epithelial cells. There is a strong body of evidence that the extracellular milieu of the fibroglandular tissue is as important as the epithelium in carcinogenesis. Following microdissection of epithelium from the surrounding tissues, transcriptional profiling can differentiate the effects related to these epithelial cells verses the stroma, consisting of fibroblasts, myoepithelial cells and extracellular matrix. Carcinoma-associated fibroblasts (CAF) are shown to promote tumorigenic conversion of initiated epithelial cells when added to epithelial cell cultures. Fibroblasts and myoepithelial cells from normal tissue are shown to suppress this transition. The transformation of these stromal cells is key in the transition of normal epithelial cells to invasive disease.[42,43] Stroma and the extracellular milieu are integral to cancer development.

Other biochemical interactions related to breast density involve insulin like growth factor -1 (IGF-1) and the IGF-binding protein 3 (IGFBP-3). IGF-1 influences breast development and higher levels are found in women with dense breast tissue. Interestingly, breast density and IGF-1 decrease with age. Tamoxifen also decreases IGF-1 levels.[44]

IGFBP-3 is responsible for involution of breast tissue, increasing with both age and post-lactation, and promoting apoptosis and decreased breast density.[45] High levels of IGFBP-3 are also associated with lower mammographic density in premenopausal women.[44]

Summary

PBD is a surrogate for breast cancer risk. As an independent marker, it can also be influenced by interventions such as hormone therapy, diet, physical activity, and SERMs. In addition, high breast density decreases the conspicuity of breast lesions, and delay in the diagnosis of breast cancer remains in the top five errors in radiology malpractice claims.

Increased density is present in 30% of postmenopausal women, occurring with greater frequency than other well recognized risk factors. Cyclical hormone changes influence breast density, but effect is conveyed long-term effect is uncertain. The potential to prevent more cancers through intervention is an attractive subject of much research.

Beyond the action of state legislatures, current trends suggest that the FDA may include this metric for MQSA certification. Commercialization of volumetric technology that provides an objective quantification of breast density is available and its use is becoming wide spread. Incorporation of this information in the breast cancer risk assessment should be studied and its value to population health management determined. New data derived from technological advances in bioscience and volumetric measurement should further elucidate the important relationship between PBD and cancer. As a result, cost effective strategies for the stratification of risk and the informed application of supplemental breast cancer screening for women in any given population may be possible.

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Metastatic Invasive Breast Carcinoma

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Case Presentation:

A 58-year-old woman presented for routine screening mammography. The patient had no personal history of cancer. Family history was significant for a paternal cousin with breast cancer at age 58 and a maternal second cousin with breast cancer at age 50. At presentation the patient was noted to have right nipple inversion. The patient subsequently underwent a diagnostic mammogram and ultrasound. Based upon the diagnostic work-up, the patient underwent additional imaging, including breast MRI and a PET-CT exam. PET-CT findings prompted a transvaginal ultrasound. Representative images from the diagnostic mammogram, breast MRI, PET CT, and transvaginal ultrasound are provided (**Figs. A-D**).

