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Original Research Article

Clinicopathological and therapeutic features of metaplastic carcinoma of the breast: a study of 15 cases

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ABSTRACT

Background: Metaplastic carcinoma of the breast is a rare entity containing a mixture of malignant epithelial and mesenchymal elements. The World Health Organization only recognized it as a distinct pathological entity since 2000. The aim of this study is to better characterize this rare disease.

Methods: We reviewed retrospectively 15 cases of metaplastic carcinoma of the breast treated in our institute between 1994 and 2015. We analyzed clinical, histological, therapeutic and evolutive data.

Results: All patients were females ranging from 29 to 75 years old (median, 50). Tumor size ranged from 20 to 150 mm (median, 72 mm). The Treatment consisted of radical mastectomy in 14 cases, often combined with post-operative radiation and/or chemotherapy. There were 8 cases of carcinosarcoma, 4 cases of spindle cell carcinoma and 3 cases of squamous cell carcinoma. Follow-up data were available on 12 patients. The median follow-up was 47 months (range, 10 to 146 months). Definitive nodal metastases were identified in 6 cases. One patient developed a local recurrence. Extranodal metastases occurred in 3 patients. Three patients died at median interval of 20 months (range, 13-30). Eight patients were alive with no evidence of recurrent or metastatic disease (median, 47 months) and one patient was alive with metastatic disease.

Conclusions: Based on this series, metaplastic breast carcinoma is characterized by a large tumor size at presentation, a low frequency of nodal metastases and a high proportion of triple negativity. Our series is consistent with the literature.

Keywords: Breast, Carcinoma, Metaplastic

INTRODUCTION

Metaplastic Breast Carcinoma (MBC) is a rare subtype of invasive Breast Cancer (BC). It accounts for less than 1% of all breast carcinomas exhibiting either a mesenchymal or other non-epithelial component or epithelial with squamous differentiation.¹

This tumor is characterized by a larger size at presentation, lower rates of axillary nodal involvement,

higher rates of both local and distant recurrence, higher rates of triple-negative profile (lack of ER, PR and Her2 over expression) as well as sub-optimal response to systemic therapies when compared to other invasive breast cancers.

The World Health Organization (WHO) classified MBC into pure epithelial type and mixed epithelial and mesenchymal type.²

METHODS

Patients were selected from the database of the surgical oncology department of Salah Azaiez institute in Tunis between September 1994 and December 2015.

We excluded all patients with mixed histologies, those with a diagnosis of carcinoma in situ and those who had synchronous tumors in another organ.

We obtained and analyzed these clinical parameters: age, tumor size; lymph node status; distant metastasis, surgery performed and adjuvant therapy.

Furthermore, we analyzed all the following pathological variables: hormonal receptors (HRs), the ki-67 proliferation index (with 14% as a cut-off value) and Her2. Statistically, we analyzed recurrence, progression and survival of the patients through the last follow-up appointment.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) program, version 18.0. OS and DFS rates were estimated by Kaplan-Meier analysis.

RESULTS

We identified 15 MBC cases. All patients were female, with a median of age 50 years (range, 29 to 79). All the cases were unilateral, ten cases were localized in the left breast and five cases were localized in the right breast. The median tumor size was 72 mm (range, 20 to 150). There were seven cases classified T2, four cases T3, three cases T4b and one case T4d.

Mammography was performed to all patients. (Figure 1, Figure 2). All masses were highly dense, 8 masses were round, three lobular and four irregulars. Margins were circumscribed in three masses, microlobulated in two cases and indistinct in nine cases. One mass had speculated borders. Calcifications were observed in three cases.

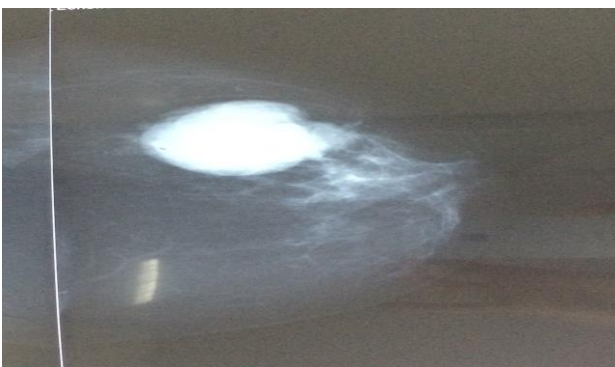


Figure 1: Mammographic appearance of a metaplastic carcinoma in a 53-year-old woman: a circumscribed highly dense mass of the left breast.

