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The unusual suspects—mammographic, sonographic, and histopathologic appearance of atypical breast masses

Muhammad Naeem, M.D.¹, Maria Zulfiqar, M.D.¹, David H. Ballard, M.D.¹, Laura Billadello, M.D.², Guihua Cao, M.D.³, Andrea Winter, M.D.², Mary Lowdermilk, M.D.²

¹Mallinckrodt Institute of Radiology, Washington University School of Medicine

²Department of Radiology, St Louis University School of Medicine

³Department of Pathology, SSM Health St Mary's Hospital

Abstract

Breast malignancy is the second most common cause of cancer death in women. However, less common breast masses can mimic carcinoma and can pose diagnostic challenges. This case-based review describes a spectrum of rare breast neoplastic and non-neoplastic masses ranging from malignant to benign entities. Malignant masses in this review include adenoid cystic carcinoma, spindle cell lipoma, granular cell tumor, angiosarcoma, glomus tumor, adenosquamous carcinoma, and myofibroblastoma. Benign masses include sarcoidosis, diabetic mastopathy, and cat scratch disease. Demographics and, when relevant, clinical presentation are summarized. Breast imaging appearance on mammography and ultrasound are highlighted along with radiology-pathology correlation with the appearance and characteristics of the histopathological specimen of these rare masses.

Correspondence to: David H. Ballard, MD, Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510 S. Kingshighway Blvd, Campus Box 8131, St. Louis, Missouri, 63110, davidballard@wustl.edu, Phone: (314) 362-2829; Fax: (314) 747-4671.

Muhammad Naeem, M.D.¹, Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510. S Kingshighway St Louis MO 63110

Maria Zulfiqar M.D.¹, Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510. S Kingshighway St Louis MO 63110

David H. Ballard, M.D.¹ (Corresponding Author), Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510. S Kingshighway St Louis MO 63110

Laura Billadello M.D.², Department of Radiology, St Louis University School of Medicine, 3635 Vista Avenue, St Louis MO, 63110

Guihua Cao M.D.³, Department of Pathology, SSM Health St. Mary's Hospital, 6420 Clayton Road St Louis, MO 63117

Andrea Winter, M.D.², Department of Radiology, St Louis University School of Medicine, 3635 Vista Avenue, St Louis MO, 63110

Mary Lowdermilk M.D.², Department of Radiology, St Louis University School of Medicine, 3635 Vista Avenue, St Louis MO, 63110

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Keywords

Breast imaging; Mammography; Breast ultrasound; Granular cell tumor; Sarcoidosis; Cat-scratch disease

1. INTRODUCTION:

Mammography is the gold standard imaging modality for early breast cancer detection with sensitivity ranging between 72–93% [1–4]. Most breast masses seen on mammography are benign [5], which stems from data of consecutive biopsy series showing a majority of benign surgical pathology results [6–8]. The most common form of breast cancer is invasive ductal carcinoma (70–80%) followed by invasive lobular carcinoma (~10%) [9]. Radiologists should be familiar with benign and malignant etiologies of breast masses. Understanding the imaging appearance of rare masses as well as their histopathological features is important to direct appropriate management. These masses may be neoplastic, including adenoid cystic carcinoma, spindle cell lipoma, myofibroblastoma, and others. Non-neoplastic systemic disorders, such as sarcoidosis, diabetes and infection, may also appear as breast masses mimicking malignancy on imaging and necessitating biopsy.

In this case-based review, we will illustrate the mammographic, sonographic, and histopathological features of rare, yet significant breast pathologies and demonstrate the importance of a pertinent history and directed physical exam in formulating a differential diagnosis.

2. RARE NEOPLASTIC BREAST MASSES:

2.1 Adenoid cystic carcinoma:

This tumor accounts for 0.5–0.8% of all breast cancers and affects women more often than men [10]. Of all anatomic sites this tumor may affect, the breast is the third most common site (13%) after the major and minor salivary glands [11]. Patients typically present with a palpable mass commonly in the subareolar location, which may be painful [12].

Adenoid cystic carcinoma typically manifests as a high density, spiculated mass or focal asymmetry on mammogram (Fig. 1). On ultrasound, it is often characterized as a hypoechoic, irregular mass with minimal vascularity on color Doppler [13]. On histopathology, it appears very similar to adenoid cystic carcinoma of the salivary glands. Specifically, the pathologist will see a biphenotypic population of basal cells that are arranged in one of a combination of three architectural patterns: cribriform; solid-basaloid; or tubular-trabecular. Areas of cystic degeneration and mucin can also be present [14].

