Aggressive Metaplastic Carcinoma of the Breast with Osteoclastic Giant Cells

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ABSTRACT

Metaplastic carcinoma of the breast is an uncommon type of malignancy that is aggressive but can mimic other benign breast neoplastic processes on imaging. We present a case of a young female patient who presented with a rapidly progressing metaplastic carcinoma with osteoclastic giant cells subtype. There have been only very rare published reports of this pathologic subtype of metaplastic carcinoma containing osteoclastic giant cells.

CASE REPORT

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A 29-year old premenopausal BRCA negative female, without significant past medical history or family history of breast cancer and history of prior fibroadenoma, presented clinically with a rapidly enlarging, tender, palpable right breast mass at the 9:00 position over a period of 1 month. Due to the patient's young age, mammographic imaging was deferred and targeted sonographic exam was instead performed for initial evaluation. Sonographic evaluation demonstrated a 1.8x1.2x1.6cm oval, circumscribed, solid mass without increased internal flow corresponding to the palpable abnormality (Figure 1). Subsequent ultrasound-guided core needle biopsy was performed. Pathology demonstrated poorly differentiated carcinoma with sarcomatoid features and osteoclast-like giant cells (Figure 2). Immunohistochemical staining showed positivity for epithelial membrane antigen (EMA). The presence of EMA confirms carcinoma cells, in this case either poorly differentiated or sarcomatoid carcinoma suggestive of metaplastic carcinoma, and not cells of a sarcoma or phyllodes tumor.

Immunohistochemistry (IHC) was negative for estrogen receptor (ER), negative for progesterone receptor (PR), and negative for HER2/neu expression. The KI-67 labeling index was 60%.

A breast magnetic resonance image (MRI) obtained approximately 2 weeks after initial diagnosis demonstrated interval increase in size of the mass to 4.6x3.1x3.7cm. Features suggestive of a complex mass with enhancing septations, areas of short tau inversion recovery (STIR) hyperintensity and T1 isointensity. Rapid washout kinetics was also demonstrated (Figure 3).

The patient elected to undergo in vitro fertilization procedure after her diagnosis because of her nongravid history and planned upcoming aggressive treatment, which postponed neoadjuvant chemotherapy. A follow-up breast ultrasound performed 6 weeks after initial diagnosis prior to chemotherapy treatment showed further interval increase in size of the mass, appearing as a complex solid and cystic mass replacing almost the entirety of the lateral breast parenchyma measuring at least 10x5x4cm (Figure 4). A fluid component was noted to extend from 2-6:00 position. On physical exam,

there was discoloration of nearly the entire breast with a red/purplish outgrowth into the skin at the 7-8:00 position (Figure 4). Due to marked tenderness, mass effect and tension caused by this rapidly enlarging mass, ultrasound-guided aspiration was performed (Figure 5) for symptomatic relief. Cytology of the aspirated fluid demonstrated primarily blood with scattered poorly differentiated sarcomatous-like cells and osteoclast-like giant cells. Gram stain and culture demonstrated no growth or bacteria. Cytology findings were confirmatory of the initial core biopsy histology, with possible differential including poorly differentiated invasive mammary carcinoma with osteoclast-like giant cells.

After completion of her in vitro fertilization egg retrieval, the patient then underwent neoadjuvant chemotherapy with 4 cycles of dose-dense doxorubicin-cyclophosphamide (AC), completed at 6 months post-initial diagnosis. Post-chemotherapy breast MRI (Figure 6) demonstrated decrease in mass size to 3.0x2.5x2.7cm, and no detectable enhancement. She subsequently underwent right breast modified radical mastectomy and left simple mastectomy, with final pathology demonstrating a right breast 3.0 cm necrotic tumor with no residual carcinoma cells (Figure 7). Twenty-six axillary lymph nodes and one intramammary lymph node were negative for metastatic carcinoma. She also then underwent adjuvant external beam radiation therapy consisting of 5000 cGy in 25 fractions with an electron patch to the right chest wall.

At the most recent follow-up 2 years post-diagnosis, she is doing well with no evidence of recurrence to date. She had minor residual intermittent pain in her right chest wall that is now mostly improved. She is also currently pregnant and doing well in her first trimester.

DISCUSSION

Etiology & Demographics

Metaplastic carcinoma (MPC) of the breast is a rare form of breast cancer, accounting for only 0.25% of all breast cancers [1]. They are ductal carcinomas that transform from the original glandular epithelium to non-glandular mesenchymal tissue, such as chondroid or osteoid tissue. The Wargotz and Norris classification contains 5 subtypes: 1) spindle cell, 2) squamous cell, 3) carcinosarcoma, 4) matrix-producing, and 5) MPC with osteoclastic giant cells (OGCs) [2]. The WHO classification is divided into 1) pure epithelial, and 2) mixed epithelial and mesenchymal type.

