



Metaplastic Breast Carcinoma: Analysis of Clinical and Pathologic Characteristics - A Case Series

Semra Salimoğlu¹, İsmail Sert¹, Mustafa Emiroğlu¹, Cem Karaali¹, Dilek Kuzukıran¹, Yasemin Akyüz Kırmızı¹, Gülden Diniz², Cengiz Aydın¹

¹Clinic of General Surgery, Tepecik Training and Research Hospital, İzmir, Turkey

²Clinic of Pathology, Tepecik Training and Research Hospital, İzmir, Turkey

ABSTRACT

Objective: Metaplastic breast cancer (MBC) is a rare type of breast cancer that is considered to be clinically aggressive. The clinical significance and prognostic risk factors of MBC are limited. This study comprises a retrospective analysis of the clinical and pathologic findings of a series of patients treated for MBC.

Materials and Methods: The files of 657 patients who underwent surgery because of breast cancer at our clinic were examined and the data found on 11 patients who were diagnosed as having MBC were analyzed.

Results: With a median age of 56 years, all patients were postmenopausal and presented with a palpable mass on physical examination. Symptoms of ulceration and skin involvement were seen in only one patient. Eight patients were diagnosed as having squamous cell carcinoma (SCC), and 3 had both SCC and osseous differentiation. The median diameter was 3.8 cm (max. 14 cm; min. 1.5 cm). Lymph node metastasis was detected in 5 (45%) patients. Progesterone (PR) and estrogen (ER) were both negative in 11 (100%) patients and 10 (90.9%) patients, respectively, and CerbB2 was negative in 7 (63.6%) patients. Patients were followed up for a median period of 15 months (range, 6-40 months); at the end of which, 10 patients survived and one died of cardiac arrest at 7 months post-operatively. No instances of local recurrence or distant organ metastasis were found in any patients. The overall patient survival rate was 90%.

Conclusion: There is no consensus on the clinical significance or best treatment approach for metaplastic carcinoma. In our study, patients with MBC were of advanced age, had tumors with large margins, high negativity for hormone receptors, and moderate- to well-differentiated histology.

Keywords: Metaplastic carcinoma, breast, prognosis, treatment, incidence

Introduction

Metaplastic breast carcinoma (MBC) is a rare but clinically aggressive type of breast cancer (1). This form of cancer comprises 1-2% of all breast cancers (2, 3). In 2000, MBC was identified by the World Health Organization (WHO) for the first time as a distant pathologic subtype (4). All breast cancers may include a small metaplastic area; however, the diagnosis of metaplastic cancer is only used for tumors dense with heterogeneous foci. The current (2012) WHO classification distinguishes five subtypes: low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, and carcinoma with mesenchymal differentiation (chondroid differentiation, osseous differentiation, and other types of mesenchymal differentiation) (5).

Most MBCs have the same clinical characteristics as basal cancers, with triple-negative biology. Despite a larger tumor size and higher histologic grade, fewer metastases to lymph nodes are seen than in more common ductal cancers. Compared with other invasive ductal breast cancers, patient prognosis is worse, but the exact clinical significance and prognosis have not yet been clarified (6, 7). The aim of this study was to retrospectively explore the demographics and pathologic, clinical, and observational data of 11 patients with MBC.

Material and Methods

A thorough investigation of our database records showed that 657 patients underwent surgery for breast cancer at our hospital between 2009 and 2014. Closer examination revealed that 11 of these patients were diagnosed as having MBC. We performed a retrospective analysis of the demographic data, clinical and pathologic characteristics, adjuvant treatment regimen, and follow-up details of these 11 patients. This study was approved by the local ethics committee.

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Address for Correspondence:

Semra Salimoğlu, e-mail: semrasalimoglu@yahoo.com.uk

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Statistical analysis

SPSS version 21.0 (SPSS Inc.; Chicago, IL, USA) was used for analysis purposes. Results were expressed as percentages or median ± SD. Patient survival rates were determined using the Kaplan-Meier method.

