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Histopathological and immunohistochemical diagnosis of advanced medullary breast carcinoma: case report

Diagnóstico histopatológico e imuno-histoquímico de carcinoma medular avançado de mama: relato de caso

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Ricardo Barbosa Lima
Graduando em Odontologia
Universidade Federal de Sergipe (UFS) - Campus Prof. Antônio Garcia Filho
Avenida Governador Marcelo Déda, São José, Lagarto - SE, Brasil, 49400-000
E-mail: ricardoblima@academico.ufs.br

Simone Yuriko Kameo
Doutora em Enfermagem Fundamental
Universidade Federal de Sergipe (UFS) - Campus Prof. Antônio Garcia Filho
Avenida Governador Marcelo Déda, São José, Lagarto - SE, Brasil, 49400-000
E-mail: simonekameo@hotmail.com

Andressa Cabral Vassilievitch
Graduanda em Medicina
Universidade Federal de Sergipe (UFS) - Campus Prof. Antônio Garcia Filho
Endereço: Avenida Governador Marcelo Déda, São José, Lagarto - SE, Brasil, 49400-000
E-mail: andressavassi98@gmail.com

Tiago Vasconcelos Fonseca
Graduando em Medicina
Universidade Federal de Sergipe (UFS) - Campus Prof. Antônio Garcia Filho
Avenida Governador Marcelo Déda, São José, Lagarto - SE, Brasil, 49400-000E-mail:
tiagovasconfonseca@gmail.com

Bruno Ferreira Amorim
Graduando em Medicina
Universidade Federal de Sergipe (UFS) - Campus Prof. Antônio Garcia Filho
Avenida Governador Marcelo Déda, São José, Lagarto - SE, Brasil, 49400-000
E-mail: brunofamorim@hotmail.com.br

Jéssica dos Santos Costa
Graduanda em Enfermagem
Universidade Federal de Sergipe (UFS) - Campus Prof. Antônio Garcia Filho
Avenida Governador Marcelo Déda, São José, Lagarto - SE, Brasil, 49400-000
jessicas_costa@outlook.com

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Glebson Moura Silva
Doutor em Educação
Universidade Federal de Sergipe (UFS) - Campus Prof. Antônio Garcia Filho
Avenida Governador Marcelo Déda, São José, Lagarto - SE, Brasil, 49400-000
E-mail: glebsonmoura@yahoo.com.br

Namie Okino Sawada
Livre-docente/Doutora em Enfermagem
Universidade Federal de Alfenas (UNIFAL) - Escola de Enfermagem
Rua Gabriel Monteiro da Silva, Centro, Alfenas - MG, Brasil, 37130-001
E-mail: namie.sawada@unifal-mg.edu.br

ABSTRACT
Medullary breast carcinoma (CMM) is a rare histological variant of breast cancer. It is a malignant and invasive tumor often observed in young women with large tumor lesions. There are still controversies about survival rates, about the histological pattern and prognosis of the CMM. The aim of this case report is to explain the histopathological diagnosis of a patient diagnosed with advanced medullary breast carcinoma, with emphasis on immunohistochemical findings. In a private oncology service, a 57-year-old woman came for treatment. At the initial clinical examination, it was observed that it presented a necrosis-like right breast tumor, firm on palpation and painful symptoms. An incisional lesion biopsy was performed and the cellular and molecular pattern traced. The report found the presence of advanced medullary breast carcinoma, necrotic malignant lesion in stage IV with bone and renal metastasis. The morphological pattern was composed of large epithelioid cells with pleomorphic and often multinucleated nuclei, with irregular chromatin distribution and atypical mitosis figures. The observed molecular pattern was focal expression of cytokeratin AE1 / AE3, smooth muscle actin, desmin, p63 and CD68. Additionally, the expressions of estrogen receptors, CD34, S-100 and CK8/18 were not observed. The tumor was unresectable and chemotherapy and radiotherapy was chosen to intervene in the disease progression, however, the patient died due to clinical complications resulting from these treatments associated with poor general health. CMM is a rare neoplasm and immunohistochemical studies may contribute to understand how morphological and molecular patterns may influence its clinical presentation.

