

BREAST METASTASIS OF A CUTANEOUS SQUAMOUS CELL CARCINOMA: CASE REPORT

Carcinoma escamocelular metastático para mama: relato de caso

Mauro Fróes Assunção¹, Larissa Santana Bitencourt^{1*}, Patrícia Lopes de Brito¹,
Sérgio Figueiredo Calmon Filho¹, Daniela Cristina Camarotti Camara Escorel Ribeiro¹,
André Vinícius Moraes Dias¹, Marinalva Oliveira Medina da Silva Filha¹, Lívia Senna Pinheiro Santos Lima¹

ABSTRACT

Breast cancer is the most frequent malignant tumor in women. However, squamous cell carcinoma (SCC) of the breast is very rare. Several pathological criteria are required to establish a firm diagnosis of primary SCC of the breast: 1) the tumor origin must be independent from the overlying skin and nipple; 2) the infiltrating component of the breast cancer must be predominantly of squamous type (>90%); 3) no other invasive neoplastic elements, ductal, mesenchymal or otherwise, must be present in the tumor; 4) another site of primary SCC in the patient must have been excluded. The metastatic lesion involving the breast may occur due to a metastasis from a contralateral mammary cancer or originate in any extramammary site. Breast metastases do not normally express estrogen, progesterone receptors or Human Epidermal growth factor Receptor-type 2 (HER2) protein. Prognosis is poor and treatment is palliative, based on systemic therapy tailored to the primary cancer, sometimes completed by comfort loco-regional treatment of the breast lesion. The present study reports the case of a woman previously treated for cutaneous SCC with breast metastasis, but more studies of these rare tumors are needed to increase our knowledge and improve patients' outcomes.

KEYWORDS: Squamous cell carcinoma; Breast neoplasms; Neoplasm metastasis; Mastectomy; Pathology.

RESUMO

O câncer de mama é o tumor maligno mais frequente em mulheres, no entanto o carcinoma epidermoide primário da mama é muito raro. Vários critérios patológicos são necessários para estabelecer o diagnóstico de carcinoma de células escamosas (CEC) primário da mama: 1) a origem do tumor deve ser independente da pele sobrejacente e do mamilo; 2) o componente infiltrante deve ser predominantemente de tipo escamoso (>90%); 3) nenhum outro elemento neoplásico invasivo, como ductal ou mesenquimal, deve estar presente no tumor; 4) um sítio primário de CEC deve ter sido excluído. Já os tumores secundários na mama podem ocorrer em razão de tumores na mama contralateral ou ter origem em praticamente qualquer sítio extramamário. As metástases para mama, normalmente, não expressam receptores de estrogênio nem de progesterona ou proteína Human Epidermal growth factor Receptor-type 2 (HER2). O prognóstico, na maioria dos casos, é pobre e o tratamento paliativo, com base na terapia sistêmica adaptada ao câncer primário, às vezes completada pelo tratamento locoregional da lesão mamária. O presente trabalho relata o caso de uma mulher previamente tratada por carcinoma escamocelular de pele, evoluindo com metástase para mama, porém mais estudos sobre esses tumores raros são necessários para aumentar o conhecimento e melhorar os resultados obtidos por esses pacientes.

PALAVRAS-CHAVE: Carcinoma de células escamosas; Neoplasias da mama; Metástase neoplásica; Mastectomia; Patologia.

Study carried out at Obras Sociais Irmã Dulce, Hospital Santo Antônio – Salvador (BA) – Brazil.

¹Mastology Department of Obras Sociais Irmã Dulce, Hospital Santo Antônio – Salvador (BA), Brazil.

*Correspondent author: lari.bitencourt@hotmail.com

Conflicting interests: nothing to declare.

Received on: 07/05/2017. Accepted on: 10/20/2017.

INTRODUCTION

Squamous cell carcinoma (SCC) is common in skin and organs, such as in the esophagus and anus. Primary breast SCC is very rare, representing less than 0.1% of all malignant breast neoplasms¹. Several pathological criteria are necessary to establish the diagnosis of primary breast SCC:

- the tumor's origin must be independent from the overlying skin and from the nipple;
- the infiltrating component must be predominantly of squamous type (>90%);
- no other invasive neoplastic element, such as ductal or mesenchymal, must be present in the tumor;
- a SCC primary spot must have been excluded².