Given the rarity of this cancer, treatment guidelines have yet to be well established and current treatment is focused around surgical resection [15–17]. Although reported experiences are limited, data suggests that surgical resection alone is often sufficient, likely without the need for axially lymph node dissection or radiation therapy [16, 17]. The prognosis of adenoid cystic carcinoma is more favorable than a similar-sized invasive ductal carcinoma [16, 17]. It is usually ER/PR/HER2 negative. Metastases are rare. However, if

metastatic disease is present, it tends to first metastasize to the lungs before the ipsilateral axillary lymph nodes [18, 19].

2.2 Spindle cell lipoma:

This is a rare variant of lipoma with a predominantly adipocytic component, also known as '*benign stromal spindle cell tumor*'. It commonly occurs in the subcutaneous tissues of the upper back and posterior neck and rarely occurs in the breast [20]. These comprise approximately 1.5% of all fat-containing neoplasms and have an equal tendency to affect men and women [21]. Common presentation is a palpable mass which is painless and mobile.

Mammographically, it commonly appears as a well-circumscribed high density mass without calcification (Fig 2.). On ultrasound, the mass has a homogenous hypo to hyperechoic appearance with minimal posterior shadowing [22]. Histologically, spindle cell breast lipomas are composed of bland spindle cells intermingled with mature adipocytes, and collagen bundles (Fig. 2) [23]. Local excision is curative and prognosis is excellent from limited data [24]. Data for breast spindle cell neoplasms is more robust [25, 26] and large cohorts with follow-up for local recurrence for spindle cell lipoma has not been reported to the best of our literature search.

2.3 Granular cell tumor:

Previously called breast granular cell myoblastoma, granular cell tumor is an uncommon neoplasm of the peripheral nervous system originating from the Schwann cells. Although preponderant in the head and neck, these tumors can also occur in the breast in about 6% of cases [27]. Clinically, patients present with a hard, painless mass and may notice associated skin retraction and nipple inversion, simulating breast cancer [28].

Imaging features are variable. On mammogram, the mass can be round or oval with circumscribed or spiculated margins [29] (Fig. 3). The sonographic appearance also varies; a granular cell tumor often presents as a hypoechoic mass with circumscribed or irregular margins, with or without posterior acoustic shadowing. A peripheral echogenic halo may be seen [30, 31].

Wide local excision is usually recommended. Although only 1% of cases are malignant, local recurrence has been reported after incomplete excision [27, 28]. Microscopically, these tumors are comprised of closely packed nests of cells containing numerous fine eosinophilic granules in ample cytoplasm [31, 32].

2.4 Angiosarcoma:

A malignancy of endovascular origin, angiosarcoma accounts for approximately 1% of all soft tissue breast tumors [33]. The primary form of angiosarcoma has no identifiable precursor and usually occurs in a younger demographic between 30 and 50 years of age. The secondary form occurs in relatively older women between 65 and 70 years of age following a latency period of 5 to 10 years after radiation treatment for breast cancer and portends a poor prognosis [34, 35].

Clinically, primary angiosarcoma presents as a rapidly growing palpable mass. Large masses have a tendency for platelet sequestration [36]. Secondary angiosarcoma is commonly multifocal and can appear misleadingly innocuous as patients may present with painless bruising of the skin or an eczematous rash. It can also present as a palpable mass or diffuse unilateral breast swelling [35].

Mammogram may be normal or may show only skin thickening. Masses, when present, may be ill-defined or circumscribed (Fig. 4). On ultrasound, angiosarcoma is usually very hypervascular with a heterogeneous appearance secondary to intratumoral hemorrhage [37]. Microscopically, irregular vascular configurations are seen with spindle shaped cells and pleomorphic nuclei with high mitotic activity. Immunohistological staining for CD31 endothelial marker is considered highly specific and sensitive for angiogenic proliferation. Other vascular markers such as factor VIII will also stain positive [33, 38]. Local surgical excision or mastectomy with neoadjuvant chemotherapy and/or radiation are usually employed for management. Overall, the tumor has a poor prognosis with high recurrence rate [33].

