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Relationship between age and progesterone receptor expression with presence of central nervous system metastases in breast invasive ductal carcinoma

Relação entre idade e expressão do receptor de progesterona com presença de metástases no sistema nervoso central no carcinoma ductal invasivo da mama

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ABSTRACT

Introduction: Breast invasive carcinoma of no special type (NST) is characterized by great morphological heterogeneity, and accounts for about 70%-80% of malignant breast tumors. The main prognostic factors are tumor size, degree of differentiation, and status of axillary lymph nodes. NST represents 15%-18% of central nervous system metastases (CNSm), and generally the response to systemic treatment/chemotherapy is unsatisfactory. **Objective:** To estimate the association between clinical and pathological findings of NST with CNSm. **Method:** Clinical data of 171 specimens of lumpectomy/mastectomy with axillary dissection in NST were evaluated, as well as the following pathological variables: tumor size, histological grade, nodal status, expression of estrogen (ER) and progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER-2/neu) oncogene (c-erb B2), and presence of CNSm. The cases of CNSm in NST underwent resection, and the primary site was identified by immunohistochemistry. **Results:** The prevalence of CNSm was 9.4% ($n = 16$), and was related to age ($p = 0.01$), and the expression of PR ($p = 0.004$). Although cases of NST with CNSm showed correlation with greater tumor size, higher histological grade and nodal metastases, there was no statistical association ($p = 0.221$, $p = 0.224$ and $p = 0.99$, respectively). Expression of ER and c-erb-B2 was not significant between the two groups ($p = 0.072$ and $p = 0.31$, respectively). **Conclusion:** This study showed that younger patients and the expression of RP correlate with the presence of CNSm. The evaluation of specific pathological findings in NST can help establish risk factors and/or clinical parameters associated with the development of CNSm.

Key words: central nervous system; carcinoma; breast; neoplasm metastasis; pathology.

INTRODUCTION

Breast invasive carcinoma is a group of neoplasias with great morphological heterogeneity[1-3]. Approximately 70%-80% of these cases are classified as breast invasive ductal carcinoma of no special type (NST). The main prognostic factors are tumor size, degree of differentiation, and lymph node status[1-3]. Although the etiology of breast carcinoma is unclear, some factors seem to increase the risk of the disease. Around 5%-10% of breast cancer cases are inherited[2, 3]. The main risk factors are female sex, age over 40 years, personal history of ovarian or endometrial cancer, family history, early menarche, white race, nulliparity, age older than 30 at first delivery, estrogen exposure and presence of acinar-ductal proliferative lesions[2-4].

Approximately 50% of the patients with NST present metastases to axillary lymph nodes at the moment of diagnosis; up to 25% develop metastases to the central nervous system (CNS), what is an important cause of mortality and morbidity in these patients[5-8]. Breast invasive carcinoma represents 15%-18% of brain metastases, which are seldom the presenting sign of breast cancer[5-9].

In general, brain metastases from breast carcinoma occur in advanced stages of the disease, and frequently show little response to systemic treatment/chemotherapy[8-10]. The average survival of patients with invasive breast carcinoma and metastasis to CNS

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(CNSm) is approximately four months, and the one-year survival rate is 20%; recurrence, survival time and treatment response are quite different among the neoplasia subtypes[10-13]. The subtypes of breast cancer associated with certain metastatic sites exhibit a characteristic genetic expression, and the immunohistochemical expression of the human epidermal growth factor 2 (HER-2/neu/receptor) oncogene (c-erb-B2) has been associated with worse clinical outcome, when brain metastases are present[11-15]. In the present study, the authors list certain anatomopathological characteristics of NST aiming at estimating possible factors related to the presence of CNSm.

