

Medullary breast carcinoma: anatomico-radiological correlation*

Carcinoma medular da mama: correlação anatomo-radiológica

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Abstract **OBJECTIVE:** To evaluate radiological findings in patients submitted to surgical treatment for medullary breast cancer at Instituto Nacional de Câncer (INCA), Rio de Janeiro, RJ, Brazil, correlating them with histological results. **MATERIALS AND METHODS:** A retrospective descriptive study was developed with patients submitted to surgery at INCA, in the period from January 1997 to December 2006, for identifying the presence of medullary breast carcinoma and analyzing radiological findings. **RESULTS:** Among 21,287 patients diagnosed with carcinoma, 76 (0.357%) had typical medullary breast carcinoma. The age range of these patients was 32–81 years (mean = 59.1 years). Mammography demonstrated lesions in 19 of these patients, 17 (89.5%) of them with masses, and 2 with focal asymmetry. Among the patients with masses, 15 (88.1%) presented with high density and 2 (11.9%) with isodensity. Twelve patients presented sonographic findings, 11 (91.6%) of them with hypoechoic masses, and one with an anechoic mass with areas of cystic degeneration. **CONCLUSION:** Nodular mass was the predominant radiological finding (89.5%), 88.1% of them corresponding to masses with high density and circumscribed margins. Despite the radiological characteristics of benignity, a solid, fast-growing, highly dense mass with circumscribed margins should be further investigated to confirm the diagnosis. **Keywords:** Medullary breast cancer; Radiological findings; Diagnosis.

Resumo **OBJETIVO:** Avaliar as características radiológicas do câncer de mama medular em pacientes submetidas a tratamento cirúrgico no Instituto Nacional de Câncer (INCA) – Ministério da Saúde, Rio de Janeiro, RJ, correlacionando os achados com estudo histopatológico. **MATERIAIS E MÉTODOS:** Foi realizado estudo descritivo retrospectivo de mulheres submetidas a tratamento cirúrgico no INCA, no período de janeiro de 1997 a dezembro de 2006, para identificação das pacientes com carcinoma medular e análise dos achados radiológicos. **RESULTADOS:** Foram identificadas 21.287 pacientes com diagnóstico de carcinoma neste período, sendo 76 pacientes com diagnóstico de carcinoma medular típico (0,357%). Nessas pacientes selecionadas, a idade média foi de 51,9 anos (32 a 81 anos). Dezenove pacientes apresentavam lesão na mamografia, sendo 17 (89,5%) nódulos e 2 assimetrias focais (10,5%). Entre as pacientes com nódulo, 15 (88,1%) apresentavam alta densidade e 2 eram isodensos (11,9%). Doze pacientes apresentavam achados ultrasonográficos e, destas, 11 (91,6%) apresentavam nódulos hipoeecóicos. Foi observada uma paciente com nódulo anecóico com áreas de degeneração cística. **CONCLUSÃO:** O nódulo foi o achado radiológico dominante (89,5%), dos quais 88,1% apresentaram nódulos com alta densidade e margens circunscritas. Apesar das características radiológicas de benignidade, um nódulo com alta densidade, sólido, margens circunscritas e crescimento rápido deve ser investigado para confirmar o diagnóstico. **Unitermos:** Câncer de mama medular; Achados radiológicos; Diagnóstico.

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INTRODUCTION

In Brazil, breast cancer is the most frequent malignant neoplasm among women. According to Instituto Nacional de Câncer (INCA), the city of Rio de Janeiro presents the highest incidence, with Porto Alegre in the second place⁽¹⁾.

Reduction in the mortality rate depends on the early detection and an appropriate therapeutic planning⁽¹⁾. Mammography plays a significant role in the diagnosis of

breast diseases, and is considered as the golden-standard for screening of minimal breast lesions^(2,3). The utilization of mammography as a screening method for women with > 40 years of age is defined in the United States of America⁽⁴⁻⁶⁾. In Brazil, this method is recommended for women aged between 50 and 60 years, according to the INCA consensus on breast cancer⁽¹⁻⁷⁾. In Canada and United Kingdom mammography is recommended for asymptomatic women from 50 years of age⁽⁸⁻¹¹⁾.