MPC with OGCs was first described as a subtype of MPC by Wargotz and Norris in 1990, based on the clinical and pathological evaluation of 29 cases [2]. They described this subtype histologically as containing a predominantly sarcomatous or spindle cell background, admixed with infiltrating ductal or intraductal carcinoma, and also admixed with cellular stroma that contained OGCs [2]. Hemorrhage and hemosiderin deposition were common in these cases [2], which explains its imaging features described below. The mechanism for formation of osteoclast-like giant cells is still unknown [3]. The OGCs are felt to be of different origin than the carcinoma and likely a result of reactive infiltrate [3]. The breast tumoral histology, over the presence of OGCs, is felt to have the most impact on prognosis [3]. There have been no published cases of the subtype of MPC with OGCs focusing on imaging features to date. Due to the rarity of the subtype of MPC with OGCs, there is no published data on incidence, demographics, and imaging features separate from MPC.

Varying data with no consistent age demographic difference for MPC compared to those with invasive ductal carcinoma (IDC) has been shown. Pezzi et al. [1] showed a higher mean age of MPC at 61.1 years old compared to IDC at 59.7 years old (P = 0.001). However, Yang et al. [4] demonstrated a younger age demographic in MPC compared to IDC, with median ages of 46 versus 53 years old (P=0.048), respectively. Gunhan-Bilgen, et al. [6] reported a mean of 53.8 years in their MPC data group with a range of 44-63 years old.

MPC spreads by hematologic rather than lymphatic routes of metastasis, and usually presents as a locally aggressive mass without nodal involvement at time of detection [1].

Clinical & Imaging findings

Clinically, patients frequently present with a rapidly growing, relatively large breast mass [1].

Mammographically, MPC presents as a very dense noncalcified mass with variable shapes and margins, but is most commonly oval and circumscribed [4-6].

Sonographically, it most often demonstrates an irregular shape, microlobulated margin, complex echogenicity, and parallel orientation [5]. MPCs often demonstrate posterior acoustic enhancement in contrast to the posterior acoustic shadowing that is more often seen with invasive ductal carcinomas [4]. It can often mimic a benign mass such as a complicated cyst or fibroadenoma in its early stages [7]. On magnetic resonance imaging, MPC may present as a round to lobulated mass with smooth margins with T2 hyperintense signal due to necrosis and cystic degeneration, rim-like enhancement, and type III washout kinetics, corresponding to the enhancing peripheral portion of the mass [5].

Treatment & Prognosis

MPC is an aggressive form of breast cancer with worse prognosis compared to most breast cancers. It has a high incidence of local recurrence and is therefore more aggressively treated [8].

Some predictors of poorer outcome include presence of skin invasion, presentation at age less than 39 years of age, and presence of squamous cell carcinoma in the lymph nodes [9]. Our patient presented with 2 of these 3 predictors, suggesting worse outcome.

The reported 5-year survival rate for patients with metaplastic carcinoma with OGC is 68%, which is less than the estimated 95% for invasive ductal carcinoma without lymph node involvement and 96% for invasive ductal carcinoma with occult lymph node metastasis [10].

Current treatment commonly involves modified radical mastectomy, adjuvant chemotherapy and postoperative radiotherapy [11].

Differential Diagnosis

Invasive ductal carcinoma-NOS

Invasive ductal carcinoma - NOS is the most common type of breast malignancy. Characteristic imaging features of IDC include irregular shape and spiculated margins, pleomorphic calcifications, and posterior acoustic shadowing. These characteristics are not common in MPC [4]. MPC presents with larger tumor size, less nodal involvement, higher tumor grade, and hormone receptor negativity compared to IDC. Patients with MPC are treated more aggressively than IDC (more often with mastectomy and chemotherapy) because of a higher stage at presentation [1].

Sarcoma

Breast sarcomas are neoplasms of stromal origin, that comprise <1% of breast malignancies. Similar to MPC, they present clinically as aggressive rapidly enlarging masses. They appear as large oval dense masses on mammography, and as oval complex solid and cystic masses with posterior acoustic enhancement on ultrasound, like MPC. However, they can sometimes show coarse calcification on mammography and tend to be hypervascular on ultrasound, which are not as commonly seen with MPCs. On MRI, they demonstrate heterogeneous enhancement, T2 hyperintensity, with rapid washout type III kinetics [11,12].

Fibroadenoma

A fibroadenoma is a benign fibroepithelial tumor composed of stromal and epithelial elements. It is the most common breast mass in women under 35 years old, with mean age at diagnosis of 30 years old [13]. It often presents on physical exam as a mobile, painless, firm rubbery mass. As mentioned, fibroadenomas can mimic the early stages of MPC. However, unlike MPC, they do not rapidly enlarge. Their mean diameter enlargement typically is less than 20% over 6 months [14].

Typical imaging findings on mammography are of an oval circumscribed mass, similar to MPC. Some can contain coarse popcorn or heterogeneous calcifications, which MPCs do not typically demonstrate. Ultrasound features include a circumscribed oval hypoechoic or isoechoic mass, like MPCs. Unlike MPCs, they are most often homogeneous, and do not demonstrate complex or cystic components. They often do not demonstrate increased internal vascularity on Doppler, but sometime peripheral vessels can be seen [15]. On MRI, they often present as an oval circumscribed enhancing mass [16]. Some can demonstrate dark internal septations. They are often T2 or STIR hyperintense due to their myxoid components.