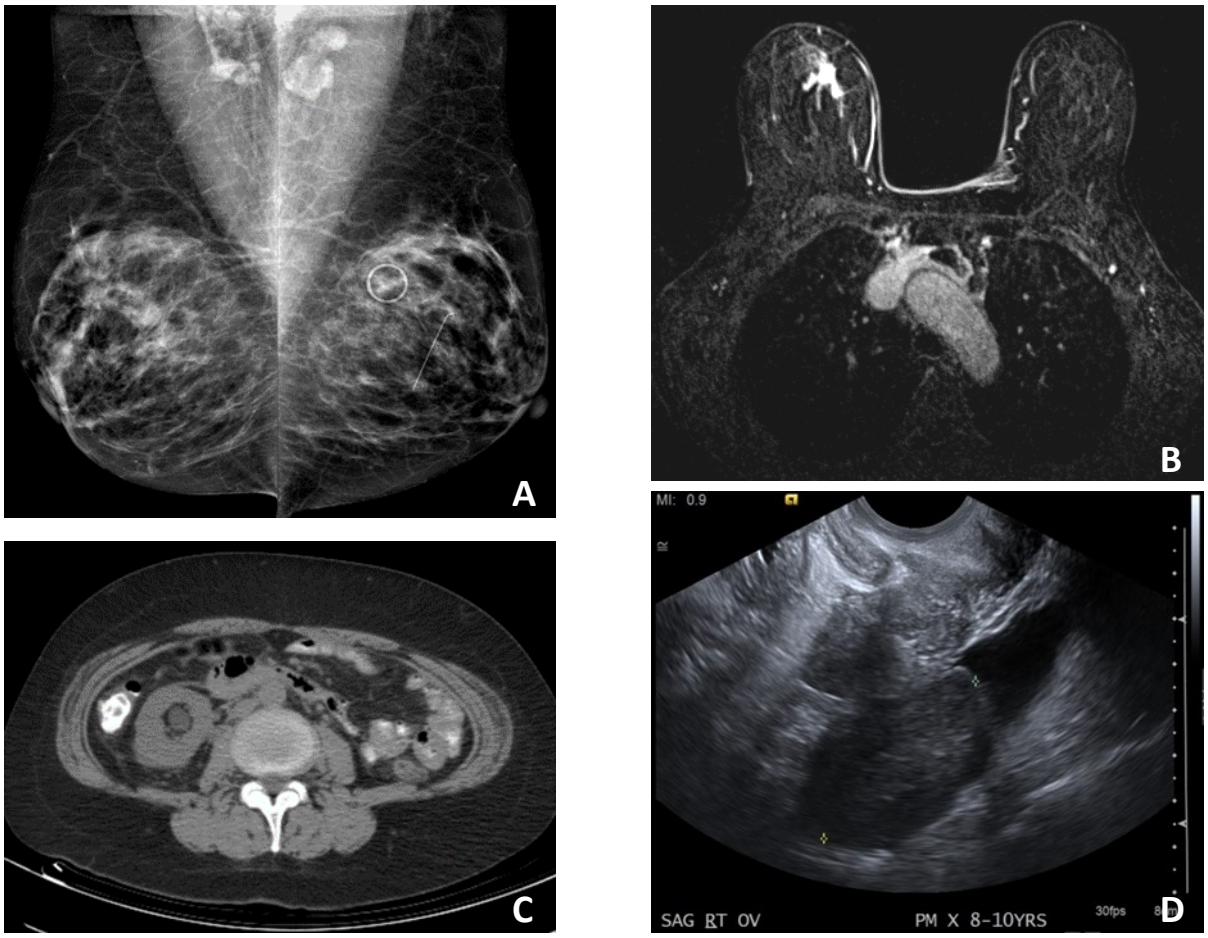

Figure. Bilateral MLO views (**A**) demonstrate an area of architectural distortion in the right breast at 12 o'clock with associated nipple retraction and a morphologically abnormal right axillary lymph node. Subsequent targeted ultrasound demonstrated an irregular antiparallel mass with spiculated margins (images not shown). Axial T1 post-contrast subtracted breast MRI image (**B**) reveals an irregular-shaped enhancing mass, corresponding to the mass seen on mammography and US. Also seen is stranding in the anterior mediastinal soft tissues as well. Unfused axial CT image from the patient's staging PET-CT exam (**C**) demonstrates unilateral right hydronephrosis and subtle right retroperitoneal fat stranding. Enlarged FDG avid ovaries were noted on the PET CT spurring evaluation with transvaginal ultrasound. A representative image from the transvaginal ultrasound is provided (**D**), demonstrating a rind of hypoechoic soft tissue encasing the ovaries.

Key Clinical finding

Nipple retraction

Key imaging findings

Nipple retraction

Architectural distortion with underlying spiculated mass

Morphologically abnormal right axillary lymph node

Secondary imaging findings

Unilateral hydronephrosis and retroperitoneal fat stranding

Soft tissue encasing the enlarged ovaries

Differential diagnoses

Metastatic IDC not otherwise specified

Metastatic Invasive Lobular Carcinoma

Discussion

Breast cancer remains the most commonly diagnosed malignancy in women and accounts for 14% of cancer deaths.[1] An estimated 226,870 new cases were diagnosed in 2012.[1] The majority of newly diagnosed invasive cancers are invasive ductal adenocarcinoma (IDC). Invasive lobular carcinoma (ILC) accounts for approximately 10-15% of invasive breast cancers and represents the second most common histologic subtype of breast cancer.[2,3] Twenty percent of invasive lobular carcinomas are bilateral.[3]

Invasive lobular carcinoma is often clinically and mammographically elusive. ILC often fails to present as a palpable abnormality and rarely presents as a discrete mass mammographically.[3] Clinically the neoplasm is rubbery and poorly-defined on physical exam, in contrast to the hard, well-defined masses commonly found with invasive ductal carcinomas.

