Imaging aspects of a rare invasive breast carcinoma: the medullary subtype

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Learning objectives

The objectives of this educational exhibit are:

• to describe the most common imaging findings of breast carcinoma with medullary features;
• to describe the diagnostic histological criteria of medullary carcinomas;
• to correlate the imaging features with the histological findings;
• frequency and epidemiology of this special subtype of breast carcinoma;
• to illustrate the imaging aspects that can raise the possibility of this diagnosis and its main differential diagnosis.
Background

Medullary breast carcinomas are rare tumors that represent less than 1% of invasive lesions. Most commonly, affect young women, and there is an association with BRCA1 gene mutation. In immunohistochemical analysis, triple negative is the most found profile. Despite this, the literature presents a better prognosis of this histological subtype compared to invasive ductal carcinomas no other specified (NOS).

Interestingly, there is clinically palpable axillary lymph nodes, but without metastatic involvement. Usually, these lymph nodes present with reactive findings.
Findings and procedure details

HISTOLOGICAL FEATURES

Histologically, the medullary breast carcinoma is characterized by a diffuse growth pattern without intraductal component or glandular differentiation, with microscopic circumscription. Abundant eosinophilic cytoplasm with indistinct borders creates a syncytial appearance (Fig. 1 on page 7, Fig. 2 on page 7). The tumor cells present high-grade nuclei (Fig. 2 on page 7) and high mitotic rate, arranged in broad sheets, nests, or anastomosing trabeculae. Moderate or severe cellular polymorphism, corresponding to a moderate or low level of histological differentiation (G2 or G3). A prominent lymphoplasmacytic infiltrate within and around the tumor is characteristic (Fig. 1 on page 7, Fig. 3 on page 8), and may sometimes unclear its boundaries. A pseudo capsule formed by peripheral fibrous tissue can exist.

In immunohistochemical analysis, the triple negative profile is the most found (estrogen and progesterone hormone receptors and Her2/neu negative). In doubtful cases, the absence of myoepithelial cells supports invasive process. The use of p63 and calponin is a good choice, and a variety of other markers may help (S100, actin, smooth muscle myosin heavy chain, CD 10, Maspin, high molecular weight cytokeratin).

Atypical medullary breast carcinoma presents an infiltrative margin, mild mononuclear infiltration, a low nuclear grade, and presence of an intraductal component.

In the recent 4th edition of World Health Organization Classification of Breast Tumors, carcinomas with medullary features are considered an overlapping group of tumors, including the "medullary carcinoma", "atypical medullary carcinoma" and "invasive carcinoma of no special type with medullary features". The overlapping morphological and immunohistological features and low interobserver reproducibility induced the authors to put the "medullary appearance tumors" in this bigger group.

CLINICAL ASPECTS

Carcinomas with medullary features are rare tumors, representing less than 5% of all breast cancers, and less than 1% of invasive tumors. They are more common in patients with BRCA1 gene mutations and affect mainly patients under the age of 35, although they might be present in any age.
Despite its association with the BRCA mutation and the common triple negative profile, prognosis is rather favourable comparing to invasive ductal carcinomas NOS, considering the good tumour response to chemotherapy and radiotherapy. The relatively good outcome of carcinomas with medullary features is correlated with the lymphoplasmacytic infiltrate, and the presence of a B cell/plasma cell metagene in these tumors.

It is notable that the histologic subtype of medullary breast cancer (typical and atypical) was not found to be an independent predictor of overall survival. Recurrence is very rare more than 5 years post detection.

**IMAGING FINDINGS**

The imaging findings are nonspecific and are commonly described with characteristics similar to probably benign masses, causing delay in the diagnosis of these lesions. At mammography, masses are usually oval, round with partially circumscribed or microlobulated margins (Fig. 4 on page 9, Fig. 6 on page 11, Fig. 8 on page 13, Fig. 10 on page 15, Fig. 11 on page 15). Calcifications, commonly found in invasive ductal carcinoma NOS, are uncommon in medullary carcinomas.

