

RESEARCH ARTICLE

Metaplastic Breast Carcinoma: Case Series and Review of the Literature

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Abstract

Metaplastic breast carcinoma (MpBC) is a rare disease entity, accounting for less than 1% of all breast carcinomas. Furthermore, it is a heterogenous disease with different subgroups, including malignant epithelial (carcinoma) and stromal (sarcoma) features. Here we evaluated, retrospectively, 14 female MpBC patients admitted to Ankara Oncology Training and Research Hospital between 2005 and 2011. Median age was 45.5 (range:16.0-76.0) and tumor size 57.5 mm (range: 20.0-80.0 mm). Histopathological subtypes were as follows: 5 carcinosarcoma, 5 squamous and 4 adenosquamous carcinoma. All but one with upfront lung metastasis, had their primary breast tumor operated. Axillary lymph nodes were involved in 64.3%. The most common sites of metastasis were lungs and brain. Chemotherapy including anthracycline, taxane and even platinumium was planned for adjuvant, neoadjuvant and palliative purposes in 9, 3 and 1 patient, respectively. Median cycles of chemotherapy was 6 (range:4-8). Median follow-up of the patients was 52 months (95% CI 10.4-93.6 month). Median 3 year progression free survival (PFS) and overall survival (OS) in this patients cohort were 33% and 56%, respectively. In conclusion, MpBC is a rare and orphan disease without standardized treatment approaches and the prognosis is poor so that larger studies to investigate different treatment schedules are urgently needed.

Keywords: Breast metaplastic carcinoma - rare disease - orphan status - poor prognosis

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Introduction

Metaplastic breast carcinoma (MpBC) is a rare disease entity of which it constitutes less than 1% of all breast carcinomas and first defined by Huvos et al. (Huvos et al., 1973; Tavassoli, 1992). MpBC is a heterogenous disease and includes squamous cell, spindle cell, matrix-producing, carcinosarcoma, osteoclastic giant cell metaplastic carcinoma, condroid differentiated metaplastic carcinoma and adenosquamous carcinoma subgroups (Wargotz et al., 1989a; 1989b; Wargotz, 1989a; 1990b; 1990c). Although pathogenesis and cell of origin of MpBC is still not completely clear, in some studies, it was claimed to be derived from myoepithelial origin (Tavassoli, 1992).

In comparison to classical breast adenocarcinomas, tumor size is usually greater and the incidence of axillary lymph node involvement is less in MpBC cases (Chao et al., 1999; Beatty et al., 2006). Hormone and HER2 receptor positivity rates are also lower (0% to 26% for hormone receptors) in MpBC (Khan et al., 2003; Bae et al., 2011).

The aim of this retrospective study was to evaluate MpBC patients to find out their clinical and pathological characteristics and also their treatment and probable survival difference.

Materials and Methods

Between 2005 and 2011, 14 female MpBC patients admitted to Ankara Oncology Hospital, were evaluated, retrospectively. Patients' demographic characteristics, pathological characteristics of tumors, axillary lymph node involvement, metastatic sites, treatment schedules and survival data were evaluated using the medical records of patients.

Estrogen receptor (ER), and progesterone receptor (PR) positivity was defined as immunohistochemical staining with more than 1%. Positivity for HER-2 receptor was defined as strong complete membrane staining in more than 10% of tumor cells or positive with fluorescent in situ hybridization technique (FISH).

The response was evaluated by using the "Respond Evaluation Criteria in Solid Tumors". Progression free survival (PFS) was calculated from the date of diagnosis until disease progression. Overall survival (OS) was calculated from the date of diagnosis and death for any reason or the date of last contact.

Statistical Analysis

Descriptive statistics were performed to summarize the patients' characteristics. Comparison of the characteristics

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were analyzed by using analysis of variance (ANOVA) for means and Pearson chi-square-test for frequencies. The survival of the patients was estimated by using the Kaplan-Meier method. A p value less than 0.05 was considered to be statistically significant. For statistical analysis, SPSS for Windows, version 15.0 software (SPSS Inc, Chicago, Illinois, USA) was used.

