Carcinosarcoma of the breast—a rare entity with a fatal prognosis. Case report
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Abstract

Background: Metaplastic breast carcinomas are a heterogeneous group of neoplasms that exhibit a poor prognosis compared with invasive ductal carcinoma. They correspond to <1% of all malignant neoplasms of the mammary gland. They usually present as high-grade tumors with a lower rate of lymph node metastases and decreased expression of estrogen, progesterone and Her2 receptors and increased expression of Her1 and Ki-67.

Clinical case: We report the case of a 52-year-old woman who presented with a breast carcinosarcoma with a fungated, ulcerated, polypoid left breast tumor that was 18 cm in diameter with lymph node metastases at diagnosis. She received multimodal management with neo-adjuvant chemotherapy followed by mastectomy and adjuvant chemotherapy. She presented with disease progression with lung metastases and local massive recurrence and eventually died from complications associated with the disease.

Conclusions: Metaplastic carcinomas of the breast are extremely rare entities. Due to the nature of disease and presentation, the prognosis is poor in these patients. There are several histological subtypes based on studies using hematoxylin and eosin and immunohistochemical stains. This entity requires multimodal therapy (surgery, radiotherapy and chemotherapy) for best results.

Key words: carcinosarcoma, breast cancer, cancer, metaplastic breast carcinoma

Introduction

In the U.S., breast cancer is the leading cause of cancer consultations. The incidence for 2012 was estimated at 226,870 new cases, representing 29% of the total malignant neoplasms in women. An estimated 72,590 deaths are attributed to this disease that represents 26% of all cancer deaths in women.1

In Mexico, in 2006, according to the epidemiological profile of malignant tumors, breast cancer ranked second of the neoplasms in the general population followed only by skin cancer. In women, it ranks first for neoplasms diagnosed as malignant. In that same year, 13,706 new cases were diagnosed with breast cancer, corresponding to 12.9% of all malignant tumors in women. As for mortality, in 2008 there were 4,835 deaths attributable to breast cancer, representing 14.1%, with a rate of 8.9 deaths/100,000 inhabitants.2

Metaplastic tumors in the mammary gland represent 1% of the total cases of breast cancer. They are mammary neoplasms with biological behavior and poor prognosis when compared with invasive ductal carcinoma.3 Because the disease usually occurs in advanced stages, its diagnosis is difficult through conventional methods. In order to classify the tumor, special immunohistochemistry staining is required.4

Clinical Case

A 52-year-old female patient was referred to the Surgical Oncology Service of the Medical Unit of High Specialty 48 of the Instituto Mexicano del Seguro Social (IMSS). She had a fungoid, ulcerated tumor of the left mammary gland (5 x 4 cm in diameter) with no connection with the pectoral muscle. It was not petrous, bleeding, or firmly attached to
the breast parenchyma. She also had a conglomerate of ipsilateral axillary lymphadenopathy (3 cm in diameter), movable, and irregular, with stony material located in levels I and II. Supraclavicular regions did not show evidence of metastasis. Tumor extension studies (chest x-ray, liver ultrasound, liver function tests and bone scan) were reported with normal results. Mammography was not performed due to the local conditions of the disease. Biopsy of the stained lesion with H/E showed an anaplastic malignant neoplasm with epithelial and spindle cell elements, inconclusive for left breast carcinosarcoma. Because complementation is required for histopathological examination of the biopsy through immunohistochemistry staining, the biopsy material was sent for study.

The patient had a history of a self-detected left breast tumor 6 months prior to her arrival for medical care. She was seen at a hospital where a primary care screening mammography reported probably benign changes. She received medical treatment with NSAIDs until she was assessed at a secondary level hospital with a polypoid tumor, and she was referred to a tertiary care center.

Because of the initial extent of the disease, according to the TNM classification, which corresponded to cT4b, cN2, M0, stage IIIb, neoadjuvant treatment with chemotherapy was recommended. She received two cycles of docetaxel (Taxotere®) 120 mg (80 mg/m² of body surface [SC]), 4-epirubicin of 100 mg (60 mg/m² SC) and 1,000 mg cyclophosphamide (600 mg/m² SC) cycled every 21 days. At the end of this treatment, she had clinical progression of the disease manifested by an increase of the initial volume of the lesion, which reached 18 cm in diameter.

