Autopsy and Case Reports 2014; 4(1): 53-57

Article / Clinical Case Reports
Artigo / Relato de Caso Clínico

Medullary carcinoma of the thyroid metastatic to the breast: a case report and literature review

Sebastião Nunes Martins Filho[a], Marcelo Abrantes Giannotti[a], Sheila Aparecida Coelho Siqueira[a]

Martins Filho SN, Giannotti MA, Siqueira SAC. Medullary carcinoma of the thyroid metastatic to the breast: a case report and literature review. Autopsy Case Rep [Internet]. 2014; 4(1): 53-57. http://dx.doi.org/10.4322/acr.2014.008

ABSTRACT

Breast malignancies, apart from skin cancer, are the leading cause of cancer from cancer among the female population. Unlike the high prevalence of primary mammary malignancies, metastases to the breast are uncommon, and account for only 0.2-2.7% of all malignancies affecting this organ. We report the case of a 35-year-old woman who sought medical care because of a breast lump. A mammogram suggested a breast tumor, which was biopsied. The histopathological workup resulted in the diagnosis of a metastasis from a medullary thyroid cancer. The authors review the most useful clinical, radiological, histological, and immunohistochemical features concerning extramammary malignancy to the breast.

Keywords: Breast Neoplasms; Carcinoma, Medullary; Neoplasm Metastasis.

CASE REPORT

A 35-year-old female patient sought medical care complaining of a palpable nodule in the left breast. The mammogram revealed clustered calcifications in the left upper quadrant (BIRADS 3). Complementary ultrasound showed a hypoechoic lesion, without acoustic shadow. The patient was submitted to a core needle biopsy and 12 tissue samples were obtained. The histological examination revealed a well-differentiated carcinoma infiltrating the mammary parenchyma, with peripheral microcalcifications, but an absence of the *in situ* component (Figure 1). The main diagnostic hypothesis was invasive breast carcinoma nuclear and histological (Nottingham) grade 2.

The complementary immunohistochemical research revealed positivity for E-cadherin and negativity for hormone receptors (estrogen and progesterone), as well as for oncogene HER2 (c-ERB2), besides a low proliferation index identified by less than 5% of positivity for Ki-67 (Figure 2).

The discrepancy between histological findings of invasive carcinoma and a triple negative phenotype, besides the low proliferative index, evoked an additional clinical workup. According to a clinical history, obtained in a second opportunity, the patient had previously had a total thyroidectomy for the treatment of a medullary thyroid cancer 5 years ago.

[a] Department of Pathology- Faculdade de Medicina - Universidade de São Paulo – São Paulo/SP – Brazil

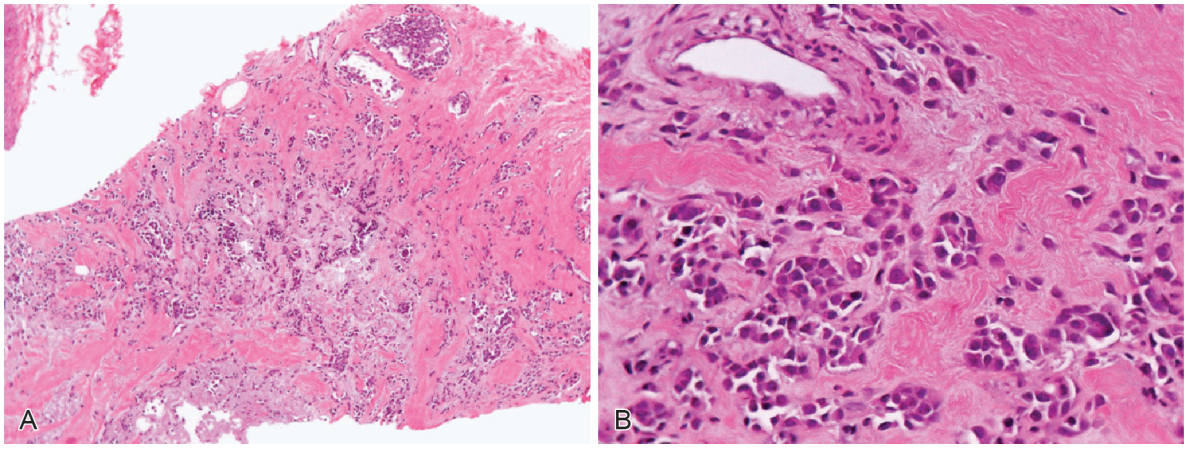

Figure 1 – Photomicrography of the biopsied specimen (mammary tissue). **A –** Well-differentiated carcinoma infiltrating the mammary parenchyma (HE, 100X). **B –** In detail: note the cellular pattern arrangement and the scarcity of mitotic figures (HE, 400X).