Results

Median age of 14 female patients was 45.5 cm (range:16.0-76.0 cm). Median tumor size was 5.7 cm (range: 2.0-8.0 cm). Histopathological subtypes were carcinosarcoma, squamous and adenosquamous carcinoma (Table 1). Although patients with adenosquamous tumor subtype had a relatively smaller tumor diameter, this was not statistically significant (median tumor diameter: 36.3 mm; range: 16.3-56.1 mm; p:0.089).

Modified radical mastectomy and axillary lymph node dissection was the surgery of choice in 11 patients. Axillary lymph nodes were involved in 64.3% (9/14) of the patients.

As a whole, patients were usually staged as 2 and 3. More than half the patients had grade 3 tumor (57.1%). Of the 4 reported cases, the median Ki-67 proliferation index was 70% (50-70%). Lymphovascular invasion was positive in 3 patients. One patient had ER positive (7.1%), 2 patients were PR positive (14.3%) and 1 patient was HER-2 positive (7.1%).

The most commonly involved distant metastatic sites were lungs and brain (4 and 3 patients). Locally recurrent disease was rare and observed in only 1 patient. One patient was initially metastatic to the axillary lymph nodes and lungs at the time of diagnosis who was also considered as inoperable.

In 2 of 3 brain metastatic MpBC patients squamous component was evident. Chemotherapy was planned for adjuvant, neoadjuvant and palliative purposes in 9, 3 and 1 patient, respectively. None chemotherapy was performed for one patient. Salvage chemotherapy with capecitabine was chosen for 2 of 3 brain metastatic MpBC patients. Median cycles of chemotherapy was 6 (range:4-8).

Adjuvant radiation therapy was received by 13 patients. Pathological complete response (pCR) was seen in 2 of 3 patients treated with neoadjuvant chemotherapy (67%). Progression of disease was seen in 4 of 9 patients, 1 of 3

Table 1. Patient and Tumor Characteristics

No. of the patients	14	
Median Age, years (range)	45.5 (16- 76)	
Median Tumor Size, mm, (range)	57.5 (20- 80)	
	No.	(%)
Menopausal Status	Pre	7 (50)
	Post	7 (50)
Tumor Size	pT2	4
	pT3	8
	pT4	1
Nodal Status	pN1	1
	pN2	3
	pN3	4
Upfront metastatic disease at presentation		1
TNM Stage	II	5
	IIIA	4
	IIIC	4
	IV	1
Positive estrogen receptor status		1 (7.1)
Positive progesterone receptor status		2 (14.3)
Positive HER-2 status		1 (7.1)
Grade 3 tumor		7 (57.1)
Histology subtype	Carcinosarcoma	5 (35.7)
	Squamous	5 (35.7)
	Adenosquamous	4 (28.6)
Type of the surgery	MRM+AND	11
	BPS +AND	1
	SM	1
	Inoperable	1
(Neo)adjuvant chemotherapy		13
Palliative chemotherapy (TEC)		1
Adjuvant chemotherapy regimens	CAP	2
	CAF	2
	CAF+TAX	5
Neoadjuvant chemotherapy regimens	CAP	1
	CAF+TAX	2
Locally recurrent disease		1 (7.1)
Site of Distant Metastasis	Lungs	4 (28.6)
	Brain	3 (21.4)
	Bone	1 (7.1)