Sonographically, the masses usually present with "benign" features, as oval morphology, circumscribed margins (Fig. 4 on page 9, Fig. 6 on page 11, Fig. 10 on page 15, Fig. 11 on page 15, Fig. 13 on page 18). Axillary assessment demonstrate cortical lymph node thickening, usually without metastatic cells at pathological analysis (Fig. 6 on page 11). More suspicious findings may also occur, like irregular shape and spiculated margins (Fig. 9 on page 14).

Iso or hypo T1 signal and iso or hyper T2 signal with well-defined contours is the most common finding in MR imaging. It may present rim enhancement and enhancing thin internal septations, with plateau or washout kinetic curves (Fig. 5 on page 10, Fig. 7 on page 12, Fig. 12 on page 16).

In summary, the imaging findings simulate benign lesions.

**DIFFERENTIAL DIAGNOSIS**

Many differential diagnosis may be cited, so it is important that the "medullary breast carcinoma" diagnosis should be given to the cases that satisfy all the pathological criteria cited above:
• The invasive ductal carcinoma NOS is indistinguishable by imaging methods and some authors prefer this nomenclature instead of "atypical medullary carcinoma", when the tumor does not satisfy all the "typical" criteria (syncytial growth pattern, microscopic circumscription, prominent lymphoplasmacytic infiltrate, absence of intraductal component or glandular differentiation, high grade pleomorphic nuclei), as it may lead to inappropriate conservative therapy;

• The large cell lymphoma may present as mostly circumscribed mass on mammogram/ultrasound (Fig. 14 on page 18) but is not microscopically circumscribed and lacks syncytial growth pattern. It may simulate medullary carcinoma because of the prominent lymphoplasmacytic infiltrate and absence of ducts or glands, but the immunohistochemistry study for lymphoid antigens and keratin can easily differentiate them;

• The fibroadenoma may have very similar imaging appearance - round circumscribed mass on mammogram and ultrasound (Fig. 15 on page 19);

• The phyllode tumor presents usually as a large round/microlobulated mass on mammogram, often presenting cystic spaces on ultrasound, which may be seen on medullary carcinoma (Fig. 8 on page 13, Fig. 16 on page 19);

• Metastatic extramammary tumors to breast are rare but may seem just like medullary carcinoma: round, circumscribed, non-calcified mass on mammogram and round hypoechoic indistinct/microlobulated mass on ultrasound. Usually the spread is hematogenic and the most common are melanoma, lung, lymphoma and müllerian (Fig. 17 on page 20).
Fig. 1: Slide of a medullary breast carcinoma showing syncytial appearance (circle) and lymphoplasmacytic infiltrate (arrow).

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**Fig. 2:** Higher magnification of the same medullary breast carcinoma shows high grade nuclei (circle) and the syncytial pattern (arrows).

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Fig. 3: Slide of another medullary breast carcinoma showing prominent lymphoplasmacytic infiltrate.

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Fig. 4: a. Craniocaudal mammography shows a round isodense microlobulated mass in the inner quadrant of the left breast. b. Ultrasound shows a solid hypoechoic microlobulated, taller-than-wide mass corresponding to the mammographic finding, assessed as BI-RADS 4. Core-needle biopsy showed triple negative medullary breast carcinoma.

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Fig. 5: MR imaging - T1WI (a); T2WI FS (b); T1WI C+ FS (c); subtraction (d) - of the same patient of figure 1, shows irregular and spiculated nodule in the lower quadrants of left breast, with heterogeneous internal contrast enhancement and plateau kinetic curve (not shown). Susceptibility artifact in the center of the nodule is due to biopsy marker.

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Fig. 6: a. Mediolateral oblique mammography shows a round isodense microlobulated mass in the projection of the lower quadrants of the right breast. b. Ultrasound shows a solid hypoechoic microlobulated mass corresponding to the mammographic finding, assessed as BI-RADS 4. Core-needle biopsy showed medullary breast carcinoma. c. Right axillary ultrasound shows an enlarged hypoechoic lymph node, without the central echogenic fatty hilum. Fine-needle aspiration showed reactive findings, with no metastatic cells.