Phyllodes

Phyllodes tumors are fibroepithelial neoplasms. Imaging, clinical, and pathologic differentiation from the more common benign fibroadenomas can be difficult [16,17].

While fibroadenomas can mimic the early stages of MPC, phyllodes can mimic the counterpart later stages of MPC. Similar to MPC, they often clinically present as a rapidly enlarging circumscribed mass [18]. Unlike MPC, the majority are pathologically benign (although they can be locally aggressive), with a minority pathologically borderline or malignant.

Phyllodes can present similarly to MPC on mammogram and ultrasound [19]. On mammography, they present as a dense round or oval mass with mostly circumscribed margins. Sonographic imaging findings are an oval or round mass with variable posterior acoustic features and increased vascularity, sometimes demonstrating cystic spaces. MRI findings can also be similar to that of a MPC demonstrating a rapidly enhancing lobulated mass with T2 hyperintensity [19,20]. However, unlike MPC, type III washout kinetics is only seen in 33% and dark internal septations can often be seen. Cystic spaces on MRI can also be seen in phyllodes like MPC, more characteristic in the less common malignant type [19,20].

Complicated cyst

Complicated cysts are benign breast cysts filled with internal debris composed of proteinaceous, fatty, or cellular (blood or inflammatory) components [21]. They do not contain any solid component, but sonographic features can sometimes be difficult to differentiate from a solid mass on ultrasound. They present as an oval circumscribed mass with imperceptible wall, posterior acoustic enhancement, lack of internal vascularity, and homogeneous low-level internal echoes. Differentiating sonographic characteristics that help diagnose a complicated cyst rather than a solid hypoechoic mass are features of mobile internal debris, or a fluid-debris level that shifts with positioning. [22]

On mammography, they present as an oval or round circumscribed mass. Unlike solid masses, they can wax and wane in size over time [22].

MRI features are of an oval or round smoothly marginated mass that does not demonstrate enhancement. They often demonstrate T1 hyperintensity when they contain internal proteinaceous , hematologic, or fatty content. They are mostly T2 and STIR hyperintense due to fluid content, but some can also be T2 hypointense when containing blood or proteinaceous contents [22].

TEACHING POINT

Metaplastic breast carcinoma is a rare form of breast cancer that can mimic benign processes such as a complicated cyst or fibroadenoma on imaging in its early stages, commonly presenting as a small circumscribed oval mass. But it is an aggressive malignancy that rapidly evolves on imaging into a large complex cystic and solid mass with worse prognosis than invasive ductal carcinoma, and is treated aggressively.

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FIGURES

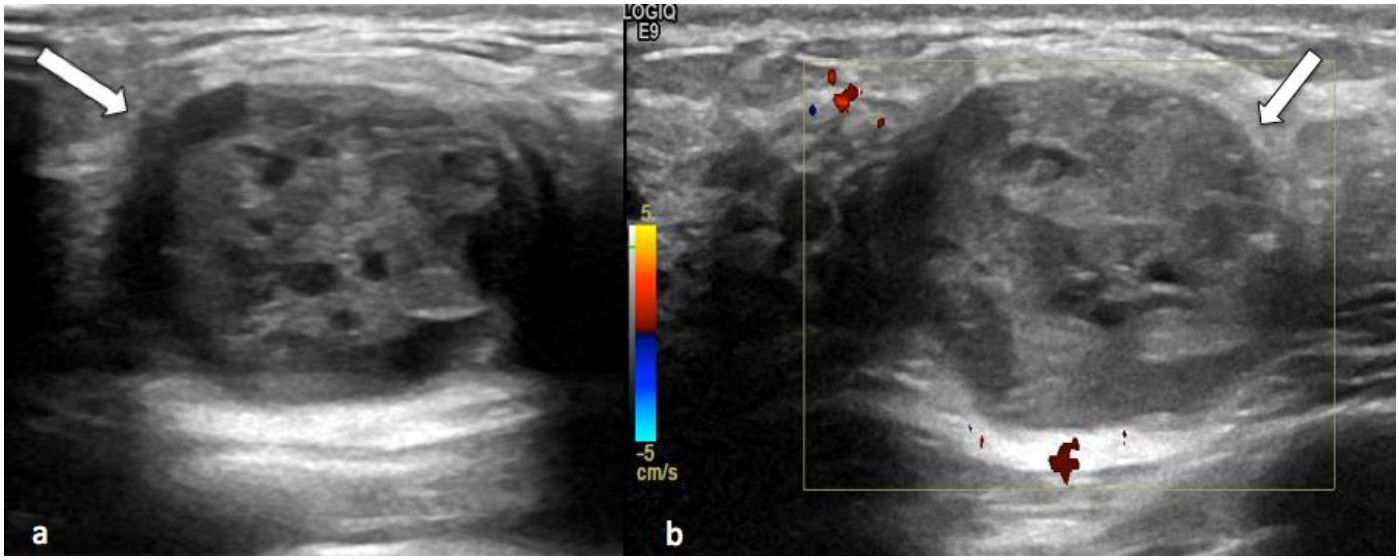

Figure 1: 29 year-old female with metaplastic breast carcinoma. a) FINDINGS: Initial diagnostic sonogram of the patient's palpable breast mass demonstrating the metaplastic breast carcinoma presenting as a 1.8 cm oval mass (white arrow) with posterior acoustic enhancement. TECHNIQUE: 16MHz linear transducer gray-scale sonographic image. b) FINDINGS: Color Doppler image of initial diagnostic sonogram demonstrating the metaplastic breast carcinoma (white arrow) without significant increased internal vascular flow. TECHNIQUE: 16MHz linear transducer color Doppler sonographic image.