Table 2. Characteristics of Metaplastic Breast Carcinoma Patients

Age	Menopausal status	Tumor size	Ve+ ALN No.	TNM Stage	ER	PR	CerbB2	Histologic subtype	Type of surgery	Neo-Adjuvant chemotherapy	Recurrence site	Salvage chemotherapy	Response to salvage chemotherapy	Last Status
1 57	Post	2	NA	IV	-	+	-	Adenosquamous	Inoperable		Lung	TEC (first line) Cisplatin+etoposide (second line)	Progression	Exitus
2 16	Pre	7	0	II	-	-	-	Carcinosarcoma	MRM+AND	CAP	-			Alive without recurrence
3 58	Post	8	2	IIIA	-	-	-	Carcinosarcoma	MRM+AND	CAF+TAX	-			Alive without recurrence
4 76	Post	4	2	IIIA	-	-	-	Squamous	SM	-	Local	CA	Stable	Exitus
5 58	Post	6	3	IIIC	-	+	-	Adenosquamous	MRM+AND	CAF+TAX	-			Alive without recurrence
6 44	Pre	7	2	IIIA	-	-	-	Squamous	MRM+AND	CAP(Neo)	-			Alive without recurrence
7 33	Pre	5.5	0	II	-	-	-	Carcinosarcoma	MRM+AND	CAP	Brain	TAX+Capecitabine	Stable	Alive with the disease
8 47	Pre	7	0	II	-	-	-	Squamous	MRM+AND	CAF	-			Alive without recurrence
9 44	Post	8	3	IIIC	-	-	+	Squamous	MRM+AND	CAF+TAX	Lung	Cisplatin+etoposide	Progression	Exitus
10 27	Pre	2	0	II	-	-	-	Carcinosarcoma	BCS+AND	CAF+TAX	-			Alive without recurrence
11 64	Post	3.5	3	IIIC	-	-	-	Adenosquamous	MRM+AND	CAF+TAX (Neo)	-			Alive without recurrence
12 37	Pre	5	3	IIIC	-	-	-	Adenosquamous	MRM+AND	CAF+TAX (Neo)	Brain+bone	Sisplatin+gemcitabine	Progression	Exitus
13 69	Post	6.5	1	IIIA	-	-	-	Carcinosarkoma	MRM+AND	CAF+TAX	Lung	-		Alive with the disease
14 32	Pre	4	0	II	+	-	-	Squamous	MRM+AND	CAF	Lung+brain	TAX+Capecitabine	Progression	Exitus

*Post: Postmenopausal, Pre: Premenopausal, ALN: axillary lymph node, ER: estrogen receptor, PR: progesterone receptor, NA: not available, MRM: modified radical mastectomy, AND: axillary lymph node dissection, SM: simple mastectomy, BCS: breast conserving surgery, TEC: cyclophosphamide (600 mg/m²) + epirubicin (90mg/ m²) + docetaxel (75 mg/ m²), CAP: cisplatin (50 mg/ m²) + doxorubicin (50 mg/ m²) + cyclophosphamide (500 mg/ m²), CAF: cyclophosphamide (600 mg/ m²) + doxorubicin (60 mg/ m²) + 5-fluorouracil (600 mg/ m²), TAX: Docetaxel (75 mg/ m²), CA: cyclophosphamide(600 mg/m²) + adriamycin (60 mg/m²).

patients and 1 of 1 patient who received adjuvant (44%), neoadjuvant (33%) and palliative chemotherapy (100%) respectively.

Six of the progressed 7 MpBC patients received salvage chemotherapy. Two adenosquamous and squamous carcinoma MpBC patients had stable whereas 4 had progressive disease after a median 6 (range: 4-8) cycles of salvage chemotherapy.

Two patients of whom PR status is positive were given tamoxifen, and one patient with ER positive given anastrozole treatment.

During the follow up of a median 52 months (range: 7-71 months), progressive disease and death was seen in 7 and 5 patients, respectively.

Patients with carcinosarcomas subtype have found a tendency of better survival although this was not statistically significant (median: 48 months, p:0.259) Median 3 year progression free survival (PFS) and overall survival (OS) in this patients group were 33% and 56% respectively (table 1 and table 2).

Discussion

The incidence of MpBC was approximately 0.2-0.3% in our breast cancer series. Although the median age of MpBC patients was over 50 years of age in the literature (Kaufman et al., 1984; Oberman et al., 1987; Rayson et al., 1999), the median age of our series was found to be about 5 years younger (45.5 years). Female preponderance is obvious but rarely male MpBC patients were reported in case series (Kuo et al., 2000).