On mammography, architectural distortion or focal asymmetry is most often seen with ILC.[4] ILC has a tendency to spread diffusely or between the collagen fibers of the breast in a classic single file-pattern and produces little desmoplastic response.[3,4] The cells generally lack cohesion which may be related to the loss of e-cadherin histologically.[5] As tumor burden increases, the breast may decrease in size mammographically (the "shrinking" breast sign) presumably due to decreased compressibility.[4] On sonography, ILC presents as an area of architectural distortion with acoustic shadowing more often than as a discrete mass.[4,5]

Approximately 20% of invasive lobular carcinomas are bilateral at presentation and are often multicentric.[3] The propensity for nodal metastases is similar between invasive lobular carcinoma and IDC, though nodal metastasis may be more difficult to diagnose in ILC.[6] The presence of morphologically abnormal axillary lymph nodes on mammography is suspicious for malignancy in a patient with invasive lobular carcinoma and should trigger further evaluation with ultrasound.

ILC has an unusual metastatic pattern compared with invasive ductal carcinoma. The metastatic rate of ILC to the liver and bone is comparable to that of IDC.[7] However, ILC is more likely to metastasize to the peritoneum, retroperitoneum, gynecologic organs, gastrointestinal tract, urogenital tract, adrenal glands, bone marrow, leptomeninges, orbit, and myocardium.[3,4,7,8]

The clinical presentation of GI metastasis due to ILC is typically vague. The clinical, radiological, endoscopic and histopathologic findings of metastatic ILC are often difficult to distinguish from primary gastric carcinoma. Patients are more likely to present to a gastroenterologist than a breast surgeon. Therefore, a high index of clinical suspicion with early endoscopy or colonoscopy in those with non-specific symptoms and a past history of breast cancer, particularly ILC, is recommended. It is imperative to differentiate between metastatic breast cancer and primary gastric carcinoma as treatment strategies differ significantly.[9] Also, at times the interval between the primary cancer and the metastatic relapse may be long; therefore, the key to the correct diagnosis and treatment requires recognition of the patient's history of breast cancer.[6]

Hydronephrosis is a commonly reported complication of metastatic ILC.[8] Patients with ILC not infrequently develop hydronephrosis due to metastasis to the retroperitoneum causing ureteral

obstruction.[10] Finally, ovarian metastases are visualized as a rind of soft tissue encasing the ovaries.

The presence of a unilateral hydronephrosis, retroperitoneal fat stranding, and a pelvic or ovarian mass in a patient with diagnosis of invasive lobular carcinoma, as seen in the above case, should trigger further evaluation to rule out metastatic disease.[4]

Diagnosis

Metastatic invasive lobular carcinoma

Summary

Although much less common than invasive ductal carcinoma, it is vitally important for radiologists to understand the common imaging presentation and metastatic patterns of invasive lobular carcinoma. The most common mammographic findings include regions of architectural distortion or focal asymmetry; occasionally, the "shrinking" breast sign may be seen. Compared to IDC, ILC is more likely to be multicentric or bilateral and has a similar propensity for region lymph node spread. The metastatic pattern is a distinguishing feature with ILC more likely to metastasize to the gastrointestinal system, gynecologic organs, and peritoneum-retroperitoneum. A basic understanding of these differences will help suggest the appropriate diagnosis and guide management decisions.

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Radiopaque Densities Within Axillary Lymph Nodes

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Case Presentation:

A 42-year-old premenopausal woman presented for a baseline screening mammogram. She had no significant past medical history. Her social history revealed prior intravenous drug abuse, multiple sexual partners, treated sexually transmitted diseases, and multiple right upper extremity decorative tattoos obtained approximately 6 years prior to her presentation for screening mammography. She denied weight loss, foreign travel, fever, or night sweats. She denied inflammatory or skin diseases. She had no palpable axillary adenopathy on physical exam.