According to the World Health Organization (WHO) classification, pure primary breast SCC belongs to the group of metaplastic breast carcinomas³. It is important to distinguish this entity from skin malignancies that cover the breast or metastasis from a SCC elsewhere in the body⁴.

Secondary breast tumors can occur due to tumors in the contralateral breast or originate in almost any extramammary site⁵. However, breast's metastatic involvement is also very rare, representing from 0.5 to 1.5% of all malignant breast neoplasms in clinical series and 6.6% in autopsies series⁶. The types most frequently associated with breast metastases spots are: skin (melanoma), lung, prostate, intestine (intestinal carcinoid), ovary, stomach, renal cell, thyroid and soft tissue (sarcomas)⁵.

Non-melanoma skin cancer is the most common in the United States, where approximately 80% are basal cell carcinomas and 20% are SCC. However, unlike basal cell carcinomas, cutaneous squamous cell carcinomas are associated with a substantial risk of metastasis⁷.

The present work reports the case of a woman previously treated for skin squamous cell carcinoma which evolved with metastasis to breast and axilla, with the objective of informing and assisting in the diagnostic evaluation of this rare disease.

CASE REPORT

60-year-old female patient, farmer, from Cruz das Almas, countryside of Bahia, referred to the mastology department of Hospital Santo Antônio, Salvador, in February 2017, with intense pain and signs of phlogosis in the right axillary region for two months, with unsuccessful antibiotic treatment.

As gynecological antecedent, she reported menarche at age 15, five pregnancies, first child at age 28, spontaneous menopause at age 45, no use of hormone replacement therapy.

As comorbidities, she presented arterial hypertension, significant smoking, type II diabetes mellitus and a moderately differentiated skin squamous cell carcinoma in anterior thoracic region, resected with safety margins and tumor thickness of 0.9 cm in June 2016, with no additional treatments.

Upon physical examination, she presented large breasts, discrete edema in the right breast's lower quadrants, significant hyperemia and hardened area in ipsilateral axillary region, with impossibility of individuation of lymph nodes upon palpation.

Bilateral digital mammography only showed bilateral benign calcifications (BI-RADS II). Breast and axilla ultrasound showed a heterogeneous area with a small amount of fluid in the right breast's lower quadrants, suggesting inflammatory process, as well as a 32.4 cm heterogeneous collection in the right axillary region (BI-RADS III) (Figure 1). Magnetic resonance imaging of breasts was not performed due to social conditions and access to the Brazilian public health system (SUS).

The patient was submitted to incisional biopsy of the hardened region in axillary extension/right axilla. While awaiting the anatomopathological result, the patient's picture evolved with a large amount of blood discharge from the operative wound, fever, tachycardia and worsen edema, requiring hospitalization for antibiotic therapy and bleeding control (Figures 2 e 3).

Pathological anatomy showed a poorly-differentiated squamous cell carcinoma in the right axillary extension of the breast, with no safety margins.

Staging examinations did not indicate pathological alterations, nor did the patient mention signs or symptoms of diseases in other organs presenting squamous epithelium such as mouth, throat, esophagus, anus or cervix.

Due to her clinical picture, the patient was submitted to modified radical mastectomy for local control of the disease. In the same period, she was evaluated by the clinical oncology staff, who agreed to perform surgical treatment before systemic therapies.

During surgery, a large-dimensioned, friable tumor was found with several areas of necrosis and adhered to the interpectoral region, limiting the access to axillary content, but all the macroscopic content of the tumor was resected.



Figure 1. Heterogeneous image in the right axillary region.

Pathological anatomy of the surgical specimen was ready after 1 month and 14 days, due to SUS limitations. Characterized as a right mastectomy product weighing 3,781 g, a small poorly-differentiated breast squamous cell carcinoma (Figures 4 e 5) measuring 12.0 × 11.0 × 10.0 cm was found, with presence of neoplastic invasion in muscles and skin, no angiolymphatic invasion detected, and absence of metastasis in five of five axillary lymph nodes identified. The immunohistochemical study concluded that there was a squamous cell carcinoma with negative Human Epidermal growth

factor Receptor-type 2 (HER2), negative progesterone and estrogen receptors, high Ki-67 (greater than 10%) and positive cytokeratin, of high intensity in the whole specimen (Figures 6 e 7).