Keywords: Delayed Diagnosis, Breast Neoplasms, Medullary Carcinoma, Medical Oncology, Prognosis

RESUMO
O carcinoma medular de mama (CMM) é uma variante histológica rara dos cânceres de mama. Trata-se um tumor maligno e de caráter invasivo, frequentemente observado em mulheres jovens como lesões tumorais de grande tamanho. Ainda existem controvérsias sobre as taxas de sobrevida, sobre o padrão histológico e prognóstico do CMM. O objetivo deste relato de caso é explanar o diagnóstico histopatológico de uma paciente diagnosticada com carcinoma medular de mama em estágio avançado, com ênfase nos achados imuno-histoquímicos. Em um serviço privado de oncologia, uma paciente de 57 anos compareceu em busca de tratamento. No exame clínico inicial, foi possível observar que a mesma apresentava um tumor na mama direita com aspecto de necrose, firme à palpação e com sintomatologia dolorosa. Foi realizada a biópsia incisional de lesão e traçado o padrão

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celular e molecular. O laudo constatou a presença de carcinoma medular avançado de mama, uma lesão maligna e necrótica em estágio IV, apresentando metástase óssea e renal. O padrão morfológico era composto de células grandes e epitelióides, com núcleos pleomórficos e frequentemente multinucleadas, com distribuição cromatínica irregular e figuras de mitose atípicas. O padrão molecular observado foi expressão focal das citoqueratinas AE1/AE3, actina de músculo liso, desmina, p63 e de CD68. Além disso, não foram observadas as expressões de receptores de estrogênio, CD34, S-100 e CK8/18. O tumor era irressecável e optou-se pelo tratamento quimioterápico e radioterápico para intervir na doença, entretanto, a paciente evoluiu ao óbito devido à complicações clínicas decorrentes destes tratamentos associadas ao estado geral de saúde frágil. CMM é uma neoplasia rara e os estudos imunohistoquímicos podem contribuir para compreender como os padrões morfológicos e moleculares podem influenciar na sua apresentação clínica.

Palavras-chave: Diagnóstico tardio, Neoplasias da mama, Carcinoma medular, Oncologia, Prognóstico

1 INTRODUCTION

Breast cancer (BC) is among the most common types of cancer, being the most common in women worldwide. In Brazil, the estimated incidence for 2018 and 2019 was 59.700 new cases of BC[1]. Among the subtypes of breast cancer, medullary breast carcinoma (MBC), first described in 1949, is a histological variant few observed in population studies, with incidence ranging from 1% to 5% of cases[2-3].

Clinically, MBC is a highly invasive malignant tumor, often seen in young women (<40 years) as large tumor lesions. There are still controversies about survival rates, the histological pattern and prognosis of this cancer. Additionally, it is necessary to differentiate it from fibroadenoma and invasive ductal carcinoma of the breast (IDC), since the three entities may have similar radiographic and macroscopic characteristics[2-4].

Clinical and histopathological features are essential for the diagnosis, prognosis and treatment of MBC, including differentiation into typical and atypical patterns. MBC is a fast growing neoplasm entity, requiring diagnostic and interventional approaches in a short period of time. Nevertheless, few scientific publications about this variant are available, especially compared to information available on other types of BC[5-6].

In this context, the aim of this case report is to explain the histopathological diagnosis of a patient diagnosed with advanced medullary breast carcinoma, with emphasis on immunohistochemical findings.

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2 THE CASE REPORT

This case report refers to a 57-year-old female farmer, melanoderma, native and resident in Arapiraca (Alagoas, AL, Brazil), with incomplete primary education. The patient was admitted to a private oncology service in the same municipality, seeking treatment for a tumor located in the right breast. She reported that her motivation was pain and difficulty to walk because of the weight of the tumor. Also, there is no family history for breast cancer.