Her screening mammogram demonstrated radiopaque densities in the right axillary lymph node region, only seen on the MLO view (**Fig. A**). No other suspicious calcifications, masses or areas of architectural distortion were identified in either breast. The left axilla was unremarkable. Subsequent spot compression views of the bilateral axillae demonstrated the morphology of the intranodal radiodensities in the cortex of a single right axillary lymph node (**Fig. B**). The remaining lymph nodes were normal in appearance. Ultrasound evaluation of the right axilla revealed a normal sized lymph node with normal morphology, preservation of the fatty hilum, and thin symmetric cortex (**Fig. C**). Subtle echogenic densities were seen within the cortex of this lymph node. Ultrasound-guided core needle biopsy was performed to exclude occult metastatic malignancy. A specimen radiograph (**Fig. D**) was immediately obtained to confirm the retrieval of the densities.

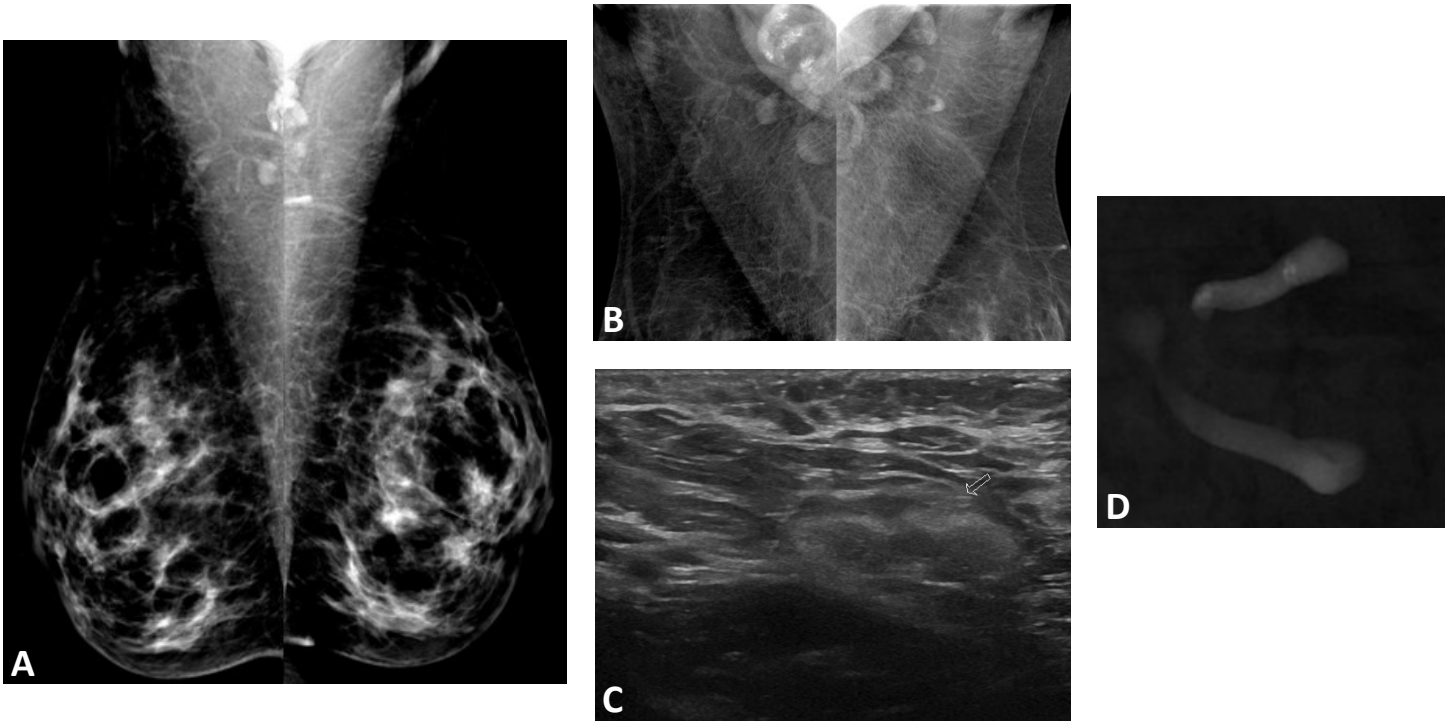

Figure. Bilateral MLO views from screening mammogram (**A**) demonstrate partially visualized indeterminate densities in a right axillary lymph node. Spot compression views of the axillae (**B**) demonstrate the unilateral intranodal cortical densities within the right axilla. Ultrasound of the right axilla (**C**) reveals a morphologically normal lymph node with subtle hyperechoic foci seen within the cortex (arrow). Specimen radiograph following vacuum-assisted, US-guided core needle biopsy (**D**) demonstrates successful sampling of the intranodal radiopaque densities.