METHOD

The present cross-sectional study examined 171 cases of NST previously analyzed at the pathology laboratory of Hospital Nossa Senhora da Conceição, Porto Alegre (RS), between May 2008 and June 2014. The sample included specimens of lumpectomy or mastectomy with the corresponding axillary node dissection, previously fixed in 10% formalin and stained with hematoxylin and eosin (HE). Only women with breast carcinoma not previously treated with radiotherapy or chemotherapy were included. Male patients, and those with other histological types of malignant epithelial and stromal breast cancer and metastases to the breast parenchyma, were excluded from the sample. Criteria from the World Health Organization (WHO) were used for NST diagnosis, as well as for clinical staging[4]. NST is routinely graded according to criteria by Bloom and Richardson modified by Elston and Ellis, which include tubule or gland formation, nuclear pleomorphism and mitotic count. Grade 1 tumors present the formation of tubules in more than 75% of the lesion, regular nuclei and fewer than four mitoses per 0.4 mm; grade 2, formation of tubules in 10%-75% of the lesion, moderate pleomorphism and nuclear size, and five to nine mitotic figures per 0.4 mm; grade 3, formation of tubules in less than 10% of the lesion, marked variation in nuclear shape and size, and 10 or more mitoses per 0.4 mm[4]. The most frequently used staging system for NST is that considering tumor (T), lymph node (N), and metastasis (M) (TNM system), in which tumor size is classified into four categories: T1 (tumors 2 cm or less in greatest dimension), T2 (tumors more than 2 cm but no more than 5 cm), T3 (lesions more than 5 cm), and T4 (lesions that invade the chest wall and/or skin, with ulceration or formation of cutaneous nodules)[4].

The variables of the present study comprised tumor size, degree of differentiation, lymph node status, immunohistochemical expression of receptors of estrogen (ER) and progesterone (PR) and of the c-erb-B2 oncogene product, and presence of CNSm. All the NST patients that presented brain metastasis underwent resection of the lesion and confirmation of the primary site by immunohistochemistry (positive expression of cytokeratin 7 [CK7], epithelial membrane antigen [EMA], mammaglobin, gross cystic disease fluid protein 15 [GCDFP-15) and trans-acting T-cell-specific transcription factor [GATA-3]; and negative expression of cytokeratin 20 [CK20], intestinal transcription factor [CDX-2], villin, cancer antigen 125 [CA125], thyroid transcription factor 1 [TTF-1], napsin A, paired box transcription factor 8 [PAX8], renal cell carcinoma [RCC]-associated antigen, and carbohydrate antigen 19.9 [CA19.9]). Secondary CNS involvement was detected by computerized tomography and/or magnetic resonance during patients' clinical follow-up. For immunohistochemistry, 3-µm-thick histological sections were obtained from each sample and placed on silanized slides. Each slide was deparaffinized with xylol and hydrated with ethanol. Antigen retrieval was carried out using a microwave oven, in a 10 mM solution of citric acid, pH 6, for two nine-minute cycles, rated at 750 W. Endogenous peroxidase blocking was performed with 3% hydrogen peroxide (10 volumes). The primary antibody was diluted in 1% albumin solution and 0.1% sodium azide, in phosphate-buffered saline (PBS), incubated in a humid chamber, during 30 minutes at 37ºC, and kept under refrigeration at 4ºC during 18 hours. Biotinylated secondary antibody was employed in a humid chamber at 37ºC, during 30 minutes, as well as the incubation with the streptavidin-biotin-peroxidase complex (Strep ABC). The used chromogenic substrate was diaminobenzidine 60 mg% in PBS, and Harris hematoxylin was used as the counterstain. The following antibodies were used (Dako Corporation or Novocastra): ER, PR, c-erb-B2, CK7, CK20, EMA, mammaglobin, GCDFP-15, GATA-3, CDX-2, villin, CA125, TTF-1, napsin A, CA125, PAX8, RCC and CA19.9.

Quantitative variables were described as mean and standard deviation, or median and interquartile range; categorical variables, as absolute and relative frequencies. In order to compare means between groups, the Student's *t* test was applied. For asymmetric distribution, Mann-Whitney test was used. For the comparison of proportions, Pearson's chi-squared test and Fisher's exact test were used. For the control of confounding factors, Poisson regression model was applied. The criterion for the inclusion of a variable in the multivariate model was that it presented a $p < 0.2$ in the bivariate analysis. The significance level adopted was 5% ($p \leq 0.05$), and the analyses were conducted in the program SPSS version 21.0.

