

CASE REPORT

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Metaplastic carcinoma of the breast with squamous differentiation: prognostic factors and multidisciplinary treatment

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Abstract

Background: The objective of this study was to analyze the characteristics of patients diagnosed with metaplastic carcinoma of the breast with squamous differentiation and to identify the particular clinical and histological characteristics that need to be taken into account in this type of tumors.

Case presentation: Retrospective observational study of two patients managed at our hospital between 2014 and 2020 (15 months mean follow-up), plus all cases published in the last 7 years (8 patients). Thus, a total of 10 cases were analyzed, all with less than 2 years mean global survival. Studied variables were: age, medical background, tumor size, axillary involvement, radiological characteristics, surgical approach, complementary treatments, histologic characteristics, and progression of the disease. In 50% of cases, the disease appeared as a palpable mass of rapid growth, associated with axillary infiltration; 80% of the tumors were triple negative; 30% of them progressed to distant metastatic disease in 30%.

Conclusions: This unusual carcinoma requires a complex multidisciplinary treatment. Its prognosis is unfavorable due to its high local aggressiveness, with rapid progression and appearance of metastatic disease. The predominance of different histological components may determine the response to medical treatments.

Keywords: Breast cancer, Metaplastic carcinoma, Squamous carcinoma, Survival

Background

Metaplastic breast carcinoma with squamous differentiation is an uncommon type of metaplastic carcinoma that accounts for less than 1% of breast carcinomas [1–3]. These tumors show an indolent course and may be associated to a preexistent benign lesion (adenomyoepithelioma, complex sclerosing lesions or fibrocystic disease) [4]. This heterogeneous type of tumors has been defined as an epithelial neoplasia of mixed squamous and

glandular differentiation, with a widely variable response to oncologic therapy [1–3]. The high-grade presentation is the most aggressive one and the star-shaped infiltrating pattern is associated with a high probability of local relapse [4, 5]. In addition, due to their particular response to oncological treatment, eventual complex surgery is often needed. Here we present our experience with two cases diagnosed at our hospital, together with an analysis of all cases published in the last 7 years, especially regarding the clinical and histological characteristics that need to be considered in this type of tumor.

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Case presentation

Here, we present a retrospective observational study of patients with metaplastic breast carcinoma with squamous differentiation, who were managed at our hospital between 2014 and 2020, plus all cases published during the last 7 years. The following variables were described and analyzed: age, medical background, tumor size, axillary involvement, radiological characteristics, surgical technique used, complementary treatments, evolution of the disease and tumor histological type, histological grade, and immunohistochemical characteristics.

Only two patients were managed for this rare condition during the mentioned period, at our hospital (mean follow-up time of 15 months). Eight additional cases were identified in the literature, with similar general characteristics and with a mean overall survival time shorter than 2 years (13.6 months; one case was excluded from the calculation of mean survival because it was a pure in situ variant [6]).

Case N°1

A 39-year-old female patient presented with a 5-cm nodule in the upper quadrants of the right breast, which had appeared 1 month before, plus inflammatory changes and palpable axillary adenopathy. She had undergone medical examination 6 years before, in a different health-care center, due to fibrocystic disease. She provided three annual ultrasound studies that showed multiple cystic formations, parenchymal disruption, and ductal ectasia. She also provided the results of a biopsy study showing abundant epithelial and myoepithelial cellularity, fibrosis, cysts with apocrine metaplasia, and sclerosing adenosis. She had not received therapy. As a part of our examination, mammography and ultrasound studies were performed, where a large area of fibrocystic changes could be observed in the upper external quadrant of the right breast, as well as a 37-mm-diameter mass in the right armpit BI-RADS VI (Fig. 1A). Such findings were confirmed in a magnetic resonance study, which showed a 40-mm adenopathy plus metastatic involvement consisting of smaller surrounding adenopathies. Core needle biopsy revealed infiltrating carcinoma, probably of ductal origin, in the breast plus well-differentiated epidermoid carcinoma (p:63 positive) in the armpit, both were triple negative, ki 67: 60%, p:53 negative and ck 19 positive. Distant disease of stage T4N2M0 was ruled out. The tumor board decided that the patient be administered neoadjuvant chemotherapy consisting of four FEC cycles (5-fluorouracil-epirubicin-cyclophosphamide) and four docetaxel cycles. The treatment produced a 50% regression of the disease in the breast but a poor response in the armpit, where the disease actually progressed