Key imaging findings

Radiopaque densities within axillary lymph node on baseline mammogram

Differential diagnoses

Occult metastatic breast carcinoma

Extramammary metastasis (e.g. ovarian or thyroid malignancy)

Granulomatous diseases (e.g. histoplasmosis, tuberculosis, or sarcoid)

Gold salt deposits

Foreign bodies (i.e. tattoo pigment, talcum)

Clumped deodorant in skin crevices

Discussion

The initial detection of intranodal axillary densities on a screening mammogram warrants further work up to exclude occult metastatic disease from mammary or extramammary malignancy, especially in the absence of a benign etiology.

Intranodal coarse, dense calcifications are usually benign and are most often associated with granulomatous disease or fat necrosis. However, intranodal microcalcifications have been reported in a number of additional disease processes, both malignant and benign.

Metastatic primary breast cancer is the most common malignancy associated with axillary lymph node calcifications. Amorphous, peripherally located calcifications have also been reported in metastatic ovarian papillary carcinoma secondary to the production of psammoma bodies.[1-3] Treatment-related punctate calcific densities have been reported in patients with long standing history of gold intramuscular injections for the treatment of rheumatoid arthritis.[4] Talcum accumulation in lymph nodes, which may resemble coarse heterogeneous calcifications, has been documented in intravenous and inhalation drug abusers.[5]

Imaging features suggestive of metastatic disease within lymph nodes include loss of fatty hilum, loss of the reniform or oval shape, ill-defined margins, increase in size, or increase in density when compared to prior mammograms.[6] In addition to the imaging characteristics, physical examination and clinical history may help guide appropriate work-up and management.

Tattoos are applied by repetitive needle puncture accompanied by the intradermal injection of metallic pigment. This initiates an inflammatory response and leads to the phagocytosis of some of the metallic fragments, which subsequently slowly migrate to lymph nodes via lymphatic channels.[7] Various metals including titanium, aluminum and iron are used in mixing the over 30 pigments commercially available.[8] These fragments create a set of heterogeneous densities which mimic calcifications and introduce a rarely encountered dilemma to a radiologist who may not be aware of this imaging finding. Unfortunately, it is impossible to differentiate tattoo pigment associated radiodensities from other worrisome sources given the varying appearance produced by the types of pigments and their metallic contents. A case report published in 2004 by Honeggar et al. demonstrated coarse heterogeneous calcifications almost entirely replacing the nodal parenchyma, while in this case the densities were confined to the nodal cortex and appeared amorphous and dystrophic.[9]

Pathologists and dermatologists encounter a similar dilemma in evaluating patients with a history of melanoma as these tattoo pigments mimic metastatic melanoma on histology slides and gross specimens.[10] Close and thorough histopathological examination of slides is crucial in excluding metastatic melanoma, as the coexistence of metastatic melanoma and tattoo pigment has been reported.[10]

Diagnosis

Tattoo pigment in a benign lymph node

Summary

When intranodal calcific appearing densities are encountered on mammography, the radiologist should be aware of the differential diagnoses associated with such findings, including occult breast or extramammary malignancy. Closely examining the morphology and the distribution of the radiodensities may help in delineating benign from pathologic etiologies. Obtaining a past medical history and examining the patient for upper extremity, breast or shoulder tattoos will aid in narrowing the differential diagnoses; however, biopsy is often necessary to exclude malignancy given the overlap in mammographic and ultrasonographic appearance of normal and pathologic lymph nodes as well as the non-specific presentation of the tattoo pigment radiodensities.