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Fig. 7: MR imaging - T1WI (a); T2WI FS (b); T1WI C+ FS (c); subtraction (d) - of the same patient of figure 3, shows irregular mass in the lower outer quadrant of right breast, with heterogeneous enhancement and washout kinetic curve.

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Fig. 8: a. Craniocaudal mammography shows a round isodense partially circumscribed mass in the lateral quadrant of the left breast, corresponding to the palpable mass. b. Ultrasound shows a complex cyst corresponding to the mammographic finding, assessed as BI-RADS 4. Vacuum-assisted biopsy showed triple negative medullary breast carcinoma.

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Fig. 9: a. Mediolateral oblique mammography shows an irregular isodense spiculated mass in the lower quadrant of the right breast. b. Ultrasound shows a solid hypoechoic spiculated mass corresponding to the mammographic finding, assessed as BI-RADS 4c. Vacuum-assisted biopsy showed triple negative medullary breast carcinoma.

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Fig. 10: a. Craniocaudal mammography shows a round isodense obscured mass in right breast, corresponding to rapid growing palpable mass. b. Ultrasound shows a solid hypoechoic ill-defined mass corresponding to the mammographic finding, assessed as BI-RADS 4. Core-needle biopsy showed triple negative medullary breast carcinoma.

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Fig. 11: a. Craniocaudal mammography shows a round isodense obscured mass in left breast, corresponding to palpable mass. b. Ultrasound shows a solid hypoechoic, irregular, circumscribed mass corresponding to the mammographic finding, assessed as BI-RADS 4. Core-needle biopsy showed triple negative medullary breast carcinoma.

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Fig. 12: MR imaging - T1WI (a); T2WI FS (b); T1WI C+ FS (c); subtraction (d) - of the same patient of figure 8, shows irregular mass in the upper outer quadrant of left breast, with rim enhancement and washout kinetic curve.

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Fig. 13: a. Mediolateral oblique mammography shows a round isodense indistinct mass in left breast. b. Ultrasound shows a solid hypoechoic, irregular, microlobulated mass corresponding to the mammographic finding, assessed as BI-RADS 4. Core-needle biopsy showed medullary breast carcinoma.

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Fig. 14: Ultrasound shows a solid hypoechoic mostly circumscribed mass. Core-needle biopsy showed large B cell lymphoma (CD20+, BCL-2+, CD10+, high Ki67 index, CD3-).

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Fig. 15: Ultrasound shows a solid hypoechoic circumscribed mass, assessed as BI-RADS 4. Core-needle biopsy showed juvenile fibroadenoma.

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**Fig. 16:** a. Craniocaudal compression mammography shows a round isodense partially circumscribed mass in left breast. b. Ultrasound shows a solid hypoechoic circumscribed mass with small cystic spaces corresponding to the mammographic finding, assessed as BI-RADS 4. Core-needle biopsy showed phyllode tumor.
Fig. 17: a. Craniocaudal mammography shows a round isodense partially circumscribed mass in right breast. b. Ultrasound shows a solid hypoechoic circumscribed mass corresponding to the mammographic finding, assessed as BI-RADS 4. Core-needle biopsy showed metastatic adenosquamous carcinoma, with immunohistochemistry study compatible with lung as primary site. c. Ultrasound of other patient shows a solid hypoechoic circumscribed mass, assessed as BI-RADS 4. Core-needle biopsy showed metastatic micropapillary carcinoma, with immunohistochemistry study compatible with serous adenocarcinoma (müllerian primary site).

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Conclusion

The aim of this paper is to review the main radiological findings of medullary invasive carcinoma to aid in the differential diagnosis of breast lesions, thus avoiding delayed diagnosis due to their benign-appearance on imaging methods.
Personal information

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