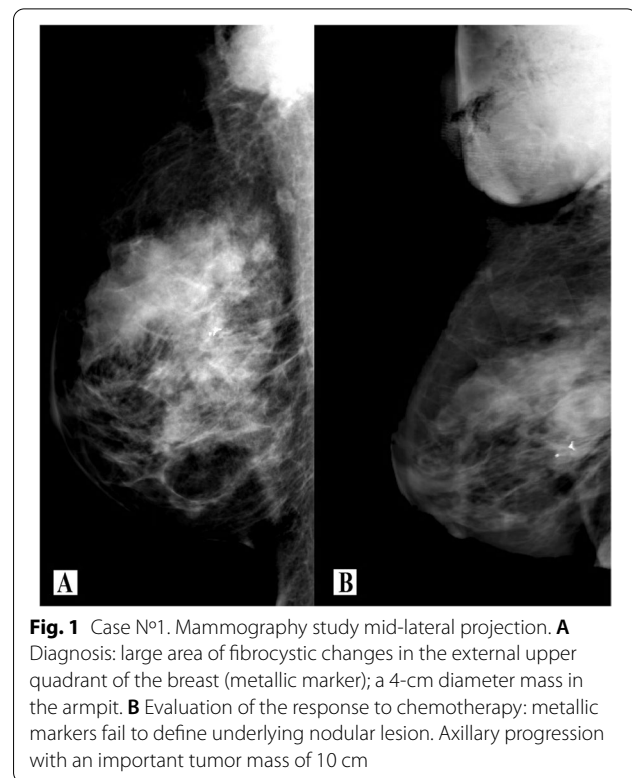


Fig. 1 Case N°1. Mammography study mid-lateral projection. **A** Diagnosis: large area of fibrocystic changes in the external upper quadrant of the breast (metallic marker); a 4-cm diameter mass in the armpit. **B** Evaluation of the response to chemotherapy: metallic markers fail to define underlying nodular lesion. Axillary progression with an important tumor mass of 10 cm

(Fig. 1B). Eventually, surgical management was scheduled (Fig. 2A).

The patient underwent skin-sparing mastectomy. Wide resection of the tumor was achieved, although an irresectable tumor residue remained, which infiltrated into the axillary vein, latissimus dorsi and right brachial plexus (Fig. 2B). The surgical specimen was collected for subsequent study (Fig. 2C). The defect was covered with a rotation myocutaneous flap of the latissimus dorsi. The donor zone was filled with flaps from the mastectomy (anterior part) and by dissecting the back until the midline and iliac crest (lower posterior part) (Fig. 2D). The surgical procedure was uneventful and the patient was discharged on day 3 postoperative. A histological study of the specimen revealed a high-grade 5-cm metaplastic ductal carcinoma with squamous differentiation, with axillary metastasis. In the breast, ductal predominance was found with associated high-grade intraductal carcinoma and free margins. In the armpit, a 12-cm ulcerated tumor mass was observed with a predominantly squamous pattern and extensive involvement of the deep margin. Adjuvant radiotherapy was initiated. However, 1 month later, ulcerations were observed in the armpit, which were related to the progression of the disease. Palliative chemotherapy was initiated. One month later, the patient reported low back pain and a D2–L1 metastatic lesion was found in bone scintigraphy. Later on,