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JAOCR at the Viewbox

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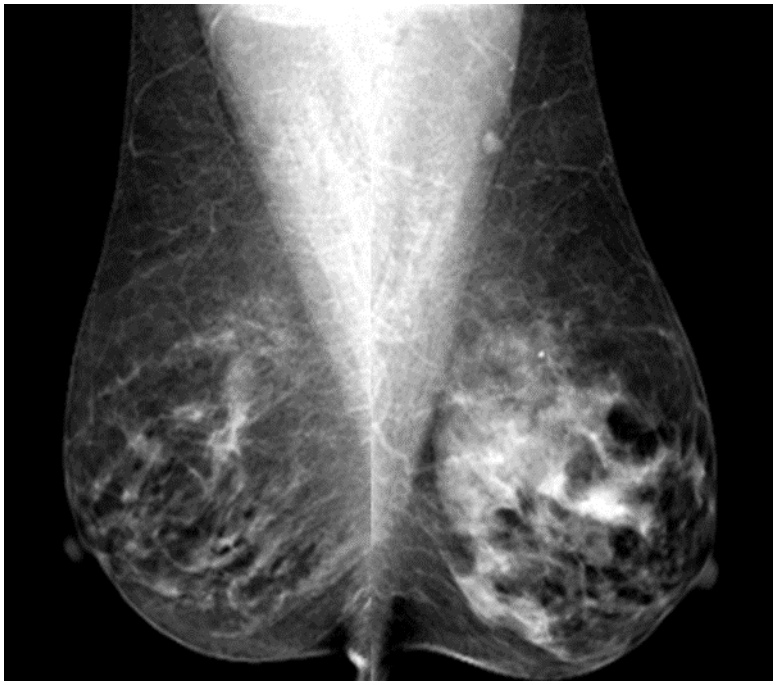

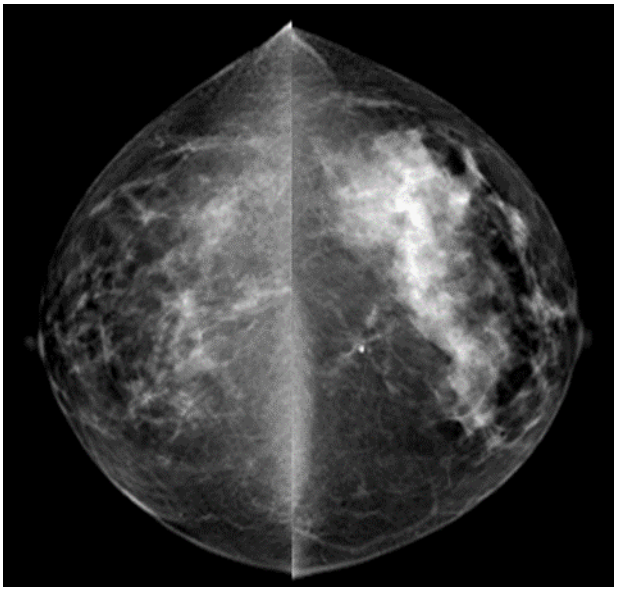

Global Asymmetry.

Breast asymmetry can prove clinically challenging. Terminology for asymmetric findings in the breast has been controversial and has undergone alteration as recent as 2003, with the fourth edition update of ACR BIRADS lexicon, changing “asymmetric breast tissue” to “global asymmetry.” Global asymmetry is increased fibro-glandular tissue in at least one breast quadrant. This appearance can cause concern and result in unnecessary biopsy or workup.

The bilateral MLO and CC views demonstrate global asymmetry in the left breast. Appropriate to the definition, this patient did not have a focal mass, architectural distortion, associated calcifications, or palpable abnormality. This setting reinforces benignity and is found in up to 3% of women. Global asymmetry is usually a normal variant. Other etiologies include hormonal influences, breast reduction surgery, pseudo-angiomatous stromal hyperplasia (PASH), and surgical excision of developing breast tissue in prepubescent girls.

It is necessary to resolve focal asymmetries with additional mammographic imaging and occasionally ultrasound. Masses will show convex margins on diagnostic imaging, while global asymmetry needs no further work-up if there is documented stability or lack of concerning features, as in the patient above.