2.5 Glomus tumor:

These are uncommon mesenchymal tumors arising from glomus bodies, which are specialized neurovascular organs. Glomus tumors are highly vascular neoplasms and are mostly benign, but can be malignant in rare circumstances. The most common site of a glomus tumor is subungual in the fingers [39]. The occurrence of glomus tumors of the breast is extremely low and only a few case reports have been reported [39–43].

Clinically, glomus tumor typically presents as a blue-red nodule, which may or may not be palpable. An associated triad of excruciating pain, pinpoint tenderness, and focal sensitivity to cold is pathognomonic [43]. Due to exquisite pain with compression, mammography may not be tolerated. However, if a mammogram is successfully performed, it usually shows a round to oval superficial mass with circumscribed or indistinct margins without any microcalcifications (Fig. 5). Sonographically, glomus tumors are generally hypoechoic and extremely vascular in appearance with turbulent flow. An associated efferent vessel is often described [39]. There are two chief components on histopathology: Aggregates of small round specialized glomus cells and branching vascular channels. Treatment is surgical excision. Incomplete excision can lead to recurrence in 1–2% of cases [43].

2.6 Adenosquamous carcinoma of the breast:

A rare form of invasive mammary cancer, adenosquamous carcinoma accounts for approximately 0.3% of all breast cancers. The majority are low grade and do not typically present with metastasis, which is most frequent to axillary lymph nodes. Distant metastasis is rare, with only 1 of 32 patients in one series reporting with distant metastasis to the lung. Local recurrence is rare in modern series, in one of the largest reported series, Van Hoesen et al. [44] 1993 study had 5 recurrences in 25 women [44]. More modern cohorts with smaller series report no local recurrences [45–46].

Adenosquamous carcinoma typically presents as a palpable, often immobile mass that has indistinct margins on mammogram (Fig. 6). Associated microcalcifications are common,

typically in benign patterns [46]. On sonogram, it typically appears as a hypoechoic, irregular mass with posterior acoustic shadowing. The tumor is histologically characterized by the presence of distinct glandular and squamous elements. Almost all adenosquamous tumors are negative for ER/PR receptors [47]. As this phenotype is exceedingly rare in the breast, a metastatic workup for a non-breast primary should be performed. Treatment includes local excision. The role of sentinel lymph node dissection or axillary dissection as well as adjuvant radiation and chemotherapy is yet to be clearly defined and standardized [44–46]; some authors have proposed that the low rate of axillary lymph node metastases may warrant omitting either sentinel lymph node biopsy or axillary dissection [46].

2.7 Myofibroblastoma:

A benign mesenchymal tumor, myofibroblastoma of the breast is seen in postmenopausal women and older men between 60 to 80 years of age and constitutes less than 1% of all breast tumors [48].

Myofibroblastoma arises from myofibroblasts and fibroblasts and has a relatively slow growth pattern. It is often discovered as a painless lump. On mammography, myofibroblastoma usually appears as a round to oval, circumscribed mass without microcalcification (Fig. 7). A well-defined hypoechoic mass is typically seen on ultrasound with or without variable degree of posterior acoustic shadowing [22]. Varying degrees of collagen and adipose tissue are seen with histological features sometimes mimicking those of spindle cell carcinoma of the breast, which can lead to misdiagnosis [49]. Local surgical excision is curative and prognosis is excellent with no recurrence reported in literature [48].

3. RARE NON-NEOPLASTIC BREAST MASSES

3.1 Sarcoidosis:

Sarcoidosis is a multisystem granulomatous disease that commonly affects the lungs, lymph nodes, skin, spleen, and liver. Less than 1% cases involve the breast [50]. When sarcoidosis involves the breasts, it is typically in patients with multisystem disease, often in their 3rd and 4th decades of life [50].

Clinically, sarcoidosis of the breast manifests as a firm palpable mass or masses. It is challenging to distinguish sarcoidosis from malignancy based on imaging alone and tissue sampling is required for diagnosis. Mammographically, an ominous appearing high density mass with spiculated margins is often identified (Fig. 8). Involvement of intramammary lymph nodes can lead to multiple round to oval masses in the breast. Ultrasound usually demonstrates a hypoechoic, irregular mass with posterior acoustic shadowing [51, 52]. Histopathology is characterized by non-necrotizing epithelioid granulomas that form nodules along the lobules and ducts [53]. Corticosteroids are the treatment of choice and in severe cases, TNF inhibitors can be used. Mastectomy may be needed for severe cases [54, 55]. The prognosis varies and depends on involvement of other organs such as lungs and heart [53].