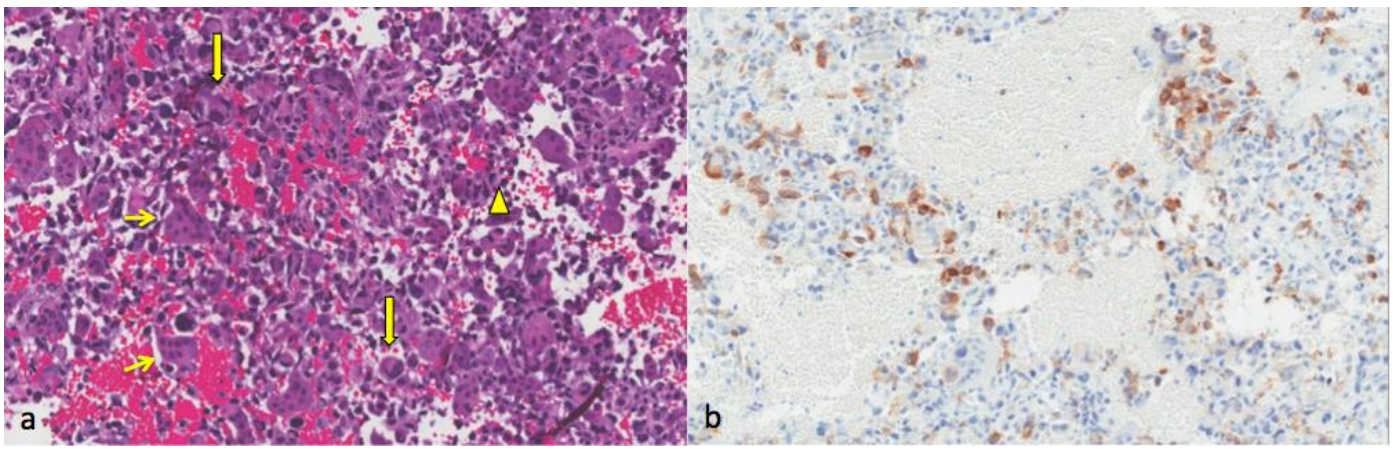

Figure 2: 29-year-old female with metaplastic breast carcinoma. a) Core sample histology hematoxylin and eosin (H&E) stain shows osteoclast-like giant cells (short arrow) interspersed with poorly differentiated carcinoma cells (triangle), rare anaplastic giant cells (long arrow), extravasated red blood cells and hemosiderin; b) immunohistochemical staining shows positivity for epithelial membrane antigen (EMA) in carcinoma cells and absence of reactivity in the sarcomatoid cells and osteoclast-like giant cells.