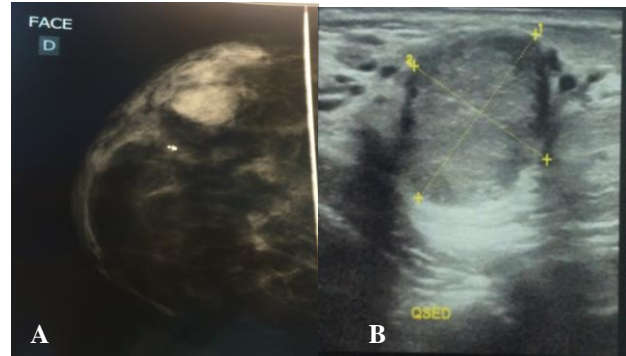


Figure 2: Metaplastic carcinoma of the breast in a 49-year-old woman: Mammography showing a highly dense relatively circumscribed mass in the upper-outer quadrant of the right breast (A) and ultrasound showing a hypoechoic solid mass (28 mm) with long axis perpendicular to the skin (B).

Thirteen patients underwent radical mastectomy and only two patients underwent a conservative surgery consisting of lumpectomy with lymph node dissection. Final histological exam showed: 8 cases of carcinosarcoma, 4 cases of spindle cell carcinoma (Figure 3) and 3 cases of squamous cell carcinoma (Figure 4).

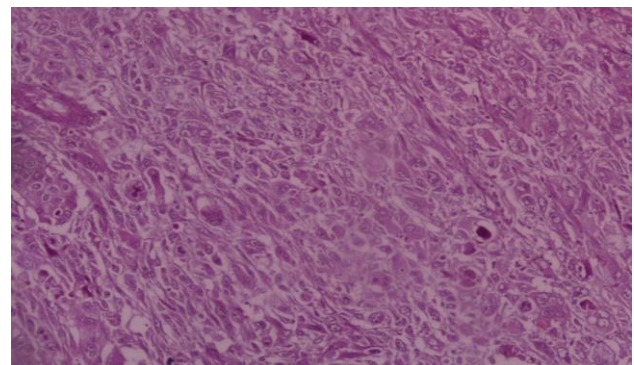


Figure 3: Microscopic examination: tumor composed of malignant spindle cells and atypical epithelial cells (Hematoxylin-Eosin, high magnification x100).

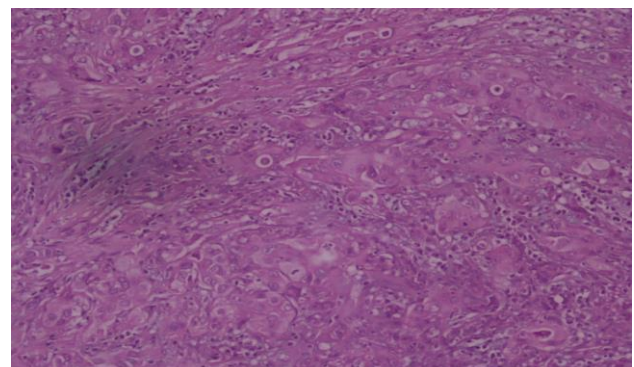


Figure 4: Microscopic examination: tumor cells showing high grade of atypical cell features with presence of squamous differentiation (Hematoxylin-eosin, high magnification x100).

We have noted 6 nodal metastases. Fourteen tumors showed negative hormonal receptors. Her2 was negative in all cases. The ki-67 proliferative index ranges from 12 to 60%, and it was high in 14 cases. (Figure 5).

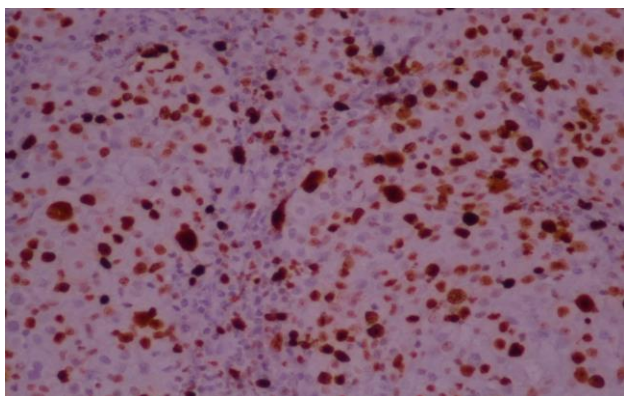


Figure 5: Metaplastic carcinoma with high proliferative index Ki67: 60% (Immunohistochemistry x 100).