3.2 Diabetic mastopathy:

This is a benign fibrotic disease of the breast seen in patients with long standing insulin dependent type I and rarely type II diabetes mellitus. It is thought that hyperglycemia causes accumulation of glycosylated end products, which trigger an autoimmune response causing lymphocytic infiltration and fibrosis which can be mass-like [56].

On physical exam, diabetic mastopathy usually presents as a palpable, painless hard mass with a tendency to be bilateral [50]. An asymmetry or ill-defined mass is often the corresponding finding on mammogram (Fig. 9). Masses may be multiple. On ultrasound, it is difficult to distinguish diabetic mastopathy from malignancy. An irregular mass with or without posterior acoustic shadowing is commonly seen. Core biopsy is performed for definitive diagnosis with histopathology demonstrating lymphocytic infiltration in a predominant periductal and perivascular distribution. Keloid fibrosis is also seen in severe cases [56] Diabetic mastopathy is usually a self-limiting condition, and requires no treatment although it may recur [57].

3.3 Cat scratch disease:

Cat scratch disease is a bacterial infection that is caused by *Bartonella henselae* and histologically characterized by granulomatous inflammatory lymphadenopathy nearby the site of inoculation from a cat scratch [58]. Patients usually present with palpable, tender lymphadenopathy involving the axillary, cervical, submandibular, or preauricular region. Close contact with a cat is reported in 90% of patients [59].

In the breast, cat scratch disease can present as unilateral mastitis or a mass. A single enlarged lymph node or a conglomerate of inflamed and enlarged intramammary lymph nodes are typically seen on mammogram as a high density mass or masses in the upper outer quadrant (Fig. 10). On color Doppler, these masses typically demonstrate hila with vascular flow consistent with enlarged intramammary lymph nodes. Biopsy may be necessary in elusive cases [60, 61]. Histopathology is characterized by reactive follicular hyperplasia and geographic microabscess formation representing necrotizing lymphadenitis [62]. Antibiotic therapy is curative [63].

4. CONCLUSION:

Benign and malignant atypical breast masses can mimic invasive ductal or lobular carcinoma along with benign breast pathology. The imaging features of these rare masses are often non-specific and biopsy with histopathologic diagnosis is required to diagnose these rare masses. This work may serve as a reference to radiologists that encounter one of these rare breast masses in determining appropriateness for biopsy or as an unexpected biopsy result in assessing radiologic and pathologic concordance.

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Highlights

- Mammographic and histopathologic images of atypical breast masses are presented.
- Highlighted rare neoplastic breast masses include adenoid cystic carcinoma, spindle cell lipoma, granular cell tumor, and others.
- Highlighted rare non-neoplastic breast masses include sarcoidosis, diabetic mastopathy, and cat scratch disease

Figure 1:

Adenoid cystic carcinoma in an 81-year-old man referred to dermatology for a palpable areolar mass associated with discoloration of the skin. Mammography MLO view of the left breast (A) and ultrasound (B), performed for evaluation of extent of disease, demonstrate an oval mass with microlobulated margins (arrows). Histopathology (C: H&E stain; magnification $\times 100$) shows islands of basaloid cells predominantly arranged in cribriform pattern with areas showing cystic degeneration and mucin (arrow).

Figure 2:

Spindle cell lipoma in a 20-year-old woman referred for evaluation of a palpable breast mass. Initially, ultrasound (A) was performed showing a predominantly hyperechoic mass (arrow), thought to be probably benign and likely representing fat necrosis. The mass was slightly larger on a 6-month follow-up, prompting mammography. The CC view of the left breast (B), shows an irregular mass (circle) with a paucity of internal fat density. Histopathology (C: H&E stain; magnification $\times 100$) shows the typical components of a spindle cell lipoma: thin, uniform spindle cells arranged in short, parallel bundles (white arrow), mature adipocytes (black arrow) and ropy birefringent collagen on a thin amorphous myxoid background.

