

# Metaplastic carcinoma of the breast

## Treatment, results and prognostic factors based on international literature



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### Metaplastic carcinoms of the breast. Treatment, results and prognostic factors based on international literature

*Metaplastic carcinoma of the breast (MCB) is a rare form of cancer containing mixture of epithelial and mesenchymal elements in variable combinations. Few and conflicting clinical data are available in the literature addressing optimal treatment modalities, prognosis and outcome. A retrospective study was conducted to review all patients with MCB diagnosed and treated at Breast Unit of Azienda Ospedaliera "Santa Maria" Terni - Italy between 2001/2010. The aim is to describe patient's clinic pathologic features and to analyze treatment results. Six female patients were studied. The median age was 48 years (range 14/58). The median tumor size was 9 cm. (range 3/18 cm.). Two cases (33%) were identified as purely epithelial and 4 (67%) as mixed epithelial and mesenchymal metaplasia. Hormone receptors were positive in only 2 patients. Modified radical mastectomy performed in 3 patients and 5 underwent axillary node dissection. Adjuvant chemotherapy was given to all patients and postoperative radiotherapy to 4. Four patients relapsed with median time of relapse of 12 months. MCB is an aggressive form of breast cancer associated with poor outcome, high incidence of local recurrence and pulmonary metastases. The disease tends to be estrogen/progesterone receptor negative. Tumor size has an important impact on outcome. The best treatment approach is yet to be defined.*

KEY WORDS: Carcinoma of the Breast, Local recurrence, Metaplastic, Metastases, Treatment approach not yet defined.

### Introduction

Metaplastic carcinoma of the breast (MCB) is a rare type of breast cancer accounting for 1% of breast malignancies<sup>1-3</sup>. The term metaplastic carcinoma was first introduced by Huvos et al.<sup>4</sup>. Histologically, it is a poorly differentiated heterogeneous tumor containing ductal carcinoma cells admixed with areas of spindle, squamous, chondroid, or osseous elements<sup>1-3</sup>. The wide range of

microscopic appearance of MCB has resulted in variety of confusing classifications and designations including spindle cell carcinoma<sup>5</sup>, carcinosarcoma<sup>6</sup>, squamous cell carcinoma of ductal origin<sup>7,27</sup>, adeno-squamous carcinoma<sup>8</sup>, carcinoma with pseudo sarcomatous metaplasia<sup>9</sup> and matrix producing carcinoma<sup>10</sup>. The extent of metaplasia varies from microscopic foci to virtually complete replacement of the adenocarcinoma by the metaplastic elements<sup>1,11</sup>. Regardless of the morphologic pattern, immune-histochemical and ultra structural studies suggest that MCB are derived from multipotential undifferentiated cells<sup>8,12</sup>. Some authors have proposed that myoepithelial cell might be the cell origin for these tumors<sup>3</sup>. Because of the rarity of MCB, very few clinical studies are available that describe the clinical course,

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therapeutic approaches and prognostic factors. In an attempt to enhance our understanding of the natural history of this disease; we reviewed our experience on multi-disciplinary management of MCB cases treated over 10-year period at Breast Unit of Azienda Ospedaliera "Santa Maria" Terni - Italy .

## Patients and Methods

We searched the records of surgical pathology and the Tumor Registry at our institution from 2001/ 2010. We reviewed reports filed under metaplastic carcinoma of the breast as well as carcinosarcoma, sarcomatoid carcinoma, adenocarcinoma with squamous /sarcomatous metaplasia and spindle cell carcinoma to find any patients who may have been misfiled. The pathology slides were reviewed to confirm entry into the study. Cases were included if carcinoma was identified morphologically on hematoxylin and eosin stained slides and /or expressed epithelial differentiation by immunostains or cytokeratin. WHO classification system <sup>2</sup> was applied to categorize the cases into purely epithelial or mixed epithelial and mesenchymal. Only patients who had adequate clinical data for treatment and follow-up were selected. Data were gathered with regard to age, menopausal status, duration of symptoms, tumor size, clinical stage, surgical treatment, adjuvant therapy and outcome. All patients were staged at the time of diagnosis with chest radiograph, bilateral mammography, whole body bone scan, and chest and abdominal computed tomography scans. Event free survival (EFS) was calculated from the date of diagnosis till the date of relapse, death or last follow-up. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. EFS and OS were assessed for the non metastatic cases and were estimated according to the Kaplan-Meier method. Univariate analysis was performed to assess if any prognostic variables conferred an improved survivorship. These included age, menopausal status, tumor size, disease stage, surgical procedure, nodal status and use of adjuvant therapy. Cumulative survival rates were compared by the log-rank test with p-values  $\leq 0.05$  considered to be significant.