Few days after the surgery, the patient evolved with local pain, wound dehiscence and purulent discharge from the right axillary region. Local care and antibiotic therapy were performed, but without success in healing, making systemic therapy more difficult. The patient's clinical picture got worse, with edema, intense local pain upon oxycodone use, gabapentin and dipyrone, showing no improvement and difficulty to elevate the right upper limb, besides increase in the amount of surgical wound discharge, becoming hematic and persistent. She was referred for evaluation to a radiotherapist, who indicated anti-hemorrhagic radiation therapy with electrons with 50 Gy/20 fractions in the right axilla.

In the third session, the patient presented drowsiness, tachycardia and fever, so radiotherapy was contraindicated in the period and hospitalization was requested. Venous antibiotic therapy with ceftriaxone and clindamycin was started and bacterial cultures were collected. After three days of hospitalization,

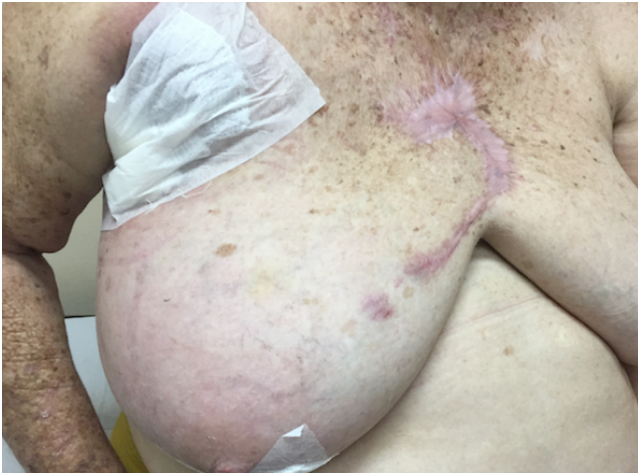


Figure 2. Image after incisional biopsy.



Figure 3. Right axillary region.

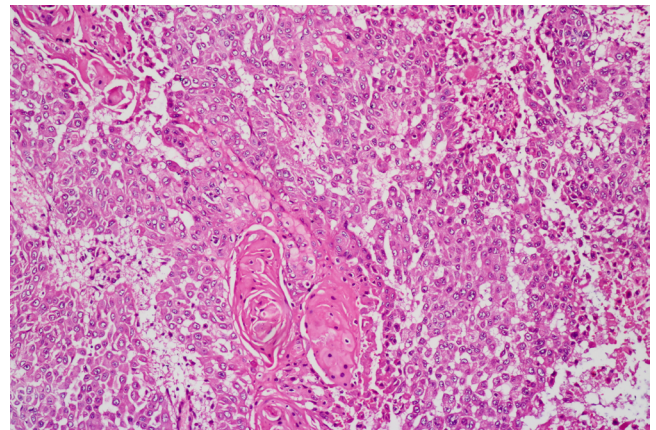


Figure 4. Infiltrative epithelial neoplasia with central keratin pearl formation.

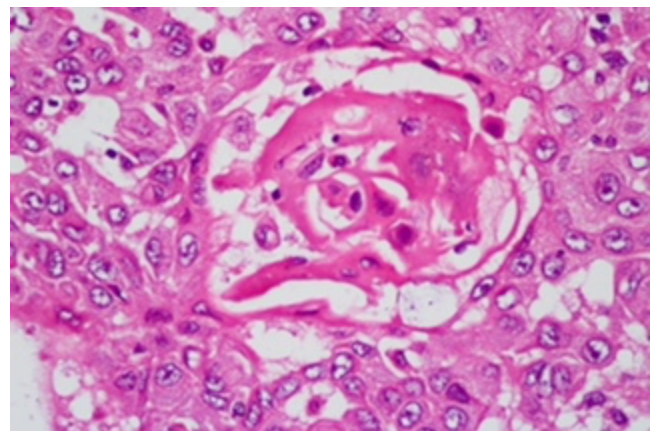


Figure 5. Atypical epithelial cell mass with central keratin pearl formation.