Mammography is highly sensitive for detecting clinically occult breast cancer. A review of clinical studies evaluating the performance of this method has demonstrated that its sensitivity ranged between 71% and 98% for yearly screening mammography^(1,10-16). However, many lesions considered suspicious and indicating the necessity of histopathological study correspond to benign alterations. In the United States of America, the positive predictive value of biopsies performed because of mammographic findings, i.e., the proportion of malignant lesions diagnosed in a total of biopsies performed ranges between 15% and 40%. Both cost and morbidity of interventions for diagnosis of these lesions are taken into consideration for confirming the utilization of mammography as screening for breast cancer^(12,13,15-19).

Medullary breast carcinoma, currently considered as basal carcinoma, corresponds to a subgroup of malignant tumors most frequently detected as an "interval cancer" in comparison with tumors diagnosed in the mammographic screening⁽²⁰⁻²⁶⁾. This tumor represents 2% to 7% of breast cancers and is most frequently found in young women⁽²⁷⁻³⁰⁾.

One of the difficulties observed in the analysis of the images is the absence of pathognomonic features in a great number of diagnosed lesions. Knutzen and Gisvold⁽⁹⁾ have developed a study about the likelihood of malignancy in several categories of non-palpable lesions detected by mammography, with the objective of defining the necessity of follow-up or biopsy for these lesions. The authors have observed that if morphological criteria were taken into consideration in the evaluation of these lesions, the rate of malignant lesions submitted to biopsy could reach 40%. Few studies in the literature have evaluated this type of breast cancer.

The relevance of the investigation of these lesions as well as their imaginological features increases, considering that many times medullary breast cancer presents morphologically like a benign lesion, and that this histological type of lesion is associated with high-risk patients. The present study was aimed at evaluating mammographic and sonographic findings of medullary breast carcinoma.

MATERIALS AND METHODS

In the period between January 1997 and December 2006, 21,287 patients were diagnosed with breast carcinoma at INCA-III. Among these patients, 76 (0.357%) presented a diagnosis of medullary carcinoma. Out of these 76 patients, those who had not a pure medullary carcinoma were excluded ($n = 4$), as well as those whose previous radiological studies could not be found ($n = 53$). Among the patients without previous radiological studies ($n = 53$), 20 had radiological reports with no image, and 33 had neither radiological report nor image, like one patient with a large ulcerated blastoma referred for investigation with no previous radiological study of the involved breast.

Seventy-six records and radiological studies were retrospectively evaluated, and 19 patients diagnosed with typical medullary carcinoma and with preoperative radiological study were included in the present study. Radiological findings, BI-RADS[®] category, tumor size at diagnosis and patient's age were analyzed.

The present study was approved by the INCA Council of Ethics in Research under the number 041/08.

RESULTS

Nineteen patients were included because they had preoperative radiological imaging studies. The mean age of these selected patients was 51.9 years (32 to 81 years). All of them had their lesions detected by mammography with the following findings: 17 masses (89.5%) and two focal asymmetries (10.5%). Among the masses, 15 (88.2%) presented high density and two (11.9%) were isodense. Twelve patients presented sonographic findings, 11 (91.6%) of them with hypoechoic masses. Anechoic mass with areas of cystic degeneration was found in one patient.

Lobulated margin was most frequently observed in 11 patients (64.7%), and microlobulated margins in 9 (52.9%). Mean tumor size was 27.2 mm (14–50 mm). Most frequently, the tumors were classified as BI-RADS category IV (52.7% of the patients).

The prevalent morphological aspect was mass, in 89.5% of the patients, with a

lobular shape in 11 (64.7%) and irregular shape in 6 (35.3%) patients. Microlobulated margin was found in 9 patients (52.9%), obscured margin in 4 (23.5%), speculate in 2 (11.8%) and indistinct in 2 patients (11.8%). High density was observed in 15 patients (88.1%), while isodensity was found in only 2 patients (11.8%). Architectural distortion and microcalcifications were not observed. Two patients presented "focal asymmetry" as a sole radiological alteration.

DISCUSSION

Breast cancer is a multifactorial disease, and in most of cases is considered as being of epithelial origin, and is divided into an array of histological types whose behavior varies according to several factors such as degree of histological differentiation, subtype, etc. Some histological types of breast tumors such as medullary carcinoma, mucinous carcinoma and tubular carcinoma are associated with a better prognosis. Although rarely reported, other malignant tumors such as lymphomas, sarcomas and melanomas can also occur in the breast⁽²²⁾.

Among the malignant tumors of the breast, infiltrating ductal carcinoma is the most frequently found neoplasm. Prognosis is unfavorable in cases of isolated lesions, contrarily to the cases with association of other histological types of tumors such as tubular, invasive cribriform, cystic adenoid, mucinous and papillary, especially in cases where these tumors constitute more than 90% of the mass.