## Results

### CLINICAL DATA

Six patients with the diagnosis of MCB were identified. All patients were female. The median age at presentation was 48 years (range, 14/58). The most frequent presentation was a unilateral rapidly enlarging breast mass. One patient presented with inflammatory breast cancer <sup>28</sup>. The duration of symptoms ranged from 1 to 24 months, with a median of 8 months. The median tumor size at diagnosis was 9 cm (range, 3/18). Three patients

(50%) had stage III disease and two (33,3%) had metastatic disease to the liver at presentation.

## PATHOLOGICAL FEATURES

Two cases (33.3%) were classified as adenocarcinoma with spindle cell differentiation (SpCd) (Figg. 1, 2) while another 2 (33,3%) as carcinosarcoma with malignant mesenchymal component. Three patients had heterologous tissues, 2 with chondroid and 1 with osseous metaplasia (Fig. 3). Among the 6 patients known to have had an ALND, 4 (66,6%) were node positive. The histological subtype of the primary tumor in node positive patients was purely epithelial in all cases (2 adenocarcinoma with SpCd ) and mixed epithelial with chondroid metaplasia in 2. The median number of axillary lymph nodes (ALN) dissected was 12 (range, 2/24) and the median number of positive nodes was 2 (range, 1/9). The nodal metastases demonstrate only malignant epithelial elements. Estrogen/progesterone receptor (ER/PR)