The patient was evaluated by the service team and, in fact, had a necrotic, grayish right breast tumor, firm to palpation, with painful symptoms. Histopathological diagnosis with immunohistochemical exams was requested and performed by means of material collected by incisional biopsy of the lesion. When questioned about, she reported that she does not remember when she realized the progress of the tumor and could not justify why she did not seek the oncology service before (figures 1 and 2).

Additionally, during all stages developed in the oncology service, the patient was shy due to her current health condition. Reported financial difficulties to feed and move to that service. In general, signs of malnutrition and dehydration, poor personal hygiene, and poor general health could be observed.

Figure 1 - The tumor in right breast seen from the patient's right side

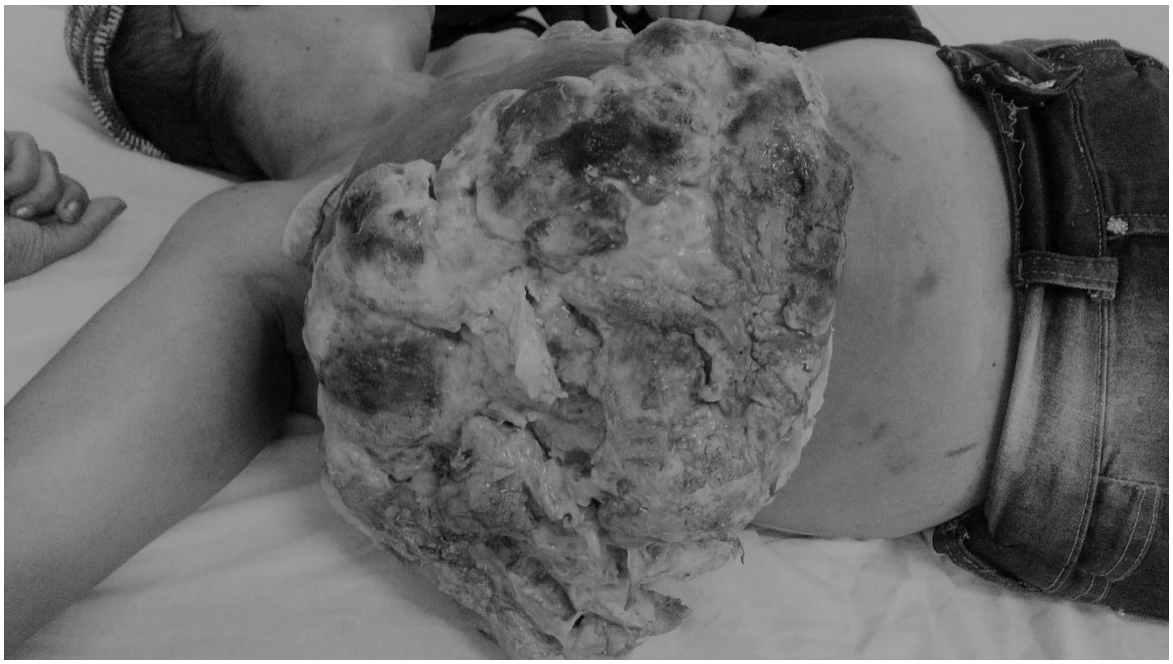

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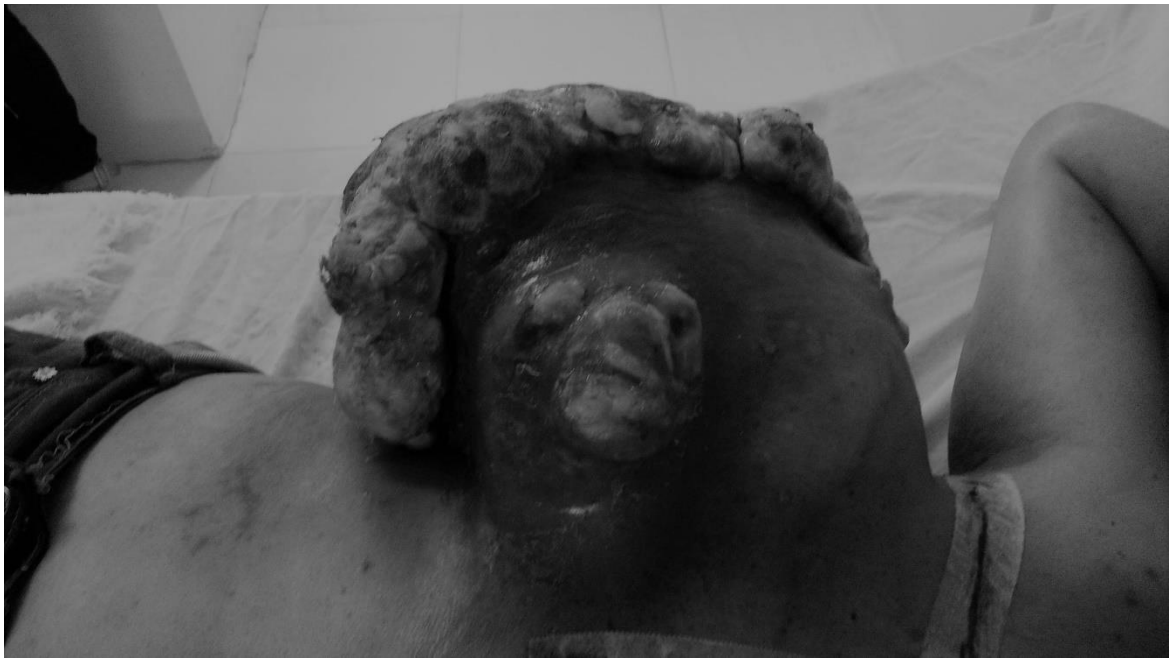
Figure 2 - The tumor in right breast seen from the patient's left side.



3 HISTOPATHOLOGICAL DIAGNOSIS AND IMMUNOHISTOCHEMICAL PROFILE

The histopathological examination of the lesion was requested by the oncology team and performed by incisional biopsy. The collected material was stored in an appropriate container and sent to a laboratory specialized in human pathology for analysis. The exam indicated the presence of a metaplastic carcinoma with mesenchymal and cellular chondroid differentiation. The morphological pattern was composed of large and epithelioid cells, with pleomorphic nuclei, often multinucleated, with irregular chromatin distribution (solid cell arrangements with necrotic zones) and with atypical mitosis figures in 13/10 HPF (high-power fields). The immunohistochemical profile observed were synthesized and presented (table 1).