Results

The patient group comprised post-menopausal women with a median age of 57±8 years (range, 43-73 years). Each presented with a palpable, painless lump in the breast. With one exception, none of the patients had a history of breast cancer or had previously undergone surgery for cancer. The left breast was involved in five patients and the right breast in six. Only one patient exhibited skin involvement and ulceration. With the exception of the patients who had undergone interventions at other hospitals, further to a physical examination, ultrasonography and mammography were performed in all patients.

The diagnosis of malignancy was made through a fine-needle aspiration biopsy (FNAB) in six patients, with Tru-cut biopsy in three patients, and excisional biopsy in the remaining two. Excisional biopsy was performed at different institutions and the pathology blocks were re-evaluated at our institution. Clinical examination revealed involvement of axillary lymph nodes in five (45%) patients. At this stage, four patients were assessed as stage 2B; four patients as 2A; two patients as 3B; and one patient as stage 1. No patients had distant organ metastasis. Six patients underwent breast conserving surgery; one patient had oncoplastic breast reduction mammoplasty, and four patients underwent modified radical mastectomy (MRM). One of the patients who underwent MRM had a huge mass, ulceration, and infection. To detect the sentinel lymph node during the operation, methylene blue staining was used.

One of the patients with locally-advanced breast cancer had received neo-adjuvant chemotherapy before undergoing breast conserving surgery (BCS). Before the BCS, the tumor margin was marked using a polypropylene suture. At the time, the pathology showed stage 2 infiltrative ductal carcinoma with negative lymph node metastasis (0/5)

in the sentinel lymph node biopsy (SLNB) procedure. Five years later, a mass developed in the same location coupled with ulceration of the skin and thus a total mastectomy was performed.

Eight patients were diagnosed as having squamous cell carcinoma (SCC) and three had both SCC and osseous differentiation (Figure 1). The median diameter of the tumor was 3.8 cm (max. 14; min. 1.5). Lymph node metastases were detected in 5 (45%) patients. PR was negative in 11 (100%) patients and ER negative in 10 (90.9%) patients. CerbB2 was negative in 7 (63.6%) patients. P63 status of the patients were positive in 6 patients, focally positive in 2 patients, and negative in 3 patients. The clinical and pathologic findings are reviewed in Table 1.

Two patients (18.2%) received neo-adjuvant chemotherapy (diagnosed through incisional biopsy) and ten patients received adjuvant chemotherapy. One patient received radiotherapy only post-surgery without chemotherapy because of at high risk due to co-morbidities. Five patients were treated with doxorubicin, cyclophosphamide, and paclitaxel (AC+P); two patients with 5-fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel (FEC+D), one patient AC,

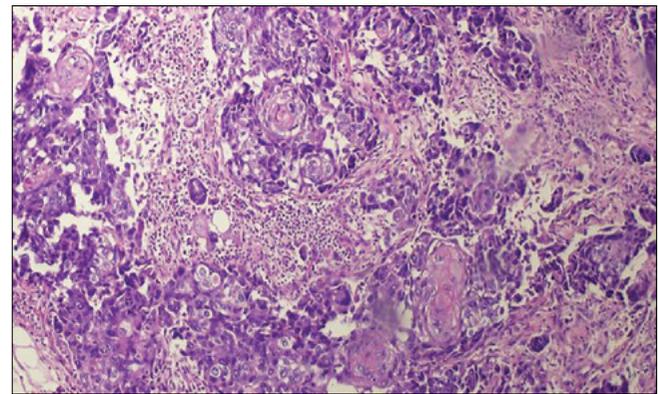


Figure 1. Squamous cell carcinoma of the breast (HE× 100)