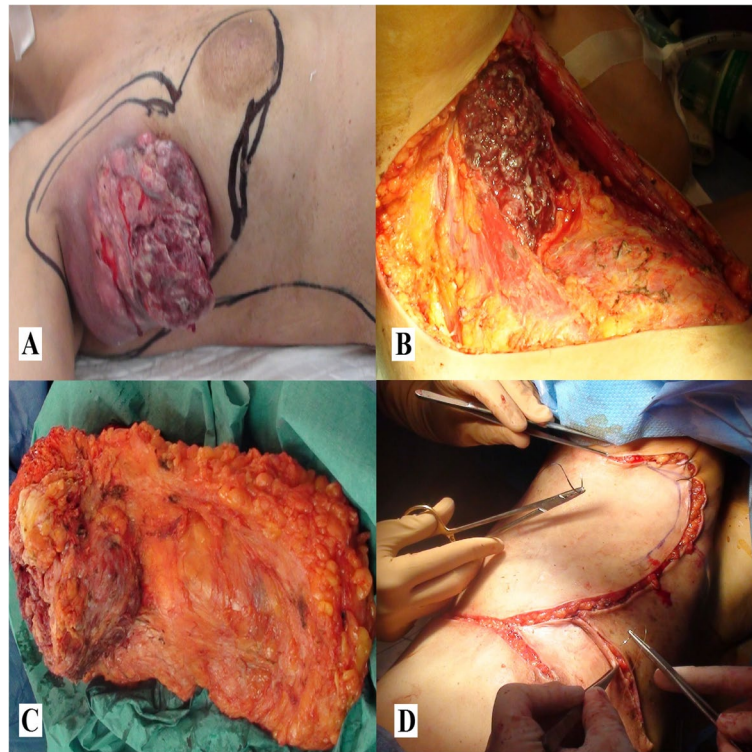


Fig. 2 Case N°1. surgery. **A** Ulcerated axillary tumoral mass of 12 cm. **B** Skin-sparing mastectomy and wide tumor resection, although leaving an irresectable tumor residue, which infiltrated the axillary vein, *latissimus dorsi* and right brachial plexus. **C** Macroscopic study of the surgical specimen: large ulcerated axillary tumor (12 × 10 cm), grayish-whitish in color with multiple necrotic and friable reddish areas, deep margin extensively involved. Dense breast parenchyma with multiple cysts; in the upper region, two adjacent zones of greater density of 3 and 2 cm that include metallic filament, free margins. **D** Close rotation myocutaneous flap of the *latissimus dorsi*

she presented dyspnea, multiple nodular lesions on both lungs and a metastatic lesion in the liver, all of which were managed with medical therapy until she died due to pulmonary embolism 11 months after diagnosis.

Case N° 2

A 57-year-old female patient presented with an 8-cm nodule in the upper quadrants plus 2-cm axillary adenopathy. She complained of a 1-month long pain in the right breast. Her medical record showed not events of interest. She underwent a mammography and an ultrasound study, which showed a hypoechoic solid nodule with internal microcalcifications, anfractuous edges, and 33 mm maximum diameter (BI-RADS V) (Fig. 3A). The ipsilateral axilla showed a ganglion with cortical thickening and infiltrative appearance. Core needle biopsy revealed metaplastic infiltrating ductal carcinoma with squamous differentiation, associated with high-grade intraductal carcinoma. Axillary lymph nodes were positive. An immunohistochemical study showed a triple negative, ki 67: 60%, p53 negative and ck 19-positive tumor. In an extension study, computed axial

tomography and positron emission tomography showed two lesions indicative of liver metastasis on segments VI and II without signs of significant metabolic activity. The disease was in stage T2N1M1. The tumor board decided to administer neoadjuvant chemotherapy consisting of 4 cycles of anthracyclines and docetaxel. The treatment produced 50% disease regression in the breast (Fig. 3B) and the armpit, although with a poor response in the liver, where the disease progressed. The case was then re-evaluated and surgery was ruled out. The patient was treated with local–regional radiotherapy plus administration of two more lines of chemotherapy, in an attempt to maintain the distance disease under control. However, the response was poor and the patient died 19 months after the diagnosis due to severe liver failure.