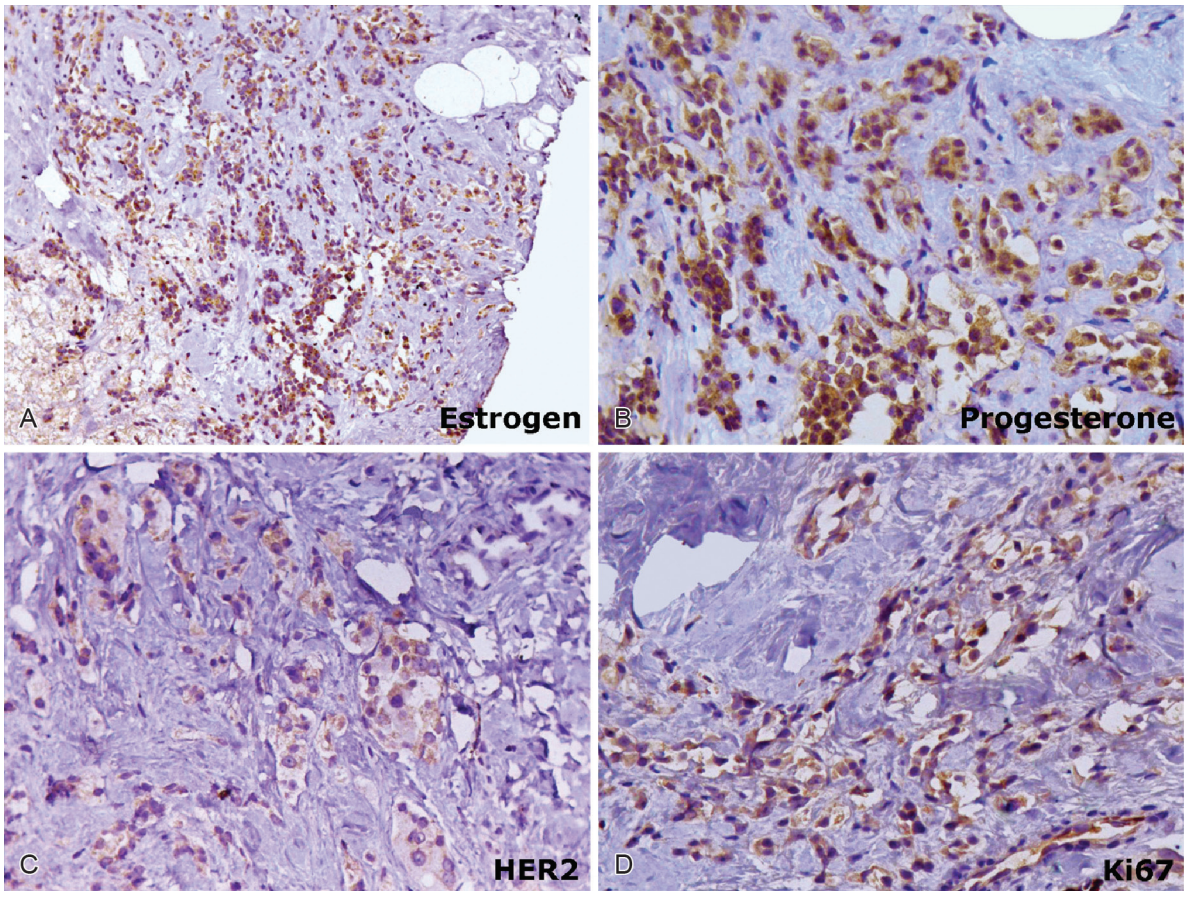

Figure 2 – Photomicrography of the biopsied specimen (mammary tissue). Immunohistochemical preliminary workup. **A –** Negative for the nuclear estrogenic receptor (200X). **B –** Negative for the nuclear progesterone receptor (400X). **C –** Negative for cEBR (HER2) (400X). **D –** Proliferative index below 5% (Ki67) (400X).