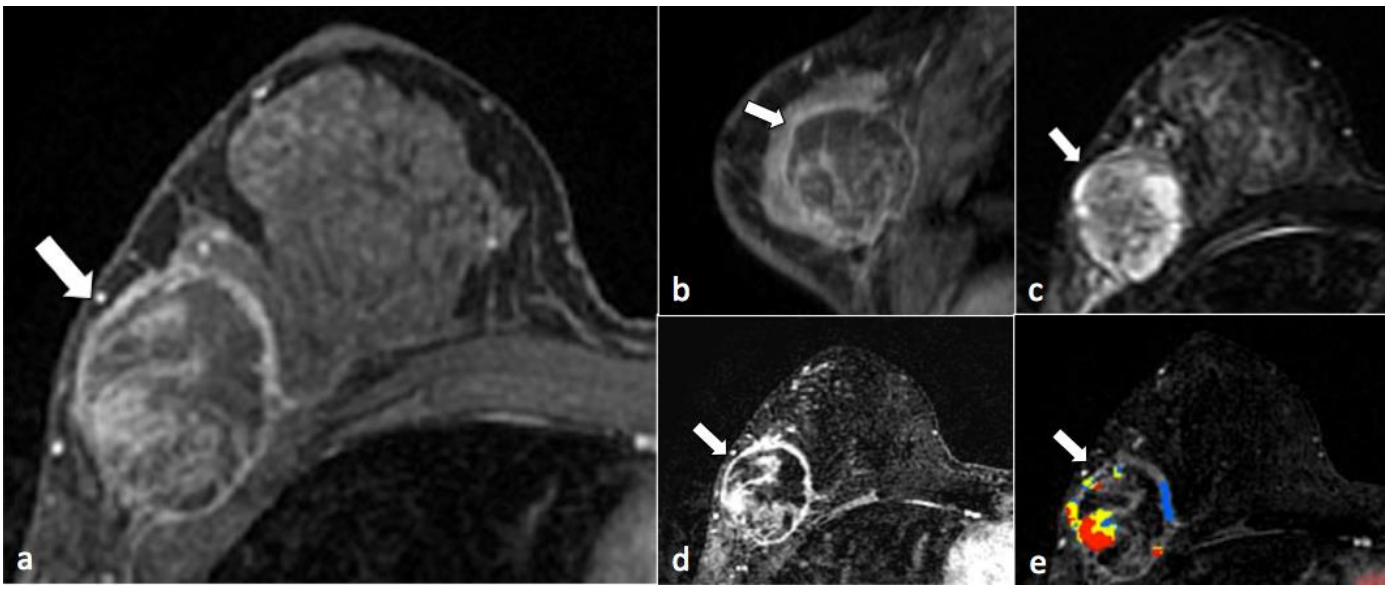

Figure 3: 29 year-old female with metaplastic breast carcinoma, 2 weeks after core needle biopsy diagnosis. FINDINGS: Pretreatment breast MRI shows the metaplastic breast carcinoma (white arrow) presenting as a 4.6 cm oval rim-enhancing mass with central heterogeneous enhancement with no clear fat plane between the mass and pectoralis major muscle. It demonstrates short tau inversion recovery (STIR) hyperintensity, and suspicious Type III rapid washout kinetics. TECHNIQUE: a) Axial 1.5T MRI 1.6mm slice thickness, TR 5.5, TE 2.6, 10.4ml IV omniscan at 90 seconds post contrast administration b) sagittal reformatted non-subtraction image, 1.5T MRI, reformatted at 0.7mm slice thickness, TR 5.5, TE 2.6, 10.4ml IV omniscan at 90 seconds post contrast administration c) axial STIR image 1.5T MRI 4mm slice thickness, TR 3000, TE 67, no contrast. d) axial T1 subtraction post contrast fat-saturated 90 second post-contrast administration axial image subtracted by T1 fat-saturated pre-contrast administration axial image, 1.5T MRI, 1.6mm slice thickness e) axial T1 subtraction with overlying angiomap, T1 fat-saturated 90 second post-contrast administration axial image subtracted by T1 fat-saturated pre-contrast administration axial image, 1.5T MRI, 1.6mm slice thickness, superimposed with kinetics angiomap of red-Type III rapid washout kinetics, yellow - Type II rapid plateau kinetics, blue - Type I rapid persistent kinetics.

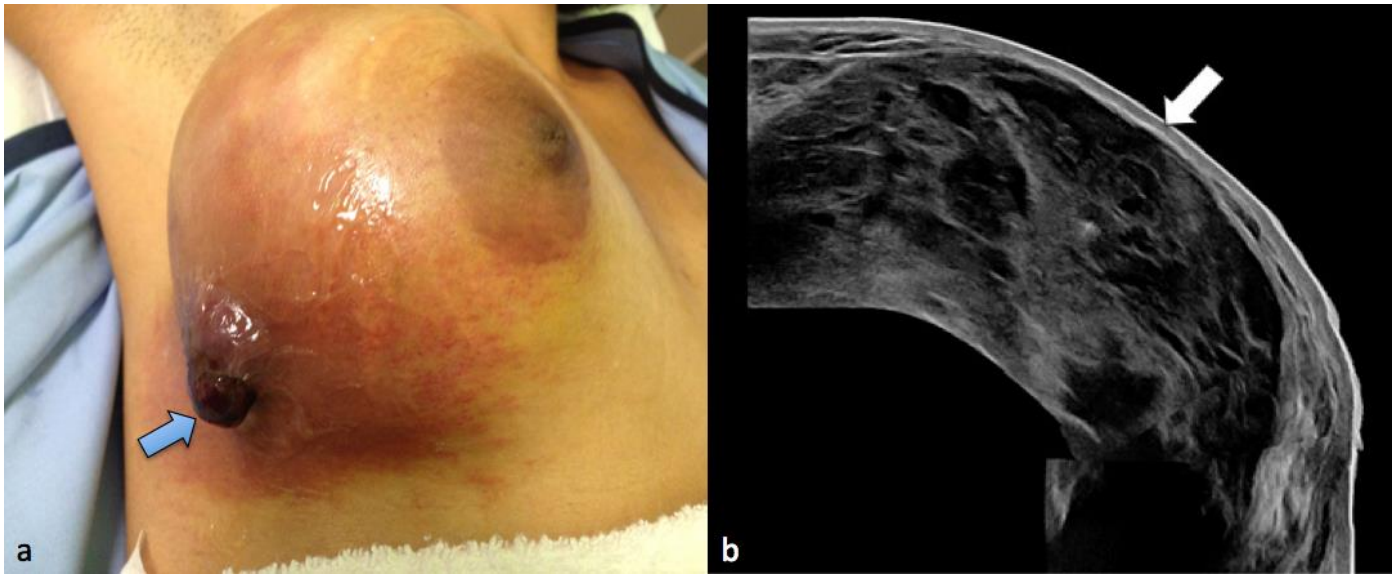

Figure 4: 29 year-old female with metaplastic breast carcinoma, 6 weeks after core biopsy diagnosis. FINDINGS: a) Physical exam findings of a right enlarged breast with discoloration of nearly the entire breast with a red/purplish outgrowth into the skin at the 7-8:00 position (blue arrow). Ultrasound gel has been applied over the skin. TECHNIQUE: photograph, 8megapixel, f/2.2 aperture b) FINDINGS: Corresponding breast ultrasound shows marked interval enlargement of the mass encompassing a majority of the breast tissue, now appearing as a 10 cm large complex cystic and solid mass (white arrow). TECHNIQUE: 16MHz linear transducer gray scale panoramic sonographic image.