Below we analyze the characteristics of our patients plus those reported in the literature (Table 1). The mean age was 52.5 years; 40% of them had pre-existing breast lesions (cases 2 [7], 5 [8], 6 [9], and 9); tumor size was large in all cases and axillary involvement was present in 50% of cases (cases 3 [10], 6, 7 [11], 9, and 10); 70% of patients presented radiological findings of a solid mass,

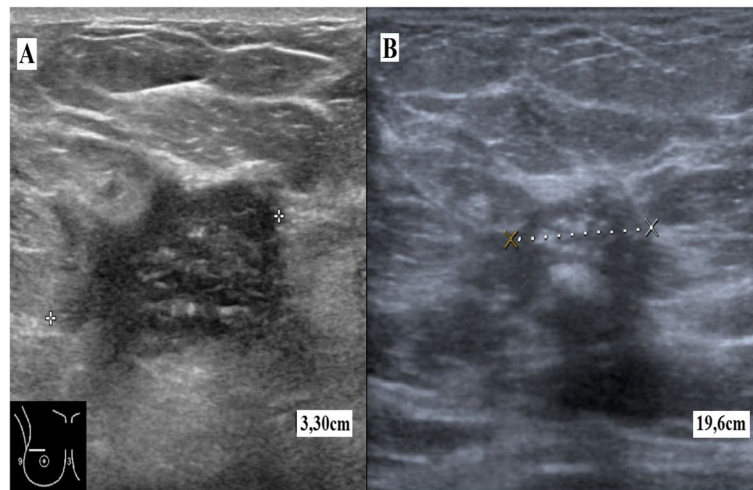


Fig. 3 Case №2. Breast ultrasound study. **A** Hypoechoic solid nodule with internal microcalcifications; approximately 33 mm maximum diameter (BI-RADS V). **B** Diffuse microcalcifications of 2 cm size, the rest without alterations

four of them in association with a cystic component (cases 1 [12], 5, 6, and 9). Less than a half of patients were diagnosed using core needle biopsy (cases 1, 4, 6, and 10) and three of them underwent an incomplete surgical resection (cases 7, 8 [13], and 9). Six patients received chemotherapy: neoadjuvant for half of them (cases 1, 9, and 10) and post-surgery for the rest of them (cases 3, 6, and 7). Radiotherapy was used in half of the patients. As much as 80% of tumors were triple negative, 30% of them progressing to distant metastatic disease (liver, lungs, and brain).

Discussion and conclusion

Metaplastic carcinoma with squamous differentiation of the breast is an uncommon neoplasia, which appears in women between 30 and 80 years of age, mostly post-menopausal. It may appear sporadically or derive from preexistent lesions involving breast glandular and tubular structures [12, 14, 15]. Clinically, a large palpable, well delimited, sometimes painful mass is observed, which has occasionally been reported as an incidental finding in an image diagnosis study [16, 17]. An ultrasound study may show an irregular hypo-echoic image; mammography may show a speculated mass or nodule, with increased density, poorly specific [17]. Core needle biopsy is not conclusive in most cases, since the whole histological architecture cannot be observed. The definitive diagnostic test is usually the histological study of the specimen [4, 14, 15].

In this series, we observe common characteristics in most cases. The onset of the disease presents as a palpable mass of rapid growth associated with axillary infiltration, with ages and radiological findings similar

to those established in the literature. Almost all tumors were triple negative with a high ki 67 proliferation index, p: 53 negative and cytokeratin 19 positive reported in our center cases. In addition, although there was good response in the breast with chemotherapy treatment, progression of the metastatic disease was observed only in three cases. The usual chemotherapy schemes were used and radiotherapy was an adjuvant treatment that partially improved the aggression of the same.

Since these tumors are very rare, there is no consensus on their treatment. In general, the same guidelines than for other breast carcinomas are observed, although with some considerations. These are aggressive metaplastic tumors with high local relapse rates; thus, obtaining suitable margins in the surgical treatment is essential to prevent relapse [2, 18, 19]. Due to their size and poor response to chemotherapy, especially in its epithelial component, most cases require mastectomy and axillary surgery. When diagnosed early, a conventional conservative treatment might be possible [18, 20].