Antibody	Clone	Expression
AE1 + AE3	AE1/AE3	Focal positivity
AML / 1A4	1A4	Focal positivity
CD34	QBEned 10	Focal negativity (positive to internal control)
CD68	KP1	Focal positivity

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		(numerous histiocytes and multinucleated cells)
CK8/18	5D3	Focal negativity (positive to internal control)
Desmin	D33	Focal positivity
P63	DAK-p63	Focal positivity
S-100 protein	Polyclonal	Focal negativity (positive to internal control)
Estrogen receptor	EP1	Focal negativity (positive to internal control)

It is a typical medullary carcinoma of the right breast, stage IV and metastatic with bone and renal metastasis. It is an advanced necrotic malignant lesion, surgically inoperable. The patient underwent four cycles of chemotherapy with the combination of four antineoplastic agents at conventional doses: paclitaxel associated with FAC (5-fluorouracil + doxorubicin hydrochloride + cyclophosphamide).

At the end of all cycles, no clinical signs of improvement were observed. Thus, oncology team decided to perform a new combination of antineoplastic agents: cisplatin associated with gemcitabine hydrochloride. Concomitantly, the patient underwent radiotherapy treatment to enhance the fight against the tumor. However, after the first cycle of the new chemotherapy, the patient had severe clinical complications. Both treatments had to be discontinued for clinical improvement, although the cause of these clinical complications has not been determined and may have been caused by single or combined therapies. Despite the efforts, the patient was fragile and died.