RESULTS

Tables 1 and **2** show the results obtained by the study. The prevalence of brain metastasis in patients with primary breast carcinoma was 9.4% (16/171), with average time of

TABLE 1 – Breast invasive ductal carcinoma and brain metastases: relationship of age, histological grade, tumor size and metastases to axillary lymph nodes

Variables	Group breast carcinoma without metastasis (n = 155) (n/%)	Group with metastasis to the CNS (n = 16) (n/%)	p value
Age (years; mean + SD)	60.2 ± 12.4	53.4 ± 8.8	0.01
Histological grade			
1	8 (5.2)	2 (12.5)	0.224
2	96 (61.9)	7 (43.75)	
3	51 (32.9)	7 (43.75)	
Tumor size			
T1	76 (49)	4 (25)	0.221
T2	60 (38.7)	9 (56.25)	
T3	19 (12.3)	3 (18.75)	
LN metastasis			
Yes	71 (45.8)	7 (43.75)	0.99
No	84 (54.2)	9 (56.25)	
Average of positive axillary lymph nodes – md (P25-P75)	7 (8-25)	3 (8-19)	0.347

CNS: central nervous system; SD: standard deviation; LN: lymph nodes; md: median; P25: 25th percentile; P75: 75th percentile.

TABLE 2 – Association of breast invasive ductal carcinoma with brain metastases: comparison between groups regarding hormone and c-erb-B2 receptors

Variables	Group breast carcinoma without metastasis (n = 155) (n/%)	Group with metastasis to the CNS (n = 16) (n/%)	p value
ER			
Negative	49 (31.6)	9 (56.25)	0.072
Positive	106 (68.4)	7 (43.75)	
PR			
Negative	62 (40)	13 (81.25)	0.004
Positive	93 (60)	3 (18.75)	
c-erb-B2			
Negative	88 (56.8)	9 (56.25)	0.31
+	34 (21.9)	3 (18.75)	
++	12 (7.8)	0 (0)	
+++	21 (13.5)	4 (25)	

CNS: central nervous system; ER: estrogen receptor; PR: progesterone receptor; c-erb-B2: oncoprotein HER2/neu/receptor of human epidermal growth factor; +: weak and incomplete positivity of the cell membrane in more than 10% of neoplastic cells; ++: weak and/or moderate complete positivity of the cell membrane in 10%-30% of neoplastic cells; +++: strong and complete positivity of the cell membrane in more than 30% of neoplastic cells.

22.1 months between diagnosis of the primary tumor and CNS involvement (**Figure**). Patients with CNSm presented mean age significantly lower than those with no metastasis (p = 0.01). Histologic grade 2 was more frequent in patients with NST without CNSm (61.9%), whereas in patients with CNSm, grades 2 and 3 presented the same prevalence (43.75%). Tumors classified as T1 were more common in the cases of NST without metastasis (49%), whereas in those with CNSm, tumors T2 were frequent (56.25%). There was a significant difference between groups as to PR (p = 0.004). Assessing ER, PR, and age in a multivariate Poisson regression model, these remained as significant variables after adjustment: PR (PR = 0.15; confidence interval [CI] 95% = 0.03-0.65; p = 0.011) and age (PR = 0.96; IC 95% = 0.92-0.99; p = 0.023). Patients with the presence of PR had a reduction in the prevalence of CNSm by 85%, whereas for the increase in one year of age, there is reduction in the prevalence of metastasis by 4%.

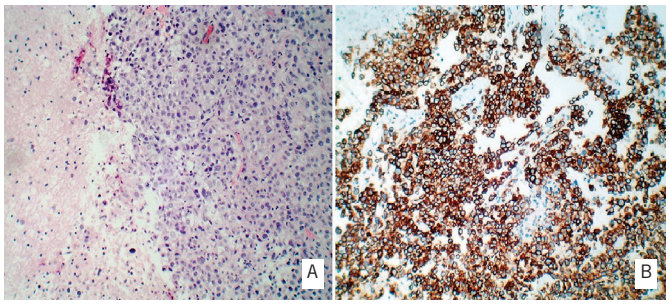

FIGURE – *Metastasis of breast invasive ductal carcinoma in CNS parenchyma*

A) invasion border of poorly-differentiated carcinoma, HE 100×; B) CK7 positive immunoexpression, streptavidin-biotin-peroxidase, 100×.

CNS: central nervous system; HE: hematoxylin and eosin; CK7: cytokeratin 7.

DISCUSSION

The development of CNSm in breast cancer patients is associated with poor prognosis, and represents a growing clinical challenge[7, 12, 15-17]. According to Wiens *et al*., breast invasive carcinoma is second only to lung cancer in frequency of metastases to the CNS[15]. There are several known risk factors for the development of brain metastasis after diagnosis of breast cancer, which include young age, poorly-differentiated tumors, and positive expression of ER, PR and c-erb-B2[15-23].