Table 1. The clinical and pathologic findings

No	Age - years	Tumor size	TNM Stage	Pathology	ER	PR	HER2	Pathology N status	Surgery	CT	Final status	Follow-up (months)
1	59	4.0 cm	2A	OD	-	-	-	0	BCS	AC	Alive	19
2	50	5.0 cm	2B	SC	-	-	+	1	BCS	-	Alive	13
3	63	1.5 cm	2B	SC	-	-	-	2	OBS	AC+P	Alive	20
4	56	3.8 cm	2A	SC	-	-	-	0	BCS	AC+P	Alive	20
5	75	5.0 cm	2B	SC	-	-	+	0	MRM	FEC	Exitus	7
6*	52	6.0 cm	3B	OD	-	-	+	0	MRM	CAF	Alive	12
7*	61	1.5 cm	2B	SC	+	-	-	0	BCS	AC+P	Alive	40
8	49	14.0 cm	3B	SC	-	-	-	2	MRM	AC+P	Alive	7
9	64	1.5 cm	1	SC	-	-	-	1	BCS	AC+P	Alive	15
10	55	1.5 cm	2A	SC	-	-	+	1	BCS	FEC+D	Alive	6
11	43	3.5 cm	2A	OD	-	-	-	0	MRM	FEC+D	Alive	24

*Neo-adjuvant chemotherapy

OD: osseous differentiation; SC: squamous cell carcinoma; BCS: breast conserving surgery; OBS: oncoplastic breast surgery; MRM: modified radical mastectomy; CT: chemotherapy; A: doxorubicin; C: cyclophosphamide; P: paclitaxel; F: 5-fluorouracil; E: epirubicin

one patient FEC, and one patient with cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF). Nine of the eleven patients received radiotherapy. The four patients who were HER-2 positive were treated with trastuzumab.

Patients were followed up for a median period of 15 months (max. 40; min. 6). At the end of the follow-up period, ten patients survived and one died of cardiac arrest at 5 months post-op. No instances of local recurrence or distant organ metastases developed in any patients during the follow-up period. The overall patient survival rate was 90%.

Discussion and Conclusion

Metaplastic breast carcinomas are a very rare form of breast tumor with a frequency of only 1-2% (2, 3). In our study, the incidence rate was 1.6%, which was compatible with the literature. This form of cancer is usually found in the 49-59 years age group (8-10). In a population-based study by Pezzi et al. (11), data from 892 patients with MBC were compared with those of patients with invasive ductal - carcinoma. Patients with MBC were most commonly found to be older, with tumors of larger size and more advanced stage; they usually tested negative for ER and the tumors were poorly differentiated (11). Clinical examination usually reveals fast-growing palpable tumors (10, 12). Most patients present with a well-defined mass over 2 cm in size, sometimes reaching 4-5 cm (3, 10, 13). A connection between tumor size, recurrence, and survival rates has been suggested (10). However, there are studies that indicated that there was no such relationship (14, 15). In our series, the median age was 56 and 90.9% of patients tested negative for ER. With the exception of four patients, the tumors were all over 3.5 cm, with a 14-cm mass in one patient. There were no malignancy-related deaths in our study, although this may be accounted for by the short follow-up period. Our approach to diagnostic imaging was similar to that of any other breast mass. Mammography, ultrasonography, and MRI were used identically in MBC as in any other invasive ductal cancer or even lesions likely to be benign (16). However, radiologic findings may change according to the makeup of the tumor (17). In mammography, MBCs may be seen as high-density, well-defined or irregular masses, spiculated or partially spiculated (16). Microcalcifications are rarely seen in these lesions (10, 13, 16); if they are present, they are amorphous, coarse, punctate or pleomorphic in pattern (18).

Ultrasonographic examination tends to reveal a solid mass of heterogeneous cystic appearance (16, 18). Masses either appear irregular in shape, microlobular, with defined borders, or with undefined borders. MRI usually reveals an irregular mass with spiculated borders; high or increased activity at T2 signal intensity; and isointense or hypointense in T1-weighted intensity is usually seen (16). In our series, mammography and breast ultrasounds were performed on all patients (except those referred from other hospitals). Additional breast MRI was requested for four patients. All patients were identified as having masses of probable malignancy as a result of testing.