JAOCR at the Viewbox

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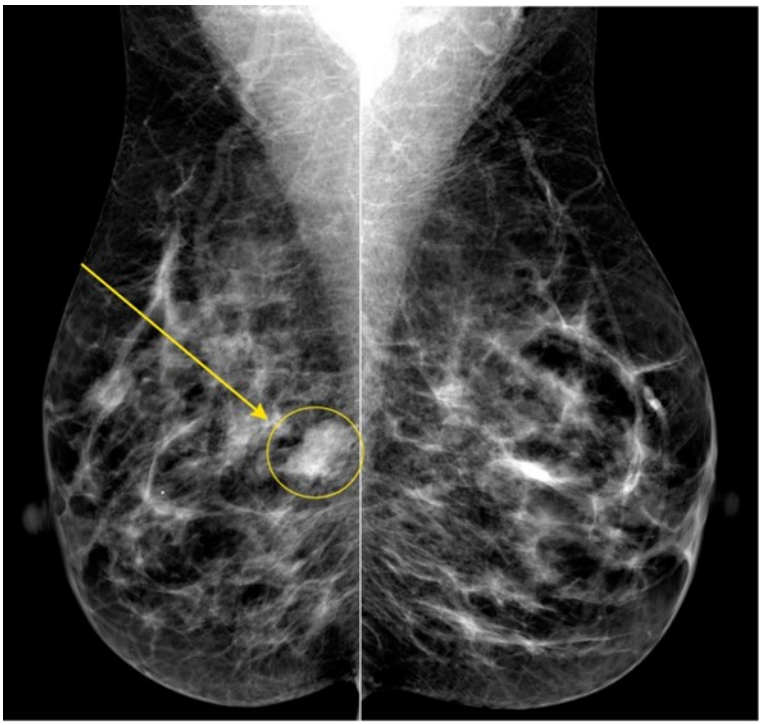

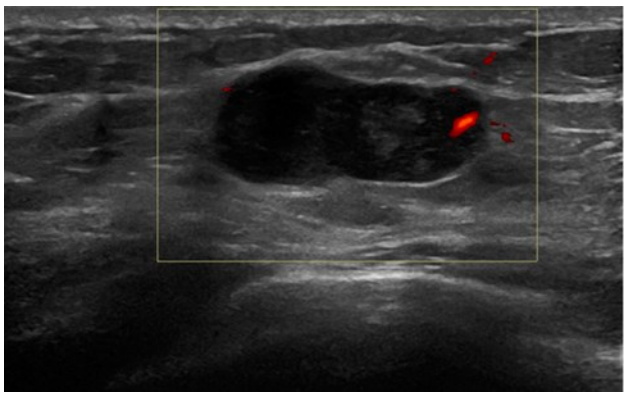

Metaplastic Breast Carcinoma.

The arrow on the mammogram points to a new screening detected lobular mass. The corresponding ultrasound image demonstrates a solid, lobular, hypervascular, hypoechoic lobular mass with circumscribed margins, parallel orientation, and posterior acoustic enhancement. Given the imaging appearance, differential considerations for this mass include infiltrating ductal carcinoma, fibroadenoma, and metaplastic breast carcinoma.

Metaplastic breast carcinoma is a rare malignancy, accounting for fewer than 5 % of breast carcinomas. It is characterized by coexisting ductal carcinoma with areas of matrix producing, spindle-cell, sarcomatous, or squamous differentiation. Metaplastic carcinoma in general displays more benign imaging features compared to invasive ductal carcinoma. On mammography, metaplastic carcinoma presents as a round or oval mass with circumscribed margins. On ultrasound, metaplastic carcinoma often demonstrates benign features such as an oval, round, or lobular shape with circumscribed margins, but interestingly demonstrates posterior acoustic enhancement. Core needle biopsy is recommended for any mammographic mass that does not fit all benign criteria by mammography or sonography.

The differentiation between invasive ductal carcinoma and metaplastic carcinoma is important for both treatment planning and prognosis. Metaplastic tumors tend to be large at presentation, hormone receptor and HER2/neu-negative, and have a low incidence of regional lymph node involvement. Traditional chemotherapy and hormonal therapies for invasive ductal carcinoma are ineffective against metaplastic carcinoma, and it is often associated with a poorer survival rate.