4 DISCUSSION

The incidence of MBC tends to increase in women under 50 years and may present a significant portion of involvement in very young women (<35 years) diagnosed with BC. For some authors, the typical histological pattern may be associated with a more favorable prognosis, although studies comparing survival rates do not support such conclusions[4-5].

MBC is a frequently triple-negative breast tumor associated with bad prognosis. In the present case, the immunohistochemical study revealed absence of estrogen receptors (ER), one of the components of the triple negative diagnosis, but data about progesterone receptor (PR) and human epidermal growth factor receptor-type 2 (HER2) were not

available in immunohistochemical analysis. However, with regard to MBC, a better prognosis can be observed in triple-negative results when compared to other cancers, such as IDC[4-5].

The bad prognosis related to the absence of RE in MBC cases may be justified by the expected poor performance of hormone suppression therapies in these patients, which limits the therapeutic options for this neoplasia[2-3]. Comparing with IDC, although some studies report a higher proportion of negative outcomes for RE in MBC, the prognosis of MBC may be better when both are triple-negative. In addition, there are no established clinical guidelines and protocols for adjuvant chemotherapy for MBC, although the reduction of N0 TN tumors larger than two centimeters can be observed[7-9].

Of the patients diagnosed with MBC, there is a tendency of metastasis after five years in more than half of those affected, with high recurrence rates. Lymphatic metastasis is uncommon in this variant of breast cancer. Considering the immunohistochemical findings investigated in the diagnosis of MBC, the scientific literature reports that positive results for p63, smooth muscle actin and cytokeratins AE1 / AE2 are frequent. On the other hand, negative results for estrogen and progesterone receptors, CD34 and desmin are expected. These findings correspond to those observed in the immunohistochemical profile of the reported case[6,9-10].

Histological and immunohistochemical variations are associated with the risk of recurrence of MBC, since they directly affect the choice and success of chemotherapy to be applied. Additionally, most patients require invasive surgical procedures, such as total mastectomies. In the case reported, tumor size made it unresectable, limiting therapeutic approaches[6,9-10].

Although some immunohistochemical studies with MBC have been performed, it is not yet possible to conclude an immunohistochemical pattern, since the expression of several markers is not completely homogeneous in diagnostic studies. The phenotypic diversity of MBC is related to a varied gene expression. Within these variations, it is suggested to identify MBC subtypes as a function of molecular expression observed in breast cancer diagnostic studies. Subtypes may be associated with various prognoses, biological responses, degrees of morphological differentiation and treatments[10-11].

In addition, pathogenic *BRCA1* mutations should be investigated in patients diagnosed with MBC, regardless of the triple-negative diagnosis. More than 16% of BRCA1-associated breast cancers are medullary histological subtype. We should consider that

changes in ER, PR and HER2 are not necessarily associated with germline mutations in *BRCA1 / 2* in patients who develop some type of breast cancer, MBC or not[12-15]. In fact, *BRC1*-associated MBC are often negative for RE, a fact that generates interest in the histopathological studies on this breast cancer. Thus, understanding mutations in this gene may help to understand the various clinical aspects of MBC[9,15].

5 CONCLUSION

The histopathological analyzes and immunohistochemical exams allow the diagnosis of several neoplasms and help to understand the prognosis factors and the search for more efficient therapies for each biological behavior of various histotypes of tumors, including MBC. Thus, advances in early diagnosis of breast cancer may be associated with more favorable outcomes, unlike those reported in this clinical case.

CONTRIBUTION OF AUTHORS

All authors referred to in this manuscript meet, without exception, the criteria adopted for the determination of authorship and contributed substantially to its elaboration.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest of any kind in all content produced and inserted in this manuscript.

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