

Multifocal Breast Cancer: Case Report

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Câncer de Mama Multifocal: Relato de Caso

Cáncer de Mama Multifocal: Relato de caso

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ABSTRACT

Introduction: Breast cancer is the neoplasm that most affects females, being the first cause of death by cancer in women. Breast carcinoma is a heterogeneous group of diseases. Individual cases differ from each other in morphology, phenotype and prognosis. Malignant breast pathologies can manifest as single, multifocal and/or multicentric tumors. The incidence of multifocal and multicentric tumors in breast cancer varies from 13% to 70%. **Case report:** Patient L.C., female, 65 years old, with a palpable nodule in the right breast in September 2015. The anatomopathological study of the nodule showed intraductal carcinoma. She underwent quadrantectomy, with anatomopathological examination that identified well-differentiated intracystic and invasive papillary carcinoma of the breast, associated with a cribriform and papillary intraductal component, with free sentinel lymph node and margins and immunohistochemistry compatible with triple negative profile. In February 2019, she presented two new lesions in contralateral breast, identified as invasive multifocal ductal carcinoma, with associated intraductal papilloma, and invasive ductal carcinoma, associated with an *in situ* intraductal component of the papillary, solid and cribriform types, with immunohistochemistry with different molecular profiles, being one lesion classified as luminal A and the other, hybrid luminal. **Conclusion:** This study reports a case of a patient who had neoplastic lesions in both breasts, at different times and with distinctive histological and immunohistochemical profiles. Thus, the rarity of the case and the relevance of the therapy aimed at specific targets are highlighted, since the patient presented lesions with different molecular profiles.

Key words: Breast Neoplasms; Carcinoma, Ductal, Breast; Mastectomy, Segmental; Chemotherapy, Adjuvant; Radiotherapy, Adjuvant.

RESUMO

Introdução: O câncer de mama é a neoplasia que mais acomete o sexo feminino, sendo a primeira causa de morte por câncer em mulheres. O carcinoma mamário representa um grupo heterogêneo de doenças. Casos individuais diferem uns dos outros na morfologia, fenótipo e prognóstico. As patologias malignas das mamas podem se manifestar como tumores unifocais, multifocais e/ou multicêntricos. A incidência de tumores multifocais e multicêntricos no câncer de mama varia de 13% a 70%. **Relato do caso:** Paciente L.C., sexo feminino, 65 anos, com relato de nódulo palpável em mama direita em setembro de 2015. O estudo anatomopatológico do nódulo mostrou carcinoma intraductal. Realizada quadrantectomia, com anatomopatológico que identificou carcinoma papilífero bem diferenciado intracístico e invasivo da mama, associado a componente intraductal cribriforme e papilar, com margens e linfonodo sentinela livres e imuno-histoquímica compatível com perfil triplo-negativo. Em fevereiro de 2019, apresentou duas novas lesões em mama contralateral, identificadas como carcinoma ductal invasivo multifocal com papiloma intraductal associado, e carcinoma ductal invasivo associado a componente intraductal *in situ* dos tipos papilar, sólido e cribriforme, com imuno-histoquímica com perfis moleculares distintos entre si, sendo uma lesão do tipo luminal A e a outra, luminal híbrido. **Conclusão:** Este estudo relata um caso de uma paciente que apresentou lesões neoplásicas em ambas as mamas, em tempos distintos e com perfis histológicos e imuno-histoquímicos diferentes. Dessa forma, destacam-se a raridade do caso e a relevância da terapia dirigida a alvos específicos, uma vez que a paciente apresentava lesões com perfis moleculares distintos.

Palavras-chave: Neoplasias da Mama; Carcinoma Ductal de Mama; Mastectomia Segmentar; Quimioterapia Adjuvante; Radioterapia Adjuvante.