JAOCR at the Viewbox

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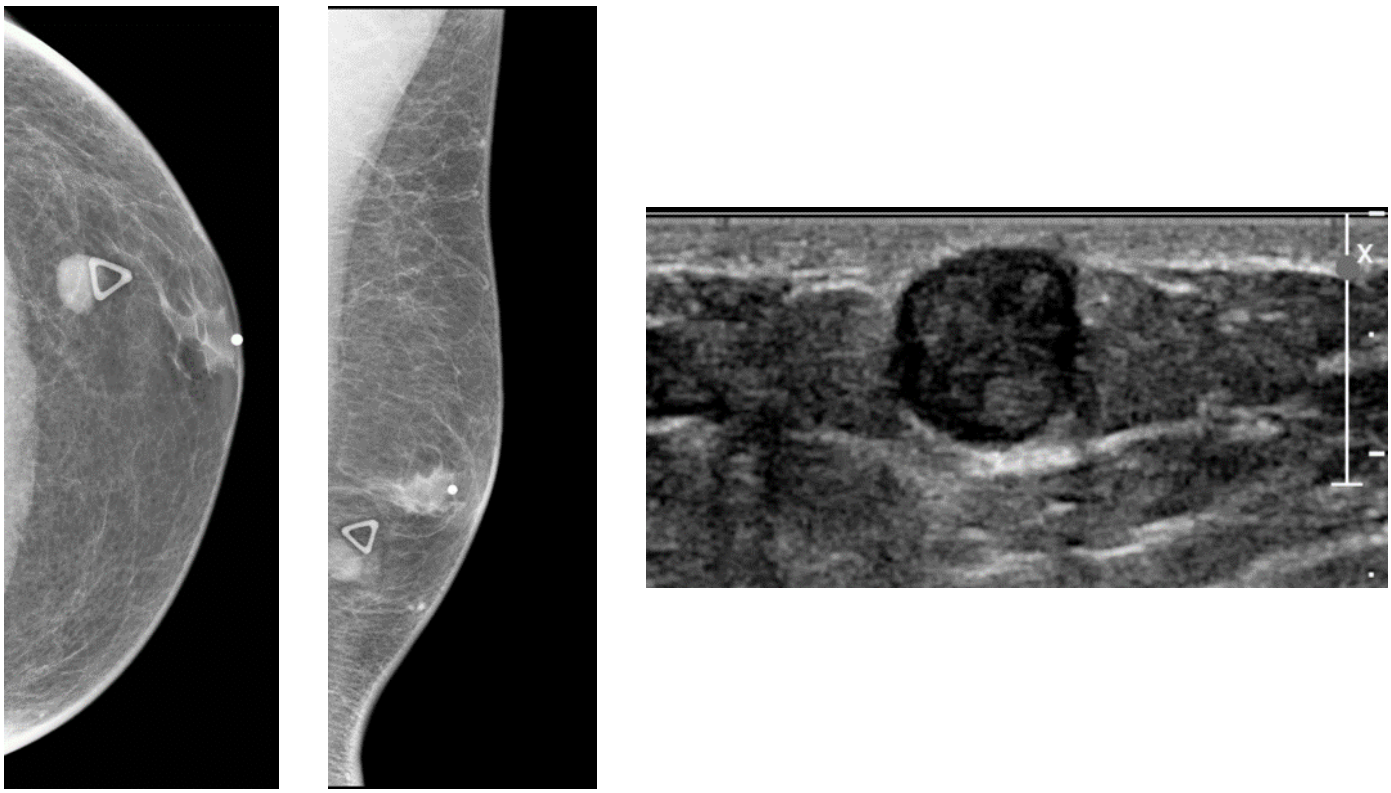

Unusual Breast Mass—Schwanomma.

A 24-year-old man presented with a 5-year history of a palpable left breast mass which was now painful and increasing in size. Physical exam revealed a firm, round mass 2cm from the nipple. Mammogram shows a corresponding circumscribed, oval, high density mass, which is heterogeneously hypoechoic, antiparallel, and in contact with the overlying dermis. There was a small amount of internal vascularity on color Doppler (not shown). No skin tract was identified.

Men present with various breast masses, most commonly gynecomastia – a benign condition characterized by tender subareolar tissue which is fan or flame-shaped on mammogram and directly behind the nipple. While this patient does have a mild degree of gynecomastia, the abnormality in question (denoted by palpable marker) does not fit those characteristics. Another consideration for this mass which abuts the skin is an epidermal inclusion cyst (EIC). EICs may show vascularity on Doppler if inflamed, though absence of a clear sinus tract to the skin surface makes this diagnosis unlikely. Since there are clinical and imaging features concerning for malignancy (firm, remote from areola, increasing size, antiparallel), this lesion was classified as a BI-RADS 4 -- suspicious abnormality, and biopsy was recommended.

The result from ultrasound-guided core tissue sampling was a schwannoma. This benign peripheral nerve sheath tumor typically occurs in the head and neck, spine, and extremities. It is rare to encounter a schwannoma in the breast, particularly in a man. Given that the mass was symptomatic/painful, the patient was referred for surgical excision.

The views expressed in this material are those of the author, and do not reflect the official policy or position of the U.S. Government, the Department of Defense, or the Department of the Air Force.