Figure 3: Granular cell tumor in a 31-year-old woman who presented with a palpable painless lump in the left breast. Diagnostic mammography MLO view of the left breast (A) was performed showing a circumscribed mass (inset) corresponding to a round to oval hypoechoic mass with an echogenic rim on ultrasound (B, arrow). Histopathology (C: Magnification x100; H&E stain) revealed sheets and nests of polygonal cells (arrows) with abundant granular eosinophilic cytoplasmic component.

Figure 4:

Angiosarcoma of the breast. 68-year-old woman with history of left breast invasive ductal carcinoma status post breast conservation therapy 12 years ago presenting with a reddish skin nodule that corresponded to a high density, irregular mass on mammography CC view of the left breast (A, circle). On ultrasound (B), the tumor is hypoechoic on grayscale (not shown) and extremely vascular on color Doppler. On histopathology (C) epithelioid and somewhat more spindle-shaped tumor cells were seen forming irregular, anastomosing vascular channels. The cells demonstrated highly atypical cellular morphology, pleomorphic nuclei, and prominent nucleoli (arrow). CD31 immunostain highlighted tumor cells with diffuse, strong, membranous reactivity (not shown), establishing diagnosis of an angiosarcoma.

Figure 5:

Glomus tumor in a 42-year-old man with family history of breast cancer in his mother presenting with a palpable and extremely painful mass in the lower right breast. Diagnostic mammography ML view of the right breast (A) shows an high density oval mass with microlobulated margins corresponding to a hypoechoic mass with marked vascularity on color Doppler imaging (B) with an efferent vessel also seen on dynamic examination. The patient complained of severe pain during ultrasound examination. Microscopic exam (C: H&E; magnification $\times 100$) shows aggregates of round blue cells and scattered vascular channels (arrow).

Figure 6:

Adenosquamous carcinoma in a 42-year-old woman presenting with a palpable right breast lump. Diagnostic mammography MLO view of the right breast (A) shows a high density mass with spiculated margins (circle). Ultrasound (B) shows a hypoechoic irregular mass with posterior acoustic shadowing (arrow). On histopathology (C), distinct squamous differentiation was evident showing broad sheets and nests of highly pleomorphic cells with few scattered glandular elements (arrow). Immunohistochemistry was positive for CK7 (not shown) which is an adenocarcinoma marker as well as E-Cadherin, CK5/6, p40 which are squamous markers, in keeping with a mixed adeno-squamous phenotype.

Figure 7:

Myofibroblastoma in a 61-year-old man presenting with a palpable area of concern in the right breast. Mammography MLO view of the right breast (A) shows a high density circumscribed mass (circle). Ultrasound (B) shows an oval, circumscribed mass with a capsule (arrow) and some internal vascularity resembling a fibroadenoma. Microscopic exam showed spindle cells (C, black arrow) and dense connective tissue confirming a myofibroblastoma.

Figure 8:

Sarcoidosis of the breast in a 63-year-old woman with known severe multi-organ sarcoidosis presenting with right breast lump. Mammography CC view of the right breast (A) shows a large spiculated high density mass in the right breast (circle). Ultrasound (B) shows a corresponding irregular hypoechoic mass with dense shadowing (arrow). Biopsy was performed showing non-caseating granulomatous inflammation (arrows) (C: H&E stain; magnification $\times 100$) consistent with sarcoidosis.

Figure 9:

Diabetic mastopathy in a 23-year-old female with type 1 diabetes presenting with an enlarging right breast mass. Ultrasound (A) was performed first, showing an irregular, hypoechoic mass with posterior acoustic shadowing (arrow). Mammography demonstrated a subtle corresponding subareolar right breast focal asymmetry (not pictured). Biopsy was performed. Histopathology (C: H&E stain; magnification $\times 200$) shows distinctive periductal lymphocytic infiltration (arrow) and extensive collagenous stromal fibrosis consistent with diabetic mastopathy.

Figure 10:

Cat scratch disease of the breast in a 48-year old woman presenting with a palpable lump in the left breast. The technologist noted erythematous scratches on the patient's breasts and chest. The mole marker indicates the site of a scratch from the patient's cat. Mammography MLO view of the left breast (A) shows a new round mass with circumscribed margins in the upper outer quadrant of the left breast in the area of palpable concern (circle). Ultrasound (B) shows an enlarged intramammary lymph node with hilar flow (arrow). Biopsy was performed with histology (C) demonstrating scattered microabscesses surrounded by granulomatous inflammation (arrows), confirming cat scratch disease.