In the course of the disease, the patient also presented suspicious metastatic lesions in the proximal tibia, sacrum e lumbar spine, mild enlargement of the mediastinal and axillary lymph nodes besides pulmonary and hepatic nodules. Biopsy of the tibia confirmed a metastatic lesion of the medullary thyroid cancer.

In the light of these histological findings and additional clinical information, a new immunohistochemical panel was tested, which showed positive for chromogranin and calcitonin (Figure 3). Based on this new data, the diagnosis could be made of metastatic medullary thyroid cancer in the mammary parenchyma.

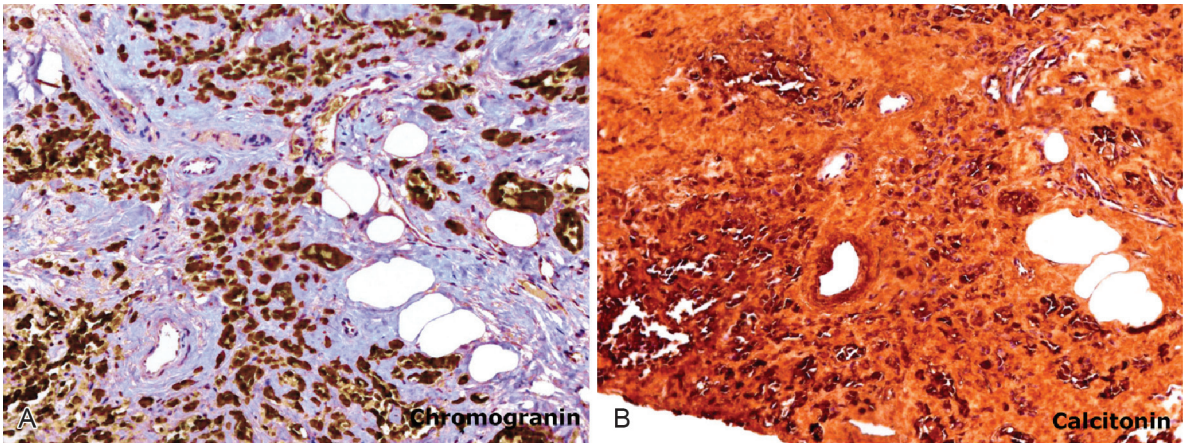

Figure 3 – Photomicrography of the biopsied specimen (mammary tissue). Complementary immunohistochemical workup. **A –** Chromogranin positive. **B –** Calcitonin positive.

DISCUSSION

Medullary thyroid cancer is an uncommon malignant neoplasia, accounting for less than 10% of all cancers of the thyroid. Local invasion is the most common behavior followed by metastatic dissemination through the cervical and mediastinal lymphatic chains. Generalized disease usually occurs late in the course of the illness and predominantly involves the liver, bones, central nervous system, and adrenal glands.[1-4]

To date, less than 10 cases of medullary carcinoma of the thyroid metastatic to the breast have been reported. The first reports date from 2007, but in all of those cases the thyroid neoplasm was previously known, even though the hypothesis of primary breast malignant disease was considered, which was probably due to the marked difference in the incidence of these two neoplasms. In all of those cases, the combined analysis, including clinical findings, radiologic examination, histologic and immunohistochemical studies, enabled the appropriate diagnosis.[3-5]

The Brazilian National Institute of Cancer (INCA) estimates that in 2014 there will be 57,120 new cases of breast cancer among females, but only only 8,050 thyroid malignancies. This high incidence of malignant breast cancer does not include breast metastatic involvement occurring independently of the primary site.[6]

The prevalence of mammary metastatic involvement (regardless of the primary site) is infrequent, varying between 0.2 and 2.7% of all malignant tumors affecting the breast.[7-11] This rate is slightly higher in post-mortem studies, where this finding reaches 7%.[7,12]