In the present study, there was a significant difference regarding patients' ages. The youngest patients seem to present higher risk for the development of brain metastasis (p = 0.01), with the age of those with metastatic disease significantly younger (53.4 years; with average time of 22.1 months between diagnosis of the primary tumor and CNS involvement). This is confirmed by Altundag *et al*., who showed the significantly higher risk of younger women to develop metastatic disease after breast cancer diagnosis,

with average time from diagnosis to CNSm estimated in 30.9 months. Patients aged 35 years or younger present a significant risk of developing metastatic disease, regardless of the biological subtype[17]. Altundag *et al*. also described that tumors classified as grade 3, T2 and N1 were the most commonly associated with metastasis to the CNS[17]. In the current study, the authors found a 45.8% prevalence of lymph node metastases in patients with NST without CNSm, while in patients with brain metastasis, a 43.75% rate of nodal metastasis was obtained, a difference with no statistical significance ($p = 0.99$). As regards the histologic grade, patients with primary breast carcinoma with no CNSm presented higher prevalence of grade 2 tumor (61.9%), whereas in patients with CNSm there was no difference between grades 2 and 3 (both with prevalence of 43.75%).

In general, 10%-13% of patients with invasive breast cancer present positive immunohistochemical expression of c-erb-B2, what is one of the most important factors for the development of brain metastasis[10, 11, 15, 16, 21, 24, 25]. In the current study, c-erb-B2 expression was not related to CNS metastasis ($p = 0,31$). Wiens *et al*. described that the positive expression of c-erb-B2 increases the risk of brain metastasis in patients with invasive carcinoma, and confers a worse prognosis[15]. Gerratana *et al*. showed that the presence of brain metastases in breast carcinoma was associated with the expression of HER2[23]. Bachmann *et al*. described that the presence of metastases to axillary lymph nodes, the negative immune expression of ER and PR, and the positive expression of HER2 were associated with the development of brain metastases in breast carcinoma. In this study, negativity for HER2 and triple-negative breast cancer determined shorter survival time[19].

Wiens *et al*., among 59 patients with breast carcinoma and brain metastases, reported that the positive expression of ER and PR was associated with longer survival time in comparison with triple-negative tumors, and that age, histologic grade and the number of metastatic lesions did not exhibit relationship with brain involvement or survival time[15]. Metastases to the CNS in SNT generally occur approximately two years after initial diagnosis of the disease, and survival time is limited[10, 11, 16, 24-26]. On average, this survival rate in a year is 20%[11, 12, 16, 24-26]. Arslan *et al*. found a shorter survival time for patients with c-erb-B2 positivity[26]. However, brain metastases seldom correspond to a sole site of systemic tumor dissemination, with frequent synchronous or metachronous metastases to liver, bones and lungs[20, 24-27].

Confirmation of CNSm in SNT, in the current study, was based on patients' clinical history, radiological alterations, and the anatomopathological and immunohistochemical findings of each case. Although the choice of antibodies for an immunohistochemical panel is a fundamental step to establish a certain diagnosis, and the cases of invasive breast carcinoma characteristically present a general pattern of positive immunoexpression (ER, CK7, EMA, mammaglobin, GCDFP-15 and GATA-3), this positivity also varies between different cases, as well as the negative immunoexpression of certain antibodies (CDX-2, villin, CK20, CA125, TTF-1, napsin A, PAX8, RCC, and CA19.9) also favors identification of the primary site of these lesions[3, 4, 9-12, 15, 19].

As regards ER, there was no significant difference between both groups of patients. Bachmann *et al.* described that the immunophenotype (expression of ER, PR, and c-erb-B2) can be different in primary lesion and metastasis, what may determine distinct clinical conducts. In general, conversion of ER and PR may occur, especially loss of ER expression[19], what was confirmed by our study, because 56.25% of the patients with CNSm presented negative ER expression. Altundag *et al*. asserted that 40% of the NST patients exhibited ER positivity, and that fact was significantly associated with increased overall survival[17]. In relation to PR, significant difference was observed between both groups. Positive PR expression was associated with the presence of CNSm ($p = 0.004$). This receptor was more prevalent in the group without brain metastasis ($n = 93/60\%$), what may suggest a possible protecting mechanism against the development of CNSm. In the group with brain metastasis, just 18.75% of the patients were positive for PR. In accordance with Wiens *et al*., ER positivity in primary neoplasia (with luminal phenotype) seems to be associated with the development of metastasis. In contrast, proliferation rates had little or no effect on long-term survival[15]. Altundag *et al*. also noticed positivity for ER in 40% and for PR in 34% of the cases of breast invasive carcinoma with CNSm[17].