she presented respiratory discomfort, hypotension and level of consciousness (LOC) lowering. Thus, orotracheal intubation was performed, vasoactive drugs were introduced, antibiotics were changed to cefepime, and the patient was referred to the intensive care unit. Despite negative cultures and normal chest radiography, she underwent a new computed tomography scan of the chest, which showed nodules with soft tissue density in the middle lobe, suggesting a secondary blastomatous process without evidence of pleural effusion, and a heterogeneous mass with 9.2 cm deep necrotic areas of into the right axillary projection. At that moment, due to the clinical picture severity and disease prognosis, palliative care was introduced as jointly agreed between the relatives and the assisting medical team. After a few days, the patient evolved with cardiorespiratory arrest and obit was attested.

DISCUSSION

Breast cancer is the most frequent malignant tumor in women⁸, however, primary breast squamous cell carcinoma is very rare⁴. Pure primary breast squamous cell carcinoma was first described in 1908 by Troell. It is an entity with a prevalence of less than 0.1% when compared to all malignant breast neoplasms. As per WHO classification, it belongs to the group of metaplastic breast carcinomas³. It is called pure SCC when malignant cells are all squamous type, without relation to the skin or any indication of primary site elsewhere in the body⁹.

Due to its relative rarity, there are still no universally accepted standards for its definitive diagnosis, adequate treatment and accurate prognosis, in which causes difficulty and confusion in the clinical practice⁸. Some authors, however, have reported that pure breast SCC is a very aggressive, negative-hormone receptor tumor whose refractory treatment has poor prognosis¹.

It is important to distinguish between pure SCC and mixed tumors, as some squamous cells can be found in breast adenocarcinomas and in SCC metastases originating in other organs.⁹

The pathological anatomy in this case report, as well as the immunohistochemical study, confirmed a poorly-differentiated breast squamous cell carcinoma with no other cell types present in surgical specimen and associated with recent history of moderately differentiated squamous cell carcinoma in anterior thoracic region, even without any other distant metastases. It all led to the final diagnosis of primary skin squamous cell carcinoma with metastasis to breast and axilla.

SCC occurs more frequently in the face, hands and forearms, with actinic keratosis being the most common precursor lesion.¹⁰. Exposure to ultraviolet radiation is the most common cause of this cancer⁷. Smoking is also a risk factor for SCC¹⁰, to which the patient had been exposed for a long time.

Unlike almost all basal cell carcinomas, skin squamous cell carcinomas are associated with a substantial risk of metastasis⁷.

Although rare, skin SCC may migrate to regional lymph nodes and other sites such as bone, brain and lungs¹⁰. The main factors affecting the risk of metastasis and recurrence are tumor size and location. Large lesions (>2 cm in diameter) reappear 15% more often and metastasize 30% more often than minor lesions. Just like depth greater than 4 mm or involvement of reticular dermis, subcutaneous fat, penetration of the fascia, muscle, bone or cartilage also increase the risk of recurrence and metastasis⁷.

Although there was an intense search, no reports describing metastasis of skin SCC to breast or axilla were found. In this case report, the initial lesion was extensive, occupying a large portion of the anterior thoracic region and 9 mm deep, despite free resection margins, which configures increased risk for distant metastasis.

The treatment for metastatic SCC may include systemic chemotherapy or treatment with biological response modifiers, but the efficacy of these methods for distant metastatic disease has not been established⁷.

Several other sites of metastasis, besides the breast, have already been described in the literature as due to the increase in survival time of patients, resulting from the multidisciplinary treatment for primary tumor⁶.