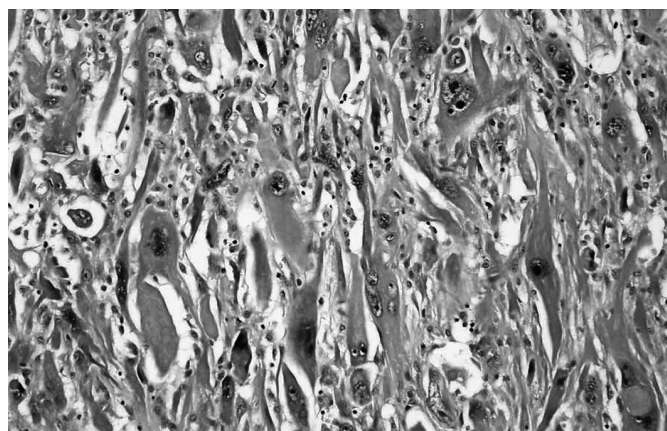


Fig. 1

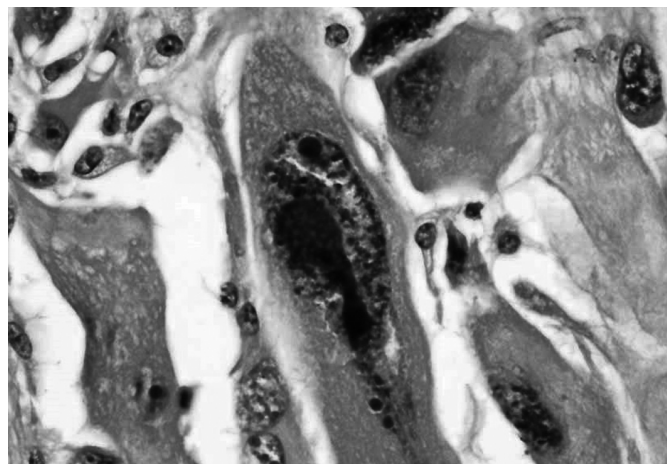


Fig. 2

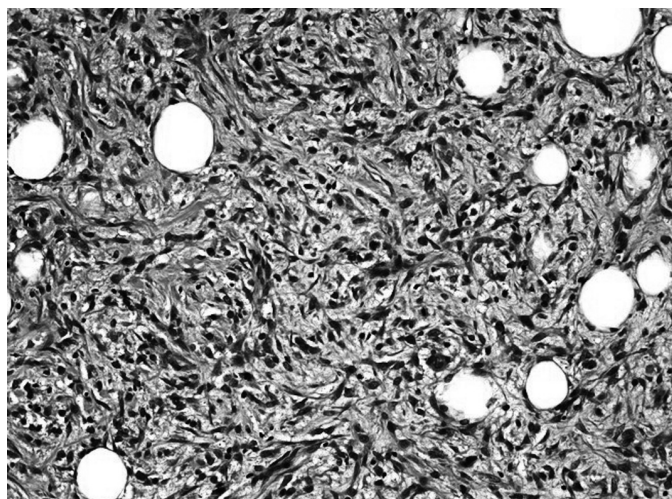


Fig. 3

immunostaining was done in 6 cases and yielded negative results in 5 (84%). HER2/neu protein overexpression by immunohistochemistry was negative in 5 of 6 tumors examined.

#### CLINICAL COURSE

All patients except one had modified radical mastectomy (MRM) and one had simple mastectomy. Axillary lymph node dissection (ALND) was performed in 6 patients. Induction chemotherapy prior to surgery was administered to 2 patients, 1 of whom received doxorubicin-based chemotherapy regimens. All patients received adjuvant chemotherapy. The regimens used were doxorubicin-based in 3 patients and CMF in 1 and docetaxel in 2. The median number of administered cycles was 4 (range 3/9). Adjuvant postoperative radiation therapy was given to all patients with doses ranged from 45/50 Gy. Two patients received tamoxifen in adjuvant setting. Four of the six patients (66.6%) who initially achieved complete remission relapsed with a median time of relapse of 12 months (range 2/28). Local recurrences occurred in 2 patients (33.4%). No malignancy developed in the contralateral breast. The two patients with isolated local recurrences achieved second CR by surgery / radiation therapy. They had a median survival of 47 months (range, 18/65) from time of recurrence. The salvage chemotherapy regimens given were diverse: 1 patients treated with gemcitabine and cisplatin combination, 1 with paclitaxel and cisplatin. One ER/PR positive patient was given letrozole on relapse and another HER2/neu positive patient was treated with herceptin/navelbine as third line therapy. Overall, there was only one short-lived partial response to salvage doxorubicin-based regimens. The median survival after distant relapse was 8 months. For the 3 patients who followed-up for more than 6 months and had loco-regional dis-

ease at presentation, the median follow-up was 21 months (range, 7/35). At the time of analysis, 3 patients (50%) have died of their disease and 9 are alive with no evidence of disease.

#### Discussion

Of the 1800 new patients with breast carcinoma seen at Azienda Ospedaliera "Santa Maria" Terni Italy over a 10-year period, 6 (0.6%) had the histological metaplastic variant. This incidence is similar to that reported previously<sup>1,2</sup>. Most of the series were published in journals of pathology, yet the classification of this disease is still confusing, and reflects opinions of expert pathologists rather than a consensus. The clinical features, treatment and outcome are equally diverse and are limited to small reports from few institutions including our own report. It has been reported that MCB is more likely to develop in women older than 50 year<sup>9,11,13,15</sup>. The median age at diagnosis in our patients was 48 years, which is by far the lowest reported. The usual presentation is a breast mass, which tends to grow rapidly<sup>3,9</sup>. The median tumor size was 9 cm compared to a maximum of 5/6 cm reported in many series<sup>10,11,13,17</sup>. In contrast to others<sup>9,14,16</sup> most of the cases in our review presented with advanced clinical stages. MCB has a low potential for lymph node metastasis. The reported incidence has been ranged from 0/50%<sup>5,9,11,13,19</sup>. In our study, the rate was 66.6% and the median number of positive ALN was 2. This is still considered low if the tumor size and stage of the disease are taken into account and if historical comparison with adenocarcinoma of the breast is considered<sup>20</sup>. In the 4 cases with pathological nodal involvement, malignant epithelial component was only seen. Many authors have reported this observation<sup>9,11,18</sup>. One of the universal finding in all studies is the high rate of ER/PR negativity, in the range of 70/100%<sup>11,13,17</sup>. This is not unexpected because these tumors typically have a high grade or poorly differentiated carcinomatous component<sup>21</sup>. The absence of predominant glandular epithelial component in many cases might also explain the paucity of ER/PR expression<sup>17</sup>. Consistent with the literature, 83% of the tumors examined in our study lacked ER/PR expression. Although data are limited in the literature, MCB rarely seems to overexpress HER2/neu oncoprotein. One of the 26 MCB cases reported by Barnes et al<sup>22</sup> was HER2/neu positive. In our review HER2/ neu over-expression was seen in only one (1/6) case with chondroid metaplasia. To date there are no standard guidelines for the treatment of MCB. Modified radical or radical mastectomy was the surgical procedure commonly performed in most of the series<sup>13,17</sup>. Because of the low risk of lymphatic spread, Caceres et al.<sup>23</sup> suggested that wide local excision with cancer-free margins would be appropriate for local control. Unlike invasive carcinoma of the breast, ALN metastases