Studies indicate that patients with CNSm negative for c-erb-B2 present shorter survival when compared with the positive cases for this antibody. C-erb-B2-positive patients can be given target therapy, while therapeutical options are limited for patients with c-erb-B2 negative status[10, 14, 20-22, 24]. In our study, c-erb-B2 positivity was not associated with the presence of CNSm ($p = 0.31$), with positivity being found (score 3+) in four patients (25%) with CNSm, what differs from some data described in the literature, which affirm that most of these metastatic lesions are positive for this antibody[10, 14, 18, 20, 26]. The authors state that the possible limitations for the present study

are the CNSm rate lower than that found in the literature and no assessment of metastases by fluorescence *in situ* hybridization (FISH) in the cases with 2+ immunohistochemical results.

The available treatment for NST patients that develop CNSm is still restricted. Early diagnosis of breast cancer continues to be the best therapeutical option to avoid metastatic disease. Neoadjuvant chemotherapy has been widely used in locally advanced breast cancer, because it has the advantage of increasing breast conservation rates, as well as overall survival, in comparison with adjuvant chemotherapy[7, 8, 10, 12, 15, 17, 22, 26].

CONCLUSION

CNS involvement is a continuous problem for breast cancer patients, being one of the factors that indicate shorter survival time. Studying the risk factors for metastatic disease is a growing challenge. The present study showed that patients' younger age and PR expression correlate with the presence of CNSm. Evaluation of certain anatomopathological findings in NST may help establish risk factors and/or clinical parameters associated with the development of CNSm.

RESUMO

Introdução: *O carcinoma ductal invasivo de tipo histológico não especial (CDINE) caracteriza-se por grande heterogeneidade morfológica, sendo responsável por cerca de 70%-80% dos tumores malignos de mama. Os principais fatores prognósticos são o tamanho tumoral, o grau de diferenciação e o* status *dos linfonodos axilares. O CDINE corresponde a 15%-18% das metástases no sistema nervoso central (MSNC) e, geralmente, sua resposta aos tratamentos sistêmicos/quimioterápicos é pouco satisfatória.* ***Objetivo:*** *Estimar a relação entre achados clínicos e anatomopatológicos do CDINE com a presença de MSNC.* ***Método:*** *Foram avaliadas as informações clínicas de 171 espécimes de setorectomia/mastectomia com esvaziamento axilar por CDINE, sendo determinadas as seguintes variáveis anatomopatológicas: tamanho tumoral, grau histológico,* status *nodal, expressão dos receptores de estrogênio (RE) e progesterona (RP) e de oncoproteína HER-2/neu/receptor do fator de crescimento epidérmico humano (c-erb-B2) e presença de MSNC. Os casos de MSNC em CDINE foram submetidos a ressecção e comprovação do sítio primário pela técnica de imuno-histoquímica.* ***Resultados:*** *A prevalência de MSNC foi igual a 9,4% (*n = *16) e apresentou correlação com faixa etária (*p = *0,01) e expressão dos RP (*p = *0,004). Embora os casos de CDINE com MSNC estivessem relacionados com maior tamanho tumoral, maior grau histológico e metástases nodais, não foi encontrada associação estatística (*p = *0,221,* p = *0,224 e* p = *0,99, respectivamente). A expressão de RE e c-erb-B2 não foi significativa entre os dois grupos (*p = *0,072 e* p = *0,31, respectivamente).* ***Conclusão:*** *O presente estudo mostrou que as pacientes mais jovens e a expressão dos RP relacionam-se com a presença de MSNC. A avaliação de achados anatomopatológicos específicos no CDINE pode ajudar a estabelecer fatores de risco e/ou parâmetros clínicos associados ao desenvolvimento de MSNC.*

Unitermos: *sistema nervoso central; carcinoma; mama; metástase neoplásica; patologia.*

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