RESUMEN

Introducción: El cáncer de mama es la neoplasia que más afecta a las mujeres, siendo la primera causa de muerte por cáncer en las mujeres. El carcinoma de mama representa un grupo heterogéneo de enfermedades. Los casos individuales diferencian entre sí en morfología, fenotipo y pronóstico. Las patologías mamarias malignas pueden manifestarse como tumores únicos, multifocales y/o multicéntricos. La incidencia de tumores multifocales y multicéntricos en el cáncer de mama varía del 13% al 70%. **Relato del caso:** Paciente L.C., mujer, 65 años, con un nódulo palpable en el seno derecho en septiembre de 2015. El estudio anatomopatológico de la lesión mostró carcinoma intraductal. La paciente se sometió a una cuadrantectomía, con un examen anatomopatológico que identificó un carcinoma papilar invasivo e intraquistico bien diferenciado de mama, asociado con un componente intraductal cribriforme y papilar, con ganglio linfático y márgenes libres e imuno-histoquímica compatible con perfil triple negativo. En febrero de 2019, presentó dos nuevas lesiones en el seno contralateral, identificadas como carcinoma ductal multifocal invasivo, con papiloma intraductal asociado y carcinoma ductal invasivo, asociado con un componente intraductal *in situ* de los tipos papilar, sólido y cribriforme, con imuno-histoquímica con diferentes perfiles moleculares, siendo una lesión del tipo luminal A y la otra, luminal híbrida. **Conclusión:** Este estudio reporta un caso de una paciente que tenía lesiones neoplásicas en ambos senos, en diferentes momentos y con diferentes perfiles histológicos e imuno-histoquímicos. Por lo tanto, se destaca la rareza del caso y la relevancia de la terapia dirigida a objetivos específicos, una vez que la paciente presentó lesiones con diferentes perfiles moleculares.

Palabras clave: Neoplasias de la Mama; Carcinoma Ductal de Mama; Mastectomía Segmentaria; Quimioterapia Adyuvante; Radioterapia Ayuvante.

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INTRODUCTION

Breast cancer is considered a public health problem, it is the malignant neoplasm with highest incidence in women worldwide¹. In Brazil, 66,280 new cases of breast cancer are expected for each year of the triennium 2020-2022, corresponding to an estimated risk of 61.61 new cases for each 100 thousand women². In 2018, 17,763 deaths occurred in the country because of breast cancer, 17,572 in females³.

Mammary carcinoma represents a heterogeneous group of diseases. The individual cases differ one another in morphology, phenotype, and prognosis. Through DNA microarray and analysis, five different genetic groups of the disease were described: luminal A, luminal B, positive human epidermal growth factor receptor 2 (HER-2), basal-like and breast common tumors. These tumor subtypes can also be identified with sufficient accuracy during the diagnostic routine through panel of immunohistochemical markers including antibodies to track estrogen receptors (ER), progesterone receptors (PR), overexpression of oncoprotein *c-erbB-2* (HER-2) and some myoepithelial markers⁴.

Breast malignant pathologies can manifest as unifocal, multifocal tumors (MF) and/or multicentric (MC). The incidence of MF and MC tumors in breast cancer varies from 13% to 70%⁵. MF and MC breast tumors were associated to adverse prognostic factors as advanced clinical staging, large tumor size and lymphovascular invasion. There is significant correlation between MF and MC breast cancers with increased rate of lymph node metastasis and axillary lymph node and higher staging N. Patients with MF and MC breast tumors have five-years lower survival and lower global survival when compared with patients with unifocal breast cancers⁶.

For practical purposes, the distinction between MF and MC tumors is based in topographic and histologic criteria. MF tumors are defined as involving only one quadrant and MC tumors when two or more quadrants are involved. Some authors also distinguish MF from MC tumors based in the assumption that MF breast cancers arise inside the same duct collecting system whereas MC breast cancers arise in duct collecting systems⁶. An exact radiological definition does not exist, but tumors are usually considered MF when the distance is less than or equal to 5 cm among the lesions and MC when the distance is more than 5 cm among lesions⁶.

The detection of MF and MC breast cancer has increased, given the advances in imaging techniques in recent years. Despite the increasing prevalence, the prognostic and management implications of MF breast carcinoma are uncertain⁷. Most of the guidelines

recommend the evaluation of biological markers only in the larger tumor foci. This approach may lead to sub-estimation of the molecular subtype and sub-treatment of patients⁸.