in MCB do not correlate with clinical outcome<sup>6,9,11,14,15,19</sup>. The higher incidence (66.6%) of nodal metastases and larger median tumor size seen in our patient cohort make us support MRM as optimal surgical treatment of choice. Some investigators have linked the risk of ALN metastases to the underlying histological subtype, being extremely low in spindle cell carcinoma<sup>5,11,19</sup>. None of the 2 cases diagnosed as carcinosarcoma with malignant mesenchymal component in this review had clinical or pathological ALN involvement. Taking these observations into consideration, ALND might be spared in-patients with small size carcinosarcoma tumors. The overall response rate was 50% with no clinical complete remission noted. Experience with neoadjuvant chemotherapy in MCB is extremely limited in the literature to evaluate its impact on the outcome. Adjuvant chemotherapy was administered to six patients and two of them experienced distant relapse upon first disease recurrence. In the study of Pitts et al.<sup>13</sup>, 7 of 34 received adjuvant chemotherapy and 4 of them remained disease free at a follow-up of 7/70 months. Rayson et al.<sup>15</sup> found that 7 of the 9 cases that received adjuvant therapy relapsed indicating ineffectiveness of adjuvant chemotherapy in this disease. In the report of Choa et al.<sup>16</sup>, 5 of 6 patients who had adjuvant chemotherapy remained disease free at follow-up period ranged from 3/9 years. The OS analysis in their study was in favor of patients who never received chemotherapy; however the difference was not statistically significant. On the other hand, Gutman et al.<sup>14</sup> noted significant OS and DFS improvements only for patients with stage I/II treated with mastectomy and adjuvant therapy. In all these studies including ours, the numbers receiving adjuvant chemotherapy remains small to reach firm recommendations regarding its use and warrants multicentric trials to examine its influence on survival. Several authors<sup>14,24</sup> found no survival advantage for patients treated with chemotherapy or hormonal therapy for metastatic disease. Rayson et al.<sup>15</sup> found only one response in seven patients, patients with loco-regional disease at diagnosis. treated with salvage chemotherapy (doxorubicin based), and reported median survival of 8 months from detection of disease relapse. Our results were similar. The median survival, after distant relapse, was short (8 months) and only one of 6 patients had short-lived partial response to doxorubicin-based therapy. Our experience with newer agents including gemcitabine, taxanes, navelbine and herceptin was not encouraging. The disease seems to be refractory in the metastatic setting to the current chemotherapeutic drugs available but the small number of cases treated makes it difficult to draw satisfactory conclusions. These data also suggests that patients with metastatic MCB should be considered for investigational phase II trials. In view that most of our patients were ER/PR negative, our experience with hormonal therapy is limited. Rayson et al.<sup>15</sup> found no response in 4 ER/PR positive patients