Like other metaplastic carcinomas, these tumors do not express hormonal receptors or Her 2, and have an unfavorable prognosis as compared with other triple-negative tumors, possibly due to their poor response to usual chemotherapeutic treatment [20, 21]. In an immunohistochemical study, marker p63 may be recognized in the squamous element, which facilitates classification; and they present positive cytokeratin [22, 23]. Radiotherapy is indicated and it is often used as an adjuvant treatment [24]. The tumor size, poor response to oncospecific treatment and local–regional relapse with subsequent distant disease are the main known prognostic factors to be considered [18, 20].

Table 1 Reported single cases of Metaplastic carcinoma with squamous differentiation of the breast (n=10)

Case	Author, Year	Age	PL	Size (cm)	LNS	Radiological findings	Diagnostic	Surgery	CT	RT	IC	Distant metastatic	Survival (months)
1	Graziano et al, 2015 [12]	59	No	Large mass	Negative	Solid/Cystic mass. No mic	CNB	R0	Neoadjuvant	NR	Triple negative	No	NR
2	Jagtap et al, 2015 [7]	45	Nipple retraction	Two Masses 9, 3	Negative	High density masses	Surgical specimens	R0	NR	NR	ER,PR negative Her 2 positive	No	NR
3	Nguyen et al, 2015 [10]	47	No	4	Positive	NR	Surgical specimens	R0	Adjuvant	Yes	ER positive PR, Her 2 negative	Lung and brain	NR
4	Arafah et al, 2016 [6]	73	No	Mic	Negative	Extensive calcifications	CNB	R0	No	No	Triple negative	No	11 years Pure insitu variant
5	Punzo et al, 2017 [8]	75	Inflamed cystic lesion	5	Negative	Solid/Cystic mass. Mic	Surgical specimens	R0	Patient refused	No	Triple negative p63 positive	No	12
6	Chahdi et al, 2018 [9]	44	Cyst lesion	5	Positive	Solid/Cystic mass. Abscess	CNB	R0	Adjuvant	Yes	Triple negative	No	9
7	Goto et al, 2018 [11]	42	No	Large mass T4	Positive	Solid mass	Surgical specimens	R1	Adjuvant	Yes	Triple negative	No	17
8	Hardy et al, 2019 [13]	44	No	11	Negative	Solid necrotic mass	Surgical specimens	R1	Patient refused	No	Triple negative p63 positive	No	NR
9	Current case 1	39	Fibrocystic disease	5	Positive	Solid/Cystic mass	Surgical specimens	R1	Neoadjuvant	Yes	Triple negative p63 positive	Lungs and liver	11
10	Current case 2	57	No	8	Positive	Solid mass. Mic	CNB	No	Neoadjuvant	Yes	Triple negative	Liver	19

PL preexistent lesions, LNS Lymph node status, CT Chemotherapy, RT Radiotherapy, IC Immunohistochemical characteristics, CNB Core needle biopsy, R0 Complete resection, R1 Incomplete resection, NR Not reported, ER Estrogen receptor, PR Progesterone receptor

Metaplastic carcinoma of the breast with squamous differentiation is a rare neoplasia that requires a complex multidisciplinary treatment. Its prognosis is unfavorable due to its high local aggressiveness, rapid progression and development of metastatic disease. Predominance of different histological components of these tumors may determine their response to treatment and should be taken into account when a therapy is selected. Although our knowledge of metaplastic tumor variability is continuously growing, more studies are needed to develop new specific therapeutic strategies adjusted to the different types of patients.

Acknowledgements

Not applicable.

Authors' contributions

All authors were involved in the preparation of this manuscript. A.T researched the literature and wrote the manuscript. A.T and V.V were involved in the patient surgical treatment. M.P was involved in patient diagnosis through pathological study. V.V and J.R reviewed the manuscript review. A.T wrote the final version of the manuscript. All authors read and approved the final manuscript.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets used and/or analyzed during the current study were available from the corresponding author on reasonable request. These data were available in the clinical records system of our hospital.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the General Surgery Department of the Complejo Hospitalario Universitario Insular Materno-Infantil. Informed consent was obtained from all patients in this study.

Consent for publication

Informed consent for publication was obtained from all patients in this study.

Competing interests

The authors declare that they have no competing interests.

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Received: 12 February 2022 Accepted: 19 March 2022

Published online: 08 June 2022

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