On January 2015, the New England Journal of Medicine published a study that evaluated the association of paclitaxel and adjuvant trastuzumab in patients with lesions of up to 3 cm and negative lymph nodes. So far, no studies addressing these group of patients existed because most of them were ineligible for pivotal trials with adjuvant trastuzumab. This study showed benefit of survival for this profile of patient⁹.

For hormone therapy in post-menopause women an Early Breast Cancer Trialists' Collaborative Group (EBCTCG)¹⁰ meta-analysis evaluated 31,920 women and compared the use of tamoxifen with aromatase inhibitors, concluding that the use of aromatase inhibitors for five years would be better than the use of tamoxifen for the same period. The study concluded still that the use of tamoxifen for two to three years followed by aromatase inhibitor for the same period or the use of aromatase inhibitor for two to three years are relatively similar, and both are more favorable than the use of tamoxifen for five years¹⁰.

The goal of this study is to report the case of a patient presenting neoplasm lesions in both breasts in different times and histological and immunohistological profiles, the rarity of the case and the relevance of therapies focused to specific targets since the patient had lesions with distinctive molecular profiles stand out.

The Institutional Review Board (IRB) of the University of Araraquara approved the present study, number CAAE: 32059020.8.0000.5383. The patient herself authorized the publication by signing the Informed Consent Form (ICF).

CASE REPORT

L.C., female, 65 years old, menarche at 12 years old, G2P2A0, hypertense, no other pathologies, personal and family cancer history, menopausal, reported palpable node in right breast in September 2015. At physical exam, presented 3 cm node in right medial upper quadrant, stiffened, and adhered to deep planes. Had mammography classified as Breast Imaging-Reporting and Data System (BI-RADS) 0 and fine needle aspiration biopsy (FNAB) that revealed cellular atypia, being referred to the Mastology Service of the Ambulatory of Women's Health in Araraquara, SP.

Core biopsy of the node revealed intraductal carcinoma. The patient underwent right quadrantectomy with biopsy of the sentinel lymph node. The anatomopathological

exam identified well differentiated papillary and invasive intracystic breast carcinoma associated to cribriform and papillary carcinoma with free margins and sentinel lymph node, measuring 2.7 x 2.0 x 1.8 cm and 1.9 cm distant from the skin, stage pT2 pN0. The immunohistochemical profile was negative for RE, RP and HER-2 and positivity of more than 90% for Ki-67, being classified as standard basal-like molecular subtype. There was no evidence of remote disease in the staging exams. The patient was referred to the Oncology Service of “*Santa Casa de Misericórdia*” of Araraquara, SP, for adjuvant treatment.

After six cycles of chemotherapy with adjuvant FAC regimen (doxorubicin 50 mg/m², associated to cyclophosphamide 500 mg/m² and 5-fluoracil 500 mg/m²) and adjuvant radiotherapy dose of 5,040 cGy in 28 FR plus boost with 1.000 cGy in 5 FR, the patient returns to the mastology ambulatory for post-treatment gynecologic follow up. On February 2019, presented mammography BI-RADS 0 and breasts ultrasound BI-RADS 4. New oval, lobulated node, larger axis parallel to the skin with 0.9 x 0.7 cm located in the transition of the medial upper quadrant with the retroareolar region of the left breast with 2 cm deep was identified. A core biopsy was requested and revealed T1N0MX invasive mammary carcinoma, a quadrantectomy with sentinel lymph node biopsy was performed later.

During the surgical act, two lesions were identified. For the larger lesion located in the central quadrant measuring 1.8 x 1.5 x 1.3 cm the anatomopathological evaluation classified the lesion as invasive ductal carcinoma MF with associated intraductal papilloma with free surgical margins of compromised neoplasm. The smallest lesion located in the union of the lateral quadrants measuring 1.1 x 1.0 x 0.8 cm was classified as invasive ductal carcinoma associated to an *in situ* intraductal component of the papillary, solid and cribriform types with free surgical margins and sentinel lymph node. Patient in stage mpT1c mpN0.