treated with tamoxifen at time of relapse. Two (33,3%) of our patient cohort experienced local relapse and two (33,3%) developed pulmonary metastases during their clinical course. Noticeable tendencies for local failure and pulmonary metastases were universal features to MCB in many reports<sup>13,15,24,25</sup>, suggesting that the clinical behavior is similar to sarcomas. The high incidence of local failure in our study could also be attributed to the large tumor size and the higher tumor stages at presentation. Rosen and Ernsberger<sup>8</sup> advised the routine use of adjuvant radiation therapy in MCB patients. It has been shown that the only patients who had survival advantage from salvage treatment were those with isolated local recurrences that could be treated with local therapy<sup>14,15,26</sup>. One case with local recurrence in our series was successfully salvaged by surgery / radiotherapy and had a median survival of 47 months. The overall survival across the studies at 3/5 years ranged from 39/72%<sup>13,17</sup>. Our low survival rate (16,7%) can be contributed to certain unique patient's characteristics: larger tumor size, higher stages, higher rate of nodal involvement and younger age group. MCB has been described to have poor outcome as compared to adenocarcinoma<sup>9,11,14,15,24,28</sup>. Conversely, few others reported favorable prognosis<sup>16,17</sup>. The tumor size at presentation best correlated with outcome<sup>7,9,11,16,26</sup>. In this review, the tumor size had an impact on EFS but not on OS, possibly because of successful salvage treatment for local recurrences. Clinical stage I/II, age 50 years and absence of nodal metastases at presentation were favorable prognostic factors found in few series<sup>9,14,16</sup>. The presence of a mesenchymal metaplastic element in carcinoma of the breast is a poor prognostic factor<sup>6,14,24,26</sup>. However, several authors showed that the differences in survival among the various subgroups of MCB are minor<sup>11,18</sup> and Pitts et al.<sup>13</sup> advised that sub-classification of MCB is of greater pathologic than clinical interest. The type of metaplasia in our report did not affect the survival but the low number of cases makes firm conclusions difficult. In conclusion, MCB is a rare form of breast cancer. The results of the present study demonstrate that MCB is an aggressive disease and has poor prognosis. Pathological classification of this disease needs to be unified. The clinical behavior is as diverse as the histology. The majority of these tumors are receptor negative. The lymph nodes are involved mainly by carcinomatous elements. The disease tends to recur locally and frequently metastasizes to the lung. The small number of patients in most of the studies makes solid conclusions as regards to the optimal treatment difficult. The prognosis reported in the literature is quite variable and the tumor size at diagnosis is the single most important prognostic factor. Multi institutional prospective trials after consensus on pathology are needed to advance our knowledge in understanding and managing this uncommon disease. The search for biological prognostic factors and innovative therapies are required to improve the outcome of this disease.

## Riassunto

Il Carcinoma Metaplastico della Mammella (CMM) è una rara forma di cancro determinato dalla miscela di elementi epiteliali e mesenchimali in combinazioni variabili. Pochi dati clinici e contrastanti sono disponibili in letteratura per affrontare modalità di trattamento ottimale, la prognosi e l'esito. Uno studio retrospettivo è stato condotto per esaminare tutti i pazienti con MCB diagnosticati e trattati nella Breast Unit dell'Azienda Ospedaliera "Santa Maria" Terni - Italia tra il 2001 ed il 2010. Sei pazienti di sesso femminile sono state studiate. L'età mediana era di 48 anni (range 14/58). La dimensione del tumore mediana era di 9 cm. (diametro 3/18 cm.). Due casi (33%) sono stati identificati come puramente epiteliale e 4 (67%) come miste, metaplasia epiteliale e mesenchimale. I recettori ormonali sono risultati positivi in soli 2 pazienti. La mastectomia radicale modificata è stata eseguita in 3 pazienti e 5 sono state sottoposte a dissezione ascellare. La chemioterapia adiuvante è stata somministrata a tutte le pazienti e la radioterapia post-operatoria a 4. Quattro pazienti hanno presentato recidiva con tempo mediano di 12 mesi. Il CMM è una forma aggressiva di cancro al seno associato ad esito sfavorevole, alta incidenza di recidiva locale e di metastasi polmonari. La malattia tende ad essere estrogeno / progesterone recettore negativo. Le dimensioni del tumore hanno un impatto importante sul risultato. L'approccio migliore trattamento è ancora da definire.

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