Because of the local clinical progression of the disease, the patient was sent for surgical consultation where updated tumor extension studies were conducted and which were normal. Therefore, it was decided to carry out the surgery. A left toilet mastectomy was performed with a resection of both pectoral muscles by direct tumor extension to the chest wall. A level III axillary lymphadenectomy was also performed (Figure 1). The patient was discharged from the hospital on the second day after surgery without apparent complications.

The final histopathology report was high-grade malignancy of the left mammary gland with a tumor of 18 × 16 cm in diameter. There were spindle cell areas in 60% of the tumor studied (Figure 2A) and cell component of infiltrating ductal carcinoma in 40% of the tumor, suggesting breast carcinosarcoma (Figure 2B). Metastases was demonstrated in 13/13 of the contained axillary lymph nodes, three with ruptured capsule and soft periaxillary tissue invasion. Immunohistochemical profile of the lesion showed cytokeratin AE-1 and AE-3 strongly positive in the neoplastic cells of epithelial component (Figure 3A), vimentin equally positive in the neoplastic cells of the fusocellular component (Figure 3B), HER2 positive 3+, actin positive in 20% (focal) and p53 positive in 20% (focal), S-100 protein negative as well as estrogen and progesterone receptors also negative. Histological diagnosis was metaplastic carcinoma of the mammary gland compatible with left breast carcinosarcoma.

The patient received adjuvant chemotherapy treatment with paclitaxel 220 mg (165 mg/m² SC) and capecitabine (Xeloda®) 1500 mg (1000 mg/m² SC). During the fourth cycle of treatment, left pleural effusion and pulmonary me-
tastases were found and the patient decided to stop the treat-
ment.

The patient experienced disease progression 3 months 
later and massive contralateral metastasis in the chest wall 
and the right mammary gland where ulceration appeared in 
90% of the skin.

The patient decided to return for palliative treatment with 
chemotherapy and she received two cycles of docetaxel 
(Taxotere®) 135 mg (85 mg/m² SC) and gemcitabine (Gem-
zar®) 1600 mg at days 1 and 8 (1200 mg/m² SC).

She was admitted to the unit 2 weeks after her last cycle 
of CT with dyspnea and general malaise. She underwent 
palliative thoracentesis with partial clinical improvement 
in ventilatory mechanics. Her death was due to respiratory 
failure due to multiple bilateral pulmonary metastases and 
disease progression.

Discussion

Metaplastic carcinoma of the mammary gland represents <1% of all malignant neoplasms of the breasts. It usually 
appears after the seventh decade of life with a peak in incidence at ~61 years of age.3

Wargotz et al. attempted to group these metaplastic breast 
carcinomas by dividing them into five different varieties: 
matrix-produced carcinomas, spindle cell carcinoma, breast 
carcinosarcoma, squamous cell carcinoma of ductal origin 
and metaplastic carcinoma of giant osteoclastic cells.4,8

These mammary gland neoplasms are a heterogeneous 
group that shares some pathological characteristics; they 
have epithelial and non-epithelial elements. The term 
breast carcinosarcoma is used for malignant neoplasms with a biphasic mammary gland origin, with at least 50% of 
the tumor composed of spindle-shaped elements that con-
sist of spindle cells and growth patterns linked to sarcoma 
(sarcoma-like) including heterogeneous elements similar to bone and cartilage, in addition to the carcinoma comprised 
of long, ductal or mixed scaly cells, which are adjacent or within the sarcomatous component.3,6 The sarcomatous 
component of the neoplasm is usually immunoreactive to 
various markers including cytokeratins 1 and 3 even at 
55%, epithelial membrane antigen (EMA) in 21%, vimentin 
in 98%, actin in 77% and S-100 protein is expressed in up to 
60% of the neoplastic cells.6

Estrogen and progesterone receptors are usually negative 
in metaplastic carcinomas of the mammary glands. These 
only appear in 3.9 and 5.9% of the cases and Her2 only 
appears in 5.7% of those tumors.9,10 EGFR has been identi-
fied in 70-80% of the cases11,12 and increased expression of Ki-67 has been demonstrated in 35.5 ± 26.2%.9

These factors have been associated with poor prognosis 
of the disease except in the study of Kyu- Hyoung et al.10 
of the Seoul National University Hospital in Korea where 
they reviewed 51 patients with metaplastic carcinoma of the 
mammary gland, of which 41 were triple-negative tumors 
(TNMC) and 10 were not triple-negative tumors (NTNMC), 
with no statistical differences between groups. Overall sur-
vival (OS) at 3 years was 93.4% in the TNMC vs. 58.2% in 
the NTNMC (p 0.007), with overexpression of HER2, 
NTNMC, tumor size >3 cm and lymph node metastases, 
prognostic factors for OS in univariate analysis. 
NTNMC and lymph node status were independent prognos-
tic factors for OS. There was no difference in disease-free 
survival between the groups studied. These investigators 
concluded that patients with triple negative metaplastic car-
cinomas of the mammary gland have a better prognosis of 
OS when compared with patients with tumors that are not 
triple-negative. Additional research is required in order to 
explore the mechanisms of the disease.