The immunohistochemical profile of the minor lesion was: RE+ 90%, RP+ 80%, HER-2-, P53+ 50%, Ki-67+ in less than 5%, with molecular standard subtype luminal A. For the larger tumor, the immunohistochemical profile was RE+ 60%, RP+ 80%, HER-2+++, P53 -, Ki-67+ 5%, with molecular pattern subtype hybrid luminal. The patient was referred again to the Oncology Service of “*Santa Casa de Misericórdia*” of Araraquara, SP, for adjuvant treatment with radiotherapy, chemotherapy and hormone therapy.

Chemotherapy TH regimen with 80 mg/m² paclitaxel weekly dosage associated trastuzumab for 12 weeks in initial dose of 8 mg/kg, followed by nine months of trastuzumab in monotherapy in maintenance dose of 6 mg/kg. It was decided to adopt hormone therapy

with tamoxifen and radiotherapy with 60 Gy in 30 FR. Currently, the patient is still in use of trastuzumab and tamoxifen.

Patient programmed to five-year hormone therapy. Based in the meta-analysis of EBCTCG, if in use of tamoxifen, the patient will switch to aromatase inhibitor until completing five-year hormone therapy.

DISCUSSION

Breast cancer is a common disease and can be classified as a problem of public health due to its high incidence. The intracystic papillary carcinoma corresponds to 0.5%-1% of all the breast carcinomas being considered a rare malignant tumor^{11,12} a lesion the patient presented initially.

There is a great variety of histological and molecular types of *in situ* and invasive breast carcinoma. The most common invasive histologic type is no special type invasive ductal carcinoma which represents from 70% to 80% of all the breast tumors¹. The patient in question presented this histological type later.

The immunohistochemical profile of the luminal types A and B usually have good prognosis and favorable response to endocrine therapy. Luminal A has better prognosis than luminal B¹³.

Basal-like breast cancers correspond to the group more investigated. These groups of tumors have differentiated genetic expression and immunohistochemical characteristics. Although there is no international consensus on the precise complement of markers that define basal-like breast cancer, most authors include absence of ER, PR and HER-2 oncogene, known as triple-negative breast cancer. Basal-like breast carcinomas are characterized by high mitotic rate and proliferative activity. They often present as a large tumor with distinct, geographic cellular zones composed of hyaline material, necrotic/ischemic tissue and collagen¹³.

When immunohistochemical HER-2 oncogene survey is positive, tumors are called HER-2 and present more aggressive biological profile. This happens in 10% of the breast tumors¹⁴. Hybrid luminal tumors are those where there is positivity for RP and/or RE associated to HER-2 positive¹⁴.

Analyzing the immunohistochemical profile of the case reported, it could be noticed that the first lesion presented by the patient was classified as triple negative. After four years when the patient presented lesion in the contralateral breast, MF tumor was observed and two lesions were different between themselves in relation to its molecular standard, one of the lesions presented standard luminal A and the other, luminal hybrid.

According to a study of Tolaney et al.⁹ the patient was submitted to association of paclitaxel and adjuvant trastuzumab. In this study, three-years invasive disease free-survival reached 98.7%⁹. In addition, according to data of EBCTCG meta-analysis, when tamoxifen is used for two years, the patient will switch to aromatase inhibitor until completing five years of hormone therapy.

CONCLUSION

This study reports the case of a patient who presented neoplastic lesions in both breasts in different times and distinctive histological and immunohistochemical profiles. The rarity of the case and the relevance of the therapy focused to specific targets since the patient's lesions had differentiated molecular profiles are highlighted.

CONTRIBUTIONS

All the authors contributed equally for the conception and/or design of the study, collection, analysis and interpretation of the data, wording, and critical review. The authors approved the final version to be published.

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DECLARATION OF CONFLICT OF INTERETS

There is no conflict of interests to declare.

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