Hematologic malignancies especially diffuse large-cell lymphomas, represent the most common source of breast metastatic disease. The differentiation between primary lymphoma of the breast or secondary involvement of the mammary parenchyma follows clinical criteria. Other hematological malignancies also related to secondary involvement of the breast include low grade lymphomas (follicular and lymphocytic), leukemia, and exceptionally, multiple myeloma.[7,13,14]

The incidence of metastatic breast involvement from solid tumors is slightly smaller. However, the morphologic similarities with primary breast tumors impose a tough diagnostic challenge, especially in the absence of clinical information and/or oncologic medical history. Gastric and pulmonary carcinomas are the solid tumors that are more likely to be responsible for breast metastatic involvement, followed by malignant melanoma, carcinoid tumors, carcinoma of the ovary (mainly the serous papillary carcinoma), liver, kidney, prostate, thyroid, and sarcomas.[7-11,15,16]

The previous or current diagnosis of malignancy of any primary site, other than the breast, consists the cornerstone for the diagnosis of secondary involvement of the mammary parenchyma. The suspicion is reinforced when multiple other sites are also involved. Clinical features that aid the diagnosis of breast metastatic involvement include a fast-growing painless breast lump, upper outer quadrant involvement and the the absence of *peau d'orange* or nipple retraction. The diagnosis of the primary tumor and the metastasis

may vary widely between null to several years, but the mean time is 12 months.[8,9]

A well-circumscribed lesion is the main finding on a mammogram, as well as on an ultrasound, in which the lesion does not present an acoustic shadow.[8,9,17] Spiculated lesions with calcifications greatly favor the diagnosis of primary breast tumors.

Histologically, these lesions are usually well circumscribed. In some cases, specific morphological characteristics may suggest secondary mammary involvement, such as the presence of pigments or nuclear inclusion bodies (in case of melanomas), large and clear cytoplasm (renal cell carcinoma), and diffuse and monotonous lymphocytic infiltrate (low-grade lymphomas). On the other hand, *in situ* carcinoma, peritumoral elastosis, and the presence of microcalcifications will favor the diagnosis of primary breast neoplasia.[7]

Finally, the unexpected discrepancy of the histological suspicion and the immunohistochemical results should raise the hypothesis of metastatic lesion. Classic lobular carcinomas, tubular, cribriform, and low-grade invasive carcinoma of no special type (invasive ductal) usually present positive immunophenotype for hormonal receptors (luminal molecular subtype). On the other hand, high-grade invasive carcinomas of no special type usually express positivity for HER oncogene (HER2/neu molecular subtype) or negativity for both (triple negative molecular subtype). The metaplastic and medullary carcinomas also are included in this latter group.[18,19] Additionally, the proliferative index (Ki-67) of the negative hormone-receptor subtypes usually express positivity greater than 20%.[20]

Any discrepancy between clinical, radiological, histological, and immunohistochemical features should always require a complementary workup for an extramammary malignancy to the breast. In these situations, widening the immunohistochemical panel is the cornerstone procedure; however, it should be directed towards the most probable primary tumor site.[7-9] We would like to emphasize, however, that the expression of an immunohistochemical marker, by itself, is not sufficient to assure a diagnosis. A positive reaction for both chromogranin and calcitonin, as shown in this case, is not pathognomonic for medullary carcinoma of the thyroid, but also are found in neuroendocrine tumors of other sites, such as lungs and stomach.[21,22]

The case reported herein represents the fundamental clinicopathological correlation in the diagnostic process of extramammary malignancies to the breast. The more clinical data that is given to the pathologist the more accurate and less expensive the final diagnosis will be. The lack of clinical data available to the pathologist is not uncommon, which challenges him to reach an accurate diagnosis without the complete clinical history.

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Conflict of interest: None

Submitted on: 16th January 2014
Accepted on: 18th March 2014

Correspondence: Sebastião Nunes Martins Filho
Rua Arruda Alvim, 145, apto 43 - Pinheiros - São Paulo/SP – Brazil
CEP: 05410-020 – Phone: +55 (11) 3081-2775
E-mail: sebnmf@gmail.com