Infiltrating ductal carcinoma and ductal carcinoma in situ represent 85% of malignant breast tumors⁽²⁰⁾. Typically, infiltrating ductal carcinoma presents as a spiculate, irregular or focal asymmetrical mass, while ductal carcinoma in situ presents as pleomorphic or linear microcalcifications⁽²²⁾.

Medullary carcinoma represents rare tumor of intermediate prognosis^(20,24), with an incidence ranging from 1% to 7% of all cases of breast cancer⁽²²⁾. In the present casuistic, medullary breast carcinomas represented 0.357% of the total number of breast cancers. This finding may be related to the high rate of cases diagnosed at INCA, considering that this institution is a

reference center for treatment of breast cancer in Rio de Janeiro. In the general population the age range of patients diagnosed with breast cancer is between 45 and 52 years. Mean age of patients in the present study was 51.9 years, similarly to data reported in the literature reviewed^(20,24,27-29). The World Health Organization describes this tumor as “a well-circumscribed carcinoma composed of poorly differentiated cells with scant

stroma and prominent lymphoid infiltration”^(23,25,29-32) (Figure 1).

It is a tumor with well-circumscribed margins with high histological and nuclear degree, composed of poorly differentiated cells, that does not present a tubular or glandular structure, but rather a prominent lymphoplasmocytary infiltrate with nuclear pleomorphism and high proliferation⁽³²⁾. The tumor cells are large, with macronuclei, syncytially arranged, with moderate,

abundant and diffuse inflammatory lymphoplasmocytary infiltrate among cell clusters. Clinically, the tumor is well-delimited, and at mammography is typically well-circumscribed (Figures 2 and 3), and may be confused with a benign lesion⁽³²⁻³⁴⁾.

Nodular, lobulated lesion with microlobulated margins was the radiological aspect most frequently found in the present casuistic, likewise in several studies in the literature^(20,23,24,28,29,32,33) (Figures 2 and 3). In the present study, high density was a preponderant finding similarly to the literature⁽³⁵⁾. The BI-RADS IV was the most frequently observed category, in agreement with the worldwide literature, although category II has also been found in the present study^(19,22,26,31). At ultrasonography, the lesion is homogeneous and hypoechoic, or hypoechoic with intermediate heterogeneity, according to the present casuistic^(26,27) (Figures 2 and 3). Macroscopically, well-delimited margins and soft consistency are observed. Hemorrhage and necrosis are frequent findings. Fibrotic stroma is scarce. These tumors are frequently associated with the BRCA1 and BRCA2 genes. They are estrogen-receptors and progesterone negative^(36,37). Despite the presence of biological markers compatible with

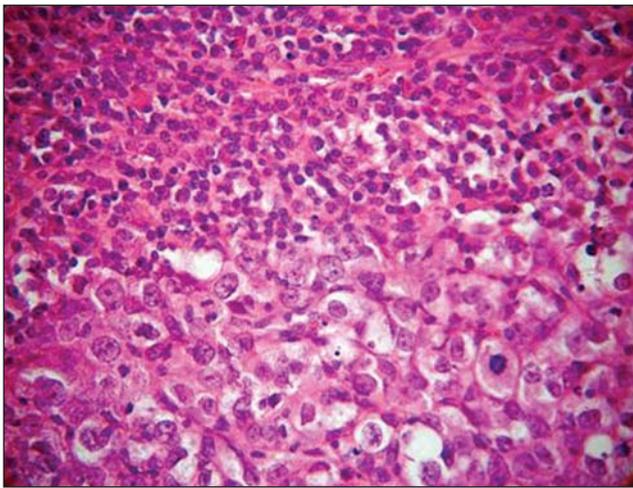


Figure 1. A well-defined lesion constituted by a sheet-shaped layer of tumor cells separated by a small amount of connective tissue. A peripheral, dense lymphoplasmocytary infiltrate is observed.