Twelve patients received adjuvant chemotherapy; eleven patients received a FEC100 (5-Fluorouracil+epirubicin+cyclophosphamide) chemotherapy with taxanes and one patient received adriamycin with 5-FU with endoxan.

Eleven patients received postmastectomy radiation therapy, and two patients had received a radiation therapy after lumpectomy.

Follow-up data were available on 12 of the 15 patients. After a median follow up of 47 months (range: 10 to 146 months), one patient had a loco-regional recurrence (an axillary nodal recurrence). Distant metastases were noted in three patients (25%) at a median interval of 15 months (range, 13 to 18 months); in the lung and the liver in two cases, and in the bone and the lung in another case. Three patients died of disease at a median interval of 20 months (range, 13- 30 months). One patient was alive with metastatic disease. Eight patients were alive without evidence of recurrent or metastatic disease. The 5-year OS (overall survival) rate was 60.5%, and the 5-year DFS (Disease Free Survival) was 50.6%.

DISCUSSION

Metaplastic carcinoma is a rare malignancy of the breast that accounts less than 1% of all mammary tumors.¹

The World Health Organization only recognized MBC as a distinct pathological entity since 2000.

Most metaplastic carcinomas are sporadic, but they may be a slight propensity for metaplastic spindle cell carcinoma to arise from pre-existing lesions, including papillomas, complex sclerosing lesions and nipple adenomas.^{2,3} Metaplastic carcinomas arising from such

lesions can show a varying degree of malignancy, ranging from low to high grade. This type of lesion should also be differentiated from the so-called reactive spindle cell nodule, which is believed to be a benign lesion and may also complicate pre-existing lesions such as papillomas or complex sclerosing lesions.⁴

The WHO classifies MBC into epithelial type and mixed type.⁵ Epithelial-type MBC is, in turn, classified into squamous cell carcinoma, adenocarcinoma with spindle cell differentiation, and adenosquamous carcinoma. Mixed type MBC is classified into carcinoma with chondroid metaplasia, carcinoma with osseous metaplasia, and carcinosarcoma.⁵ In our study, there were 8 cases of mixed type (carcinosarcoma), and 7 cases of epithelial type (4 cases of spindle cell carcinoma and 3 cases of squamous cell carcinoma).

Most studies have found that the tumor was large at the time of MBC diagnosis. Pezzi et al. reported that the larger sizes of MBC at clinical presentation appeared to result from a more rapid growth rate.⁶ MBC presented with axillary nodal involvement less frequently than did IDC (Invasive Ductal Carcinoma) of the breast. Six patients had nodal involvement in our study (40%). This is higher than what was observed in previous reports (6% to 28%).^{7,8}

Pezzi et al. noted that nodal positivity was more common among the carcinosarcoma variant.⁶ Three of the six patients who had nodal involvement in our study, had a carcinosarcoma variant. There is a high incidence of hormone receptor negativity as well as lower Her-2/neu expression in MBC.⁹

MBCs are often classified along the spectrum of basal-type breast cancers. These tumors represent 75-85% of all triple negative tumors (estrogen receptor, progesterone receptor, and Her-2 over expression negative).^{10,11} MBC represents approximately 5% of triple negative tumors.

In present study, most of the cases showed negative hormone receptors (oestrogen and progesterone receptors). There was only one case of high levels of hormone receptors. This low percentage of expression of the hormone receptors in our study (6.66%) is in agreement with the 0-25% reported in the literature.^{12,13}

Expression of Her2 was also low (we have not noted any case of over-expression of Her2). Metaplastic breast tumors do tend to express the HER1/EGFR (epidermal growth factor) receptor at a considerably higher rate than most other types of breast carcinoma, and this is a somewhat unique histological identifier for this type of breast cancer, and may lead to some new and potentially beneficial treatment strategies.