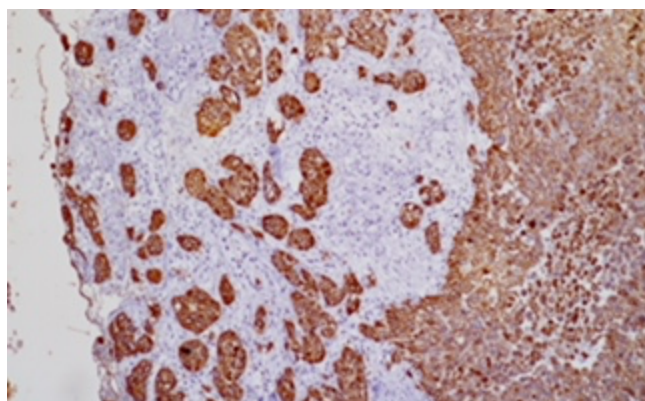


Figure 6. Diffuse positivity for high molecular weight cytokeratins (AE1 and AE3).

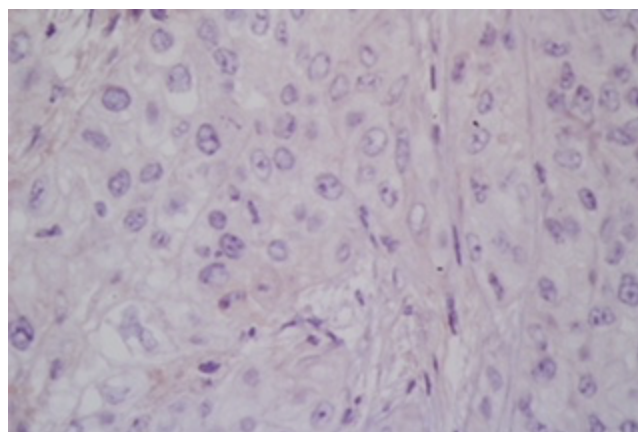


Figure 7. Negative hormone receptors.

The most common metastatic lesion affecting the breast is contralateral breast cancer metastasis.¹¹ The frequency of breast metastatic tumor with extramammary malignancy, based on histological diagnosis in clinical trials, varies between 0.2 and 1.3%. In approximately 30% of patients, breast metastasis is the first sign of malignancy. In cases with history of previous malignancy, the time between initial diagnosis and breast metastasis varies from 1 month to 15 years, taking between 1 and 5 years on average.¹² For Boff et al., the mean time to the occurrence of breast metastasis in previously treated carcinomas is two years.

The primary tumors that spread more often to the breast are, in descending order of frequency: melanoma, lymphoma, lung cancer, soft tissue sarcoma, ovarian carcinoma, gastrointestinal and genitourinary cancers⁶.

Regarding diagnosis, patients typically present a palpable mass of rapid and painless growth. Some reports emphasize that masses are often superficial, but generally do not affect the skin.¹² Mammographically, such lesions appear well defined, with non-spiculated margins, and microcalcifications are rarely present; when found, they indicate more association with metastases from ovarian tumors⁵. Ultrasound usually shows a hypoechoic mass which is sometimes heterogeneous or poorly defined¹².

The excisional biopsy is more indicated when there is suspicion of metastatic lesion, since fine needle aspiration (FNA) has little sensitivity and specificity and core-biopsy presents low specificity for differential diagnosis with primary lesion. Regarding the immunohistochemical study, no marker is 100%

sensitive or specific for any type of tumor⁵. Breast metastases do not normally express estrogen, progesterone and HER2 protein receptors⁶. The combination of cytokeratin 7 and cytokeratin 20 is useful when categorizing carcinomas¹².

Prognosis in most cases is poor, mainly because there is already a disseminated disease at the time of diagnosis, but it is also influenced by the type of primary tumor⁵.

Treatment is palliative, based on systemic therapy adapted to primary cancer, sometimes complemented by locoregional treatment of mammary lesions⁶. Mastectomy is indicated only for local control of large tumors⁵.

The present work depicts a case of breast and axilla metastasis of a skin SCC, up until then never described in the literature. Diagnosis was based on clinical, radiological and especially pathological arguments, associated with previous history of skin cancer. Differential diagnosis is crucial to adequate treatment provision and should be, where possible, considered for a patient with prior history of cancer.

CONCLUSION

Given the rarity of the clinical picture presented, the limited therapeutic arsenal and the reserved prognosis, its physiopathologic mechanisms should be better studied. This case report leads us to conclude that further studies are needed to increase knowledge and improve the outcomes of patients with breast metastasis from extramammary sites.

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