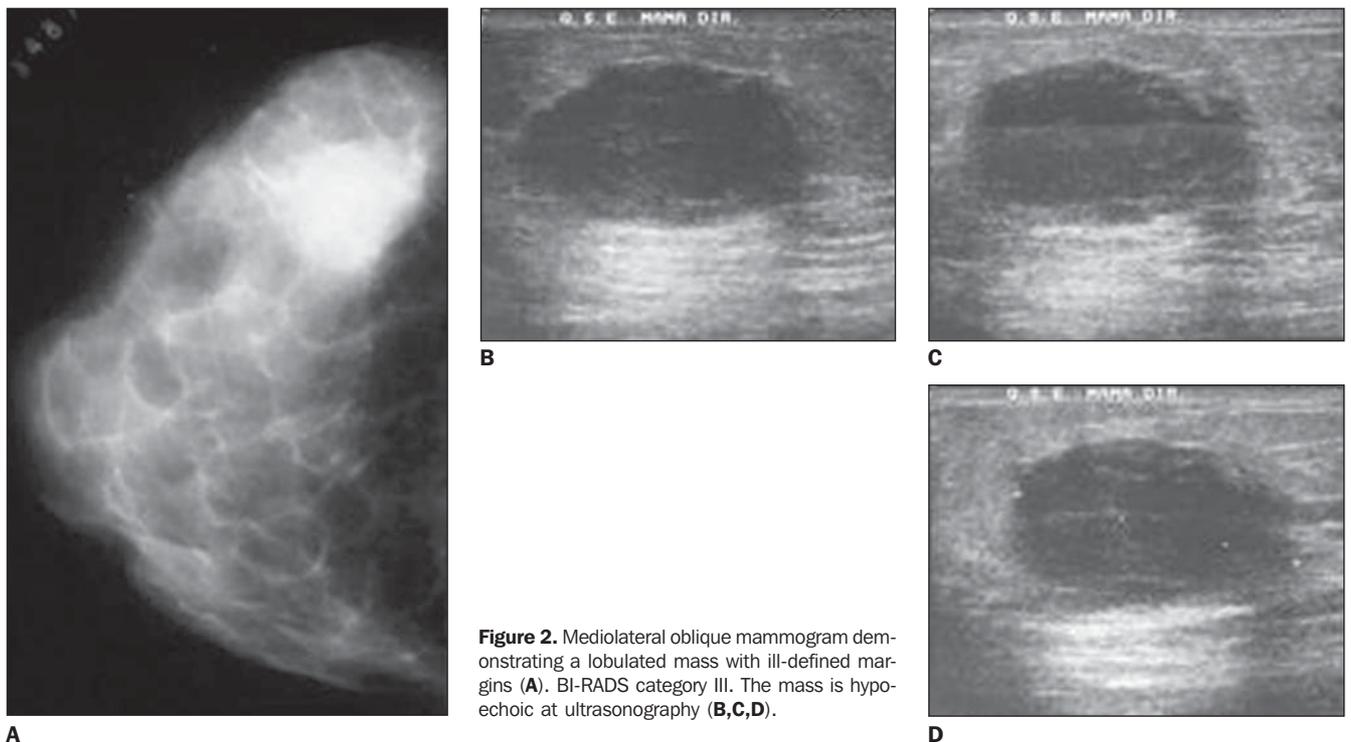


Figure 2. Mediolateral oblique mammogram demonstrating a lobulated mass with ill-defined margins (A). BI-RADS category III. The mass is hypoechoic at ultrasonography (B,C,D).