Song et al., comparing a group of 55 patients with MBC with a group of 767 age-matched patients with IDC, noted that over-expression of Ki-67 was more common in

the MBC group compared with the IDC group (Ki-67 $\geq 14\%$, 87% versus 63%, $P=0.001$).¹⁴ The surgical treatment of MBC has largely paralleled that of IDC. Relative to those with IDC, a higher percentage of patients with MBC receive mastectomy rather than lumpectomy.⁶⁻¹⁵ In our study 86.7% of the patients had a radical mastectomy.

Despite the large tumor size at presentation, MBC histology should not preclude breast conservation therapy in appropriate patients. Tseng and Martinez found no difference in overall or disease-specific survival whether MBC patients were treated with mastectomy or lumpectomy, even after controlling for known prognostic factors.¹⁶ Similarly, Dave et al. found no difference in overall or disease-free survival between patients with MBC undergoing either modified radical mastectomy or breast conservation therapy.¹⁷ Compared to stage-matched women with IDC, those with MBC receiving adjuvant chemotherapy have poor survival. Single institution retrospective studies suggest that these tumors are largely chemoresistant.¹⁸

This resistance to chemotherapies is likely a product of the complex genetic and nongenetic mechanisms within MBC that result in phenotypically diverse subclones and intratumoral heterogeneity. Information regarding the role of adjuvant radiation therapy (RT) for the treatment of MBC is sparse. Dave et al. reported a 10.5% rate of local recurrence for patients receiving lumpectomy and adjuvant radiation.¹⁷

Postmastectomy RT has a more limited role. In this setting, RT is recommended to patients with four or more metastatic axillary nodes, large ($>$ or $=$ 5 cm) primary tumors and chest wall invasion [19-20]. Tseng et al. described mastectomy patients who had received RT demonstrating a 33% decreased risk of death from any cause. Patients undergoing mastectomy with tumors ≤ 5 cm and less than 4 metastasis axillary lymph nodes, however, derived no benefit from RT.¹⁶ We have recapitulated the results of treatment in our study compared to related studies in Table 1.

Table1: Comparison of current study with related studies.

| Study | Age (years) | TN% | Type of surgery | CT% | RT% |
|------------------------------|------------------------|------|----------------------|----------------------------|------|
| Song et al. ¹³ | <50: 49,1 ≥50: 50,1 | 67,3 | MRM 92,7 BSC 7,7 | 48 | 49,1 |
| Nelson et al. ²¹ | 61 | 77,8 | MRM 53 BSC 47 | NA | 48,3 |
| Barquet et al. ²² | 49,6 | 83,6 | MRM 91,7 BSC 8,3 | ind CT 79,2 adj CT 39,6 | 47,9 |
| Current study | 50 | 93,3 | MRM 86,7 BSC 13,3 | adj CT 80 | 86,6 |

Recent studies have investigated receptors that may potentially serve as novel targets for chemotherapy regimens. One such target is EGFR (Her-1). Leibl and Moinfar found that targeted protein kinase such as gefitinib might be effective for some patients with MBC.²³ Although molecular analysis for possible genetic alterations in the EGFR might be required, there is a good possibility that women fighting MBC might benefit from treatment with protein kinase inhibitors, such as gefitinib and cetuximab. The prognosis of MBC, with respect to 'triple negative' status, is contrary to the norm. Recent studies have shown, contrary to a generally accepted view, that a non-triple-negative metaplastic breast carcinoma actually has a poorer prognosis when compared with the triple-negative metaplastic breast carcinoma.¹⁸

CONCLUSION

MCB is an infrequent entity and thus is rarely studied. It had distinct clinicopathological features, which include a

large tumor size at presentation, a low proportion of lymph node metastasis, a high proportion of triple negativity and a high ki67 proliferation index. Poor prognostic indicators for MBC include a tumor size larger than 5 cm, lymph node involvement and Ki-67 $>$ or $=$ 14%.

Due to its rarity and heterogeneity, there is no "standard" therapy for all patients with MBC. Surgical treatment and axillary staging parallel that of IDC with breast conservation therapy are appropriate for a select group of patients. Targeted therapies based on individualized gene profiling are promising for the future but are not commonly utilized. Adjuvant radiation should be considered part of the multimodality therapy for patients with MBC, regardless of the type of surgery.

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