Despite the large tumor size, lymph node involvement is rare in these cases (10, 13). The incidence rate for lymph node metastasis is between 0% and 63% (9, 10, 19, 20). In our series, lymph node involvement was seen in five patients (45%).

Metaplastic carcinomas form a heterogeneous neoplastic group. This group of neoplasia includes low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, and carcinoma with mesenchymal differen-

tiation (chondroid differentiation, osseous differentiation, and other types of mesenchymal differentiation) (5). An important factor in determining the patient prognosis is the type and spread of the metaplastic component (21). Tumors with a sarcomatous component seem to have a worse prognosis (21). In our study, three of our patients had osseous differentiation; the remainder only had squamous differentiation. Sarcomatous differentiation was not seen in our case series.

The optimum treatment regimen in MBC is still undecided. Mastectomy is most commonly performed because patients with MBC present with large size tumors (10). However, research has shown that there was no difference in the overall-survival rate or disease-free survival rate when BCS was chosen as an alternative to mastectomy (15, 22). In our study, six of our patients underwent BCS, four had MRM and one patient was treated with oncoplastic breast surgery (bilateral reduction mammoplasty).

There is very little literature to support the effective use of standard breast cancer chemotherapy regimens in patients with MBC (23). Single center retrospective studies showed that MBC tumors were resistant to chemotherapy (11, 15). In our study, all patients except one received chemotherapy.

Hormone therapy, similar to chemotherapy is also thought to be of little effect in treating MBC. In most cases of MBC, hormone receptors are negative (6). Triple-negative cases MBC usually have a worse prognosis than triple-negative invasive ductal cancers (24). In a retrospective study of 2338 patients with MBC, positive hormone receptors were not shown to lead to a better prognosis (7). In our study, PR was negative in all patients, ER was negative in ten, and CerbB2 hormone receptors were negative in seven.

The use of radiotherapy in adjuvant treatment is also unclear (3). After BCS, radiotherapy is used as standard procedure to reduce local recurrence in invasive ductal carcinomas (22). In a retrospective study that included 1501 patients with MBC, the use of radiotherapy after lumpectomy led to the death rate to be reduced by 49% (22%). In patients undergoing mastectomy, radiotherapy is recommended for those with four or more lymph node metastases, tumor spread outside the capsule, tumors larger than five cm, and those with involvement of the chest wall (25). The same study noted a 33% reduction in the risk of death for patients who received radiotherapy after mastectomy (22). Until now, radiotherapy has not been shown to provide any advantage in patients with MBC who have tumors of less than five cm and fewer than four lymph node metastases (22). However, in cases with tumors of four cm or larger or with four or more lymph node metastases, radiotherapy is considered to be a necessary part of the multimodal treatment (22). Shah et al. (23) reported in their collation that radiotherapy should be used as an adjuvant therapy, regardless of the surgical method used. In our series, all nine patients (two with MRM, six with BCS, and one with oncoplastic breast surgery) were given adjuvant radiotherapy.

In an analysis of survival rates of MBC patients based on a population in the United States of America, 1011 patients with MBC were compared with 253 818 patients with invasive ductal breast carcinoma (2). The authors of the study highlighted a worse survival rate in patients with MBC (2). As the follow up period for our patients was short in our series, no local recurrence or cancer-related deaths were noted.

There is no consensus of opinion on the clinical significance and most suitable treatment methods for patients with MBC. In our study, the

patients with MBC were of mature age with large size tumors, they had high hormone receptor negativity and their histologic stage was moderate to high. Prospective multi-center wide-scale studies should be carried out in the future to cast light on the clinical and pathologic aspects of MBC.

Ethics Committee Approval: Ethics committee approval was received for this study from local ethics committee.

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