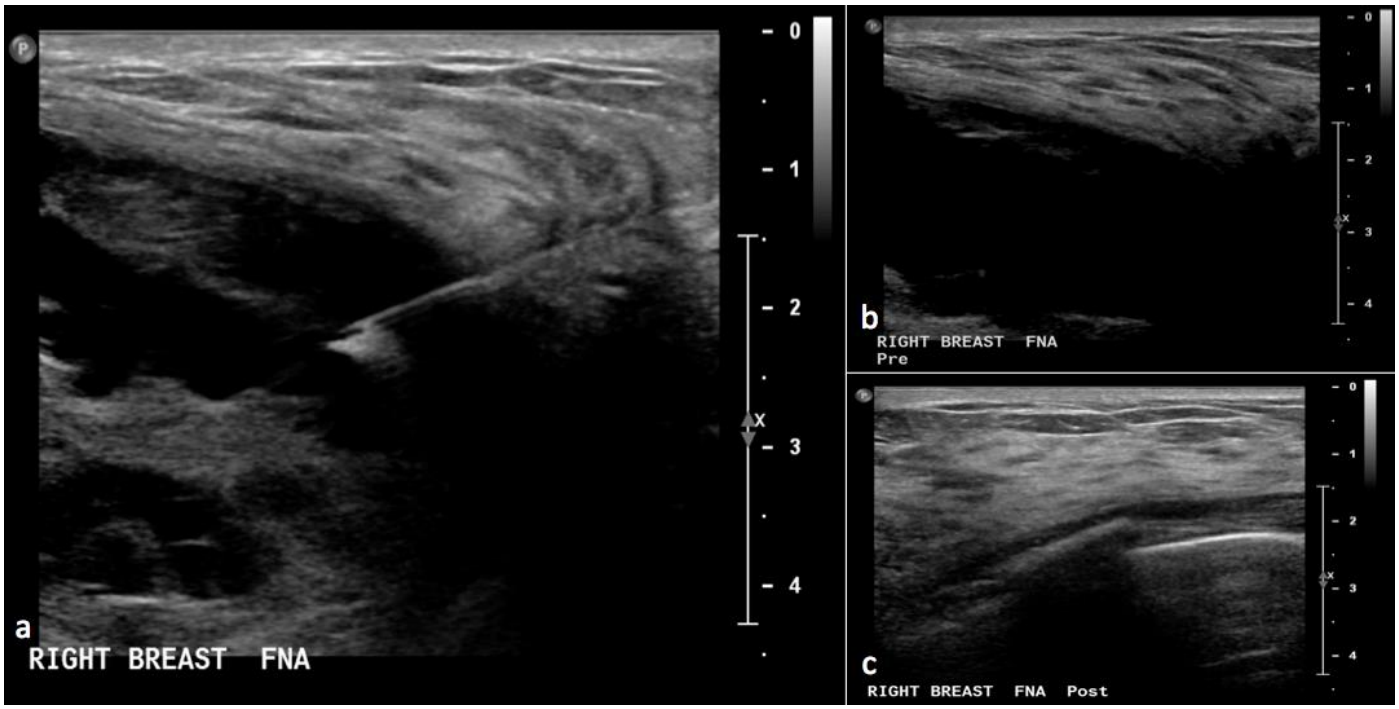

Figure 5: 29 year-old female with metaplastic breast carcinoma, 6 weeks after core biopsy diagnosis. Ultrasound-guided aspiration was performed for symptomatic relief due to marked tenderness, mass effect and tension caused by this rapidly enlarging mass. a) FINDINGS: A large 5 cm cystic component of the complex mass at the right breast 2:00 position was targeted, with aspiration needle with tip located within the fluid collection and interval decreasing size of the collection. TECHNIQUE: 12 MHz linear transducer gray-scale sonographic image obtained during mid-aspiration, using an 18-gauge 3.5inch spinal needle. b) FINDINGS: Pre-procedure image of the 5 cm cystic component of the complex mass prior to aspiration. TECHNIQUE: 12MHz linear transducer gray-scale sonographic image. c) FINDINGS: Post-procedure image showing no significant residual fluid remaining after ultrasound-guided aspiration of the cystic component of the mass. TECHNIQUE: 12MHz linear transducer gray-scale sonographic image.