A low incidence of lymph node metastasis has been re-
ported for metaplastic carcinomas of the mammary gland 
compared with ductal carcinoma. Patients with negative 
nodes (N0) usually represent 50 to 78.1% of the cases.3,13

Metaplastic carcinoma of the mammary gland demonstrate 
more poorly differentiated tumors including 67.8% of the 
cases compared with 38.8% of ductal carcinoma. Tumors 
are usually larger in size (range: 0.9-19 cm).6 In one case 
report, Esses et al. reported a tumor of 22 cm in diameter.14

Mammographic characteristics of metaplastic carci-
nomas of the breast reveal microlobulated or duly circu-
mscribed tumors in predominantly fatty breast or 
heterogeneous-dense pattern. These are usually not asso-

Figure 3. Immunohistochemical staining of the lesion shows high po-
sitivity to cytokeratin (A) and vimentin (B) (400 AR).
associated with microcalcifications or architectural breast distortion.\textsuperscript{15,16} Therefore, these tumors have become confused with low-risk malignant lesions. Ultrasound examination usually reveals well-circumscribed or microlobulated tumors, which may be masses with solid and cystic areas with infiltrative margins.\textsuperscript{16}

Nuclear magnetic resonance imaging shows lesions with irregular contours with spiculations. T2 intensity signals show a speckled pattern with hyperintense areas interspersed with areas of iso- or hypointense or intratumoral homogeneous hypersignals; rarely, they also show an isointense pattern.\textsuperscript{17}

The optimal treatment for metaplastic carcinoma of the mammary gland is still controversial. Due to the rarity of the disease, there is no reference standard for its treatment. Surgical treatment of choice for the metaplastic carcinoma of the mammary gland is a radical mastectomy if the tumors are >5 cm in diameter at diagnosis. However, conservative surgery has been used in several studies\textsuperscript{9,10,13,18,19} and is usually reserved for patients with tumors <5 cm in diameter without axillary metastases.

Tseng and Martinez\textsuperscript{18} evaluated the usefulness of radiotherapy in the treatment of metaplastic carcinoma of the breast in a review of more than 1,500 patients in the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute (NCI). In multivariate analysis, they found that patients who received radiotherapy had higher OS and disease-free survival than patients without radiotherapy treatment, regardless of the type of surgery received. Chemotherapy has been an adjunct to surgery and radiotherapy. Lack of response to conventional treatment regimens suggests that innovative drugs need to be indicated.

There is no standard treatment regimen in these patients. Given the high margin of EGFR positivity (70-80\%), indication for tyrosine kinase inhibitors has been proposed such as gefitinib (Iressa\textsuperscript{8}) or cetuximab (Erbitux\textsuperscript{8}), although its use is not yet approved for this type of neoplasm.\textsuperscript{11}

In metaplastic carcinoma of the breast, the following have been identified as adverse prognostic factors: age, carcinomas subtype, tumors >5 cm or with invasion to the skin or chest, lymph node metastasis and distant metastasis.\textsuperscript{18} Bone and lung metastases are the most frequent in the disease.\textsuperscript{3}

In conclusion, metaplastic tumors of the mammary gland are rare. Diagnosis should be based on H&E studies with confirmation by immunohistochemical markers. Significant differences are shown vs. invasive ductal carcinoma. It is common to find the disease at an advanced stage, and many poorly differentiated tumors have been described with estrogen receptor negative, progesterone receptor negative and Her2 negative, and Ki-67 and Her1 positive. Axillary metastases occur less frequently. Diagnosis of the disease must be made early with aggressive treatment with adjuvant radiotherapy and surgery (mastectomy or conservative surgery).

Chemotherapy should include innovative therapeutic agents. Targeted therapies should be considered in this type of tumor as long as the EGFR marker is always present.

References