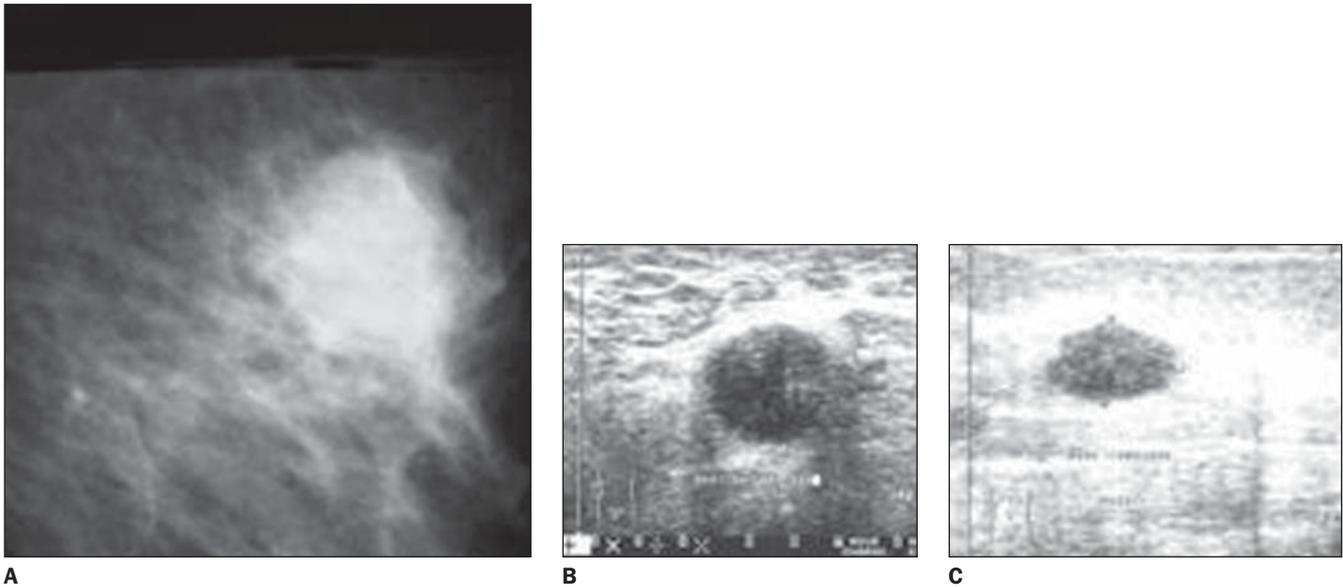


Figure 3. Mammography demonstrating an irregular mass with obscured margins (A). BI-RADS category IV. The mass is hypoechoic at ultrasonography (B,C).

high aggressiveness, the pure medullary carcinoma presents a favorable prognosis. Despite the questioning of some authors^(26, 35,36), the ten-year survival rate ranges between 50% and 90%. The differences in the diagnostic criteria can justify the characteristics of the tumor prognosis. Additionally, according to some authors, the incidence of this tumor is higher in younger women (35 years)⁽²¹⁾. Clinically, these tumors are characterized by fast growth and frequently manifest as a palpable mass⁽²⁹⁾.

According to Korsching et al.⁽²⁸⁾, medullary carcinoma is included in a subgroup of invasive breast tumors called basal carcinomas which have been focused by breast cancer research as a result of the introduction of the global gene expression analysis. This subgroup is characterized by a distinctive biology generating many questions regarding pathogenesis, chemosensitivity and optimal clinical management of these tumors. Basal carcinoma is usually estrogen-receptor, progesterone- and HER2-negative, but they are not identical to the triple negative tumors^(36,37):

Bertucci et al.⁽³⁷⁾ refer to medullary breast cancer as a rare but enigmatic tumor. Little is known about the molecular alterations associated with medullary carcinoma^(21,37). When compared with medullary carcinoma, basal-like ductal carcinoma overexpress genes involved in muscular differentiation, suggesting that medullary

carcinoma is a distinct subgroup of basal cancer with a limited myoepithelial differentiation^(28,29,31,36). In addition, Bertucci et al. report an overexpression of a series of genes located in the chromosomal regions 12p 13 and 6p 21, which are known by their pluripotential genes content⁽³⁷⁾. The majority of patients are young and asymptomatic, and can be investigated by mammography, especially if associated with clinical examination and ultrasonography.

Few studies have evaluated this type of breast cancer. Considering that, many times, medullary carcinoma presents a morphological aspect of benign lesion and that this histological type of tumor is associated with high-risk women, the radiological evaluation plays a relevant role in the diagnosis of this type of lesion.

Considering the increase in the number of cases in young women, the insidious onset and fast-growth of the disease, the increasing significance of the investigation of basal cancer, dubious prognosis, and the radiological aspect of medullary cancer similar to that of a benign lesion (false-negative), thus delaying the early diagnosis, imaginological findings are essential in the determination of the diagnosis. This study demonstrated that the findings in the sample evaluated were nodular lesion and asymmetry. In the nodular lesions, the radiological characteristics most frequently found were increased density, lobular

shape, circumscribed margins and size up to 20 mm. The relevance of this study is in the increasing correlation observed between the presence of medullary carcinoma and BRCA1, and less frequently, BRCA2 gene mutation⁽²⁶⁾ and moreover, because of the radiological aspect of these lesions which may be interpreted as benign tumors and therefore, false-negative^(25-28,34-37).

The present study was limited by rarity of this tumor and, above all, because of the radiological data loss.

CONCLUSION

In spite of being a fairly rare type of tumor, medullary breast carcinoma is found in high-risk women. Morphological characteristics on imaginological studies should be taken into consideration and the hypothesis of medullary carcinoma should not be ruled out, considering that these lesions should be investigated by histopathological study and not by radiological follow-up.

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