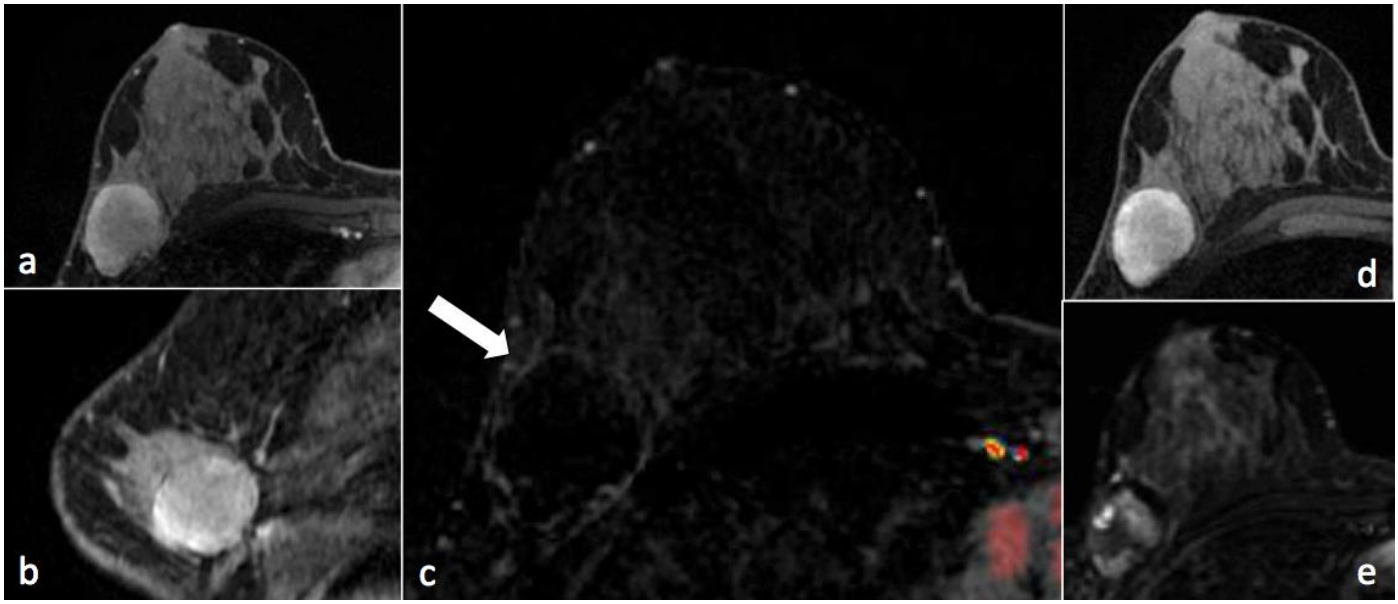

Figure 6: 29 year-old female with metaplastic breast carcinoma. FINDINGS: Post chemotherapy MRI demonstrates a right breast T1 hyperintense, STIR heterogeneously hyperintense mass with interval decrease in size to 3.0 cm, and no detectable enhancement (white arrow in Figure 6c). TECHNIQUE a) axial T1 fat-saturated post-contrast image, 1.5T MRI, 1.6mm slice thickness, TR 5.5, TE 2.6, 15ml IV omniscan at 90 seconds post contrast administration b) sagittal reformatted T1 fat-saturated post-contrast image, 1.5T MRI, 0.74mm slice thickness, TR 5.5, TE 2.6 c) axial T1 subtraction with overlying angiomap, T1 fat-saturated 90 second post-contrast administration axial image subtracted by T1 fat-saturated pre-contrast administration axial image, 1.5T MRI, 1.6mm slice thickness, superimposed with kinetics angiomap of red-Type III rapid washout kinetics, yellow - Type II rapid plateau kinetics, blue - Type I rapid persistent kinetics. d) axial T1 fat-saturated pre-contrast image, 1.5T MRI 1.6mm slice thickness, TR 5.5, TE 2.6 e) axial short tau inversion recovery (STIR) image, 1.5T MRI, 3.2mm slice thickness, TR 3000, TE 66.7

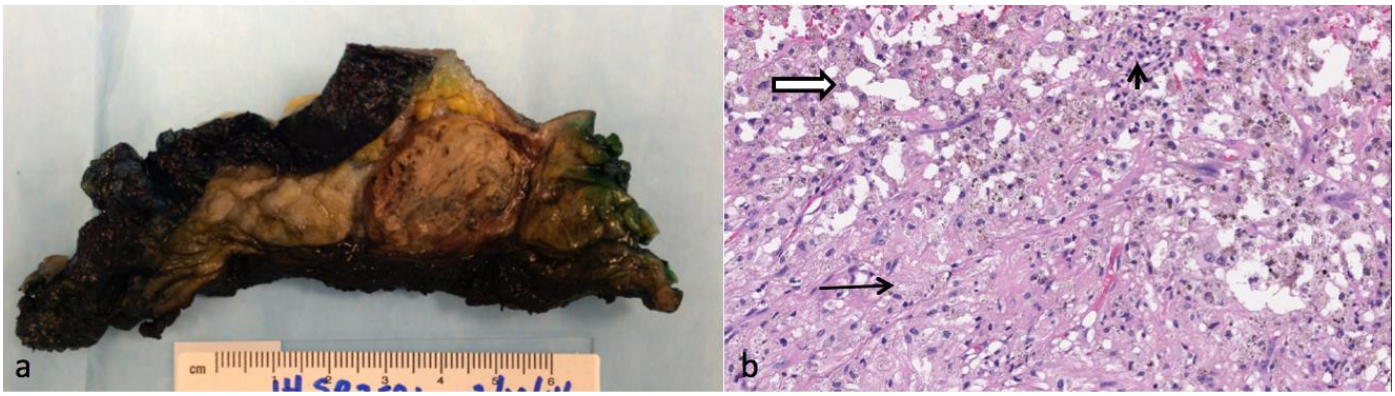

Figure 7: 29 year-old female with metaplastic breast carcinoma, status post neoadjuvant chemotherapy and right modified radical mastectomy, at 7 months post initial diagnosis. FINDINGS: a) Right breast mastectomy gross specimen of lateral right breast, with superior breast oriented to the left of the image, nipple oriented towards the upper image. Image demonstrates a partially tan-red solid 3.2cm tumor at 8-9 o'clock 4cm from the nipple. The remainder of the breast parenchyma is glistening, shiny white and rubbery to yellow and fatty. TECHNIQUE: photograph, 8megapixel, f/2.2 aperture b) Mastectomy section histology high power view hematoxylin and eosin (H&E) stain of the tumor shows fibrous stroma containing foamy histiocytes (long arrow), lymphocytes (short arrow) and hemosiderin deposition (block arrow). No tumor cells were identified, consistent with complete response.

Etiology	• Ductal carcinomas that transform from original breast glandular epithelium to non breast mesenchymal tissue
Incidence	• 0.25% of all breast cancers
Gender Ratio	• Female > Male
Age predilection	• Mean/median age compared to IDC ages vary based on study • Mean 53.8 years old [1] • Range 44-63 years old [5]
Risk factors	• No specific risk factors
Prognosis	• Aggressive, with worse prognosis compared to most breast cancers and high incidence of local recurrence • 5 year survival rate <65% • Predictors of poorer outcome include:presence of skin invasion, presentation at age less than 39 years of age, and presence of squamous cell carcinoma in the lymph nodes
Findings on imaging	• Variable shapes but commonly oval • Smooth/circumscribed margins • Can mimic benign mass such as complicated cyst/fibroadenoma in early stages (can have posterior acoustic enhancement on US) and phyllodes in later stages • MRI T2 hyperintensity • MRI Peripheral enhancing Rapid washout kinetics

Table 1: Summary table of metaplastic carcinoma of the breast.

	Mammography	US	MRI
Metaplastic carcinoma	• Dense noncalcified mass • Variable shapes, most commonly oval and circumscribed	• Microlobulated margin • Complex echogenicity • Parallel orientation • Often posterior acoustic enhancement • Can mimic a benign mass such as a complicated cyst or fibroadenoma in early stages	• Round to lobulated mass • Smooth margins • T2 hyperintensity • Rim-like enhancement • Type III washout kinetics corresponding to the enhancing peripheral portion of mass
Invasive ductal carcinoma	• Can be dense and noncalcified • Variable shapes, most often irregular	• Irregular shape • Often posterior acoustic shadowing • Antiparallel orientation	• Often irregular mass • Often irregular margins • Variant T2 signal • Type III rapid washout kinetics
Sarcoma	• Dense large mass • Oval • Noncalcified or calcified mass	• Irregular or oval shape • Complex cystic & solid mass • Frequently hypervascular	• Irregular or oval • Heterogeneous enhancement • T2 hyperintensity • Type III rapid washout kinetics
Phyllodes	• Dense • Oval/round • Most noncalcified • Circumscribed	• Oval/round shape • Hypoechoic solid mass (can have cystic component) • Commonly hypervascular • Can see posterior acoustic enhancement	• Oval/lobulated • Rapid initial enhancement • Nonenhancing internal septations in some • T1 heterogeneous hypointensity • T2 hyperintensity • Type I kinetics in approximately 1/3
Fibroadenoma	• Low density or isodensity to breast parenchyma • Oval • Circumscribed • Can have calcifications (popcorn, coarse) if involuting	• Oval • Hypoechoic, can be isoechoic solid mass • Usually not hypervascular, but can sometimes see feeding or peripheral vessels • Posterior enhancement variable	• Oval • Can have rapid initial enhancement, many with plateau delayed enhancement • No to weak enhancement if hyalinized • May have dark internal septations • T2/STIR hyper- or iso-intense relative to parenchyma
Complicated Cyst	• Varying density • Oval or round • Circumscribed • Waxing and waning size	• Oval • Homogeneous low level internal echoes • No internal vascularity • Posterior acoustic enhancement • Diagnostic if mobile internal debris or shifting fluid-debris level demonstrated	• Oval or round • Smooth margins • No enhancement • Often T1 hyperintense • Mostly T2/STIR hyperintense

Table 2: Differential table for metaplastic carcinoma of the breast.

ABBREVIATIONS

AC = doxorubicin-cyclophosphamide
EMA = epithelial membrane antigen
ER = estrogen receptor
IDC = invasive ductal carcinoma
IHC = immunohistochemistry
MPC = metaplastic carcinoma
MRI = magnetic resonance image
OGCs = osteoclastic giant cells
PR = progesterone receptor
STIR = short tau inversion recovery

KEYWORDS

metaplastic breast cancer; osteoclastic giant cells; breast; mammography; breast ultrasound; breast magnetic resonance imaging

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