MpBC is a heterogenous disease with different subgroups. Malignant epithelial (carcinoma) and malignant stromal (sarcoma) features can be found in MpBC spectrum. In our series, squamous and carcinosarcoma were found to be the most common histopathological subtypes. Sarcomatous types were reported to be as poor prognostic subtype compared to matrix producing subtype in some series (Wargotz and Norris, 1989; Tseng et al., 2011). In contrast, we have found a tendency of better survival in carcinosarcoma subtype although this was not statistically significant.

In comparison to classical breast adenocarcinomas, tumor size is usually greater, hormone receptors are negative and incidence of axillary lymph node involvement is less for MpBC patients (Chao et al., 1999; Beatty et al., 2006; Bae et al., 2011). Median size of the tumor was reported to be in the range of 3.4-5.0 cm in some series (Oberman et al., 1987; Wargotz and Norris, 1989; Chao et al., 1999; Rayson et al., 1999; Luini et al., 2007) but in other series it was found to be larger up to 9 cm (Al Sayed et al., 2006). In our series, the median tumor diameter of MpBC cases was 5.7 cm (range: 2.0-8.0 cm), compatible with the English literature.

MpBC has a lesser tendency to involve axillary lymph nodes compared to adenocarcinoma and reported to be in the range of 0-53% in some series (Gersell et al., 1981; Bauer et al., 1984; Kaufman et al., 1984; Chao et al., 1999; Rayson et al., 1999; Al Sayed et al., 2006; Bae et al., 2011). Although lower incidence of axillary lymph node involvement, classical surgery techniques such as

radical mastectomy and modified radical mastectomy including axillary dissection were the preferred surgery choices in the literature (Pitts et al., 1991; Gutman et al., 1995; Rayson et al., 1999) except for one study (Caceres et al., 2002). In our case series, axillary lymph node involvement was found to be higher (63.4 %) compared to English literature. This may be the reason of choosing more radical surgery techniques (breast conserving surgery was preferred for only 1 patient) for this cohort. Although a lesser tendency for axillary lymph node involvement and greater tumor diameter stage 4 disease at the time of diagnosis was not infrequently reported. Park et al reported an incidence 10.3% (Park et al., 2010) whereas others reported an incidence of 2.8-4.9% (Park et al., 2005; Son et al., 2006; Kim et al., 2007). In this case series, only 1 patient was presented with stage 4 disease (7.1%). Higher presentation with stage 4 disease may be explained by the limited number of patients and/or higher aggressiveness of the tumor.

MpBC is also usually presented as triple negative or basal-like breast cancer (Reis-Filho et al., 2006; Korsching et al., 2008). Lower ER, PR and HER-2 overexpression were reported in some studies (Bae et al., 2011; Lim et al., 2010; Toumi et al., 2011). Our results were similar to these studies. Because of limited number of patients included in this study, our experience about the effect of hormonotherapies in MpBC was also limited. Rayson et al. gave tamoxifen to 4 hormone receptor positive MpBC patients upon recurrence but they reported none response at all (Rayson et al., 1999). However; Bae et al. gave hormonal therapy to three patients. No recurrence was observed during follow up period (Bae et al., 2011).

More than half of the MpBC patients developed local and distant metastasis during 5 years of follow-up. Lung and bone metastasis were found to be more frequent than lymphatic spreading, in many studies (Oberman et al., 1987; Wargotz et al., 1989; Wargotz and Norris, 1989). This behaviour of MpBC resembles sarcomas. Luini et al. reported 3 locally recurrent and 8 lung and bone metastatic patients in their 37 MpBC series (Luini et al., 2007). Distant metastatic sites were mostly lungs and brain in the current study.

In routine clinical practice, there is no standard treatment regimen specific for MpBC or its subgroups, so clinical practice guidelines for invasive breast adenocarcinoma is mostly used instead (Carlson et al., 2009). In parallel to the literature, standard chemotherapy regimens for adenocarcinoma were given to the current study population. Interestingly, pathological complete response was seen in 2 of 3 patients who received neoadjuvant chemotherapy (67%) in the current study. Although it is recommended as the treatment approach in invasive breast cancer, there is limited knowledge about neoadjuvant chemotherapy use in MpBC in the literature (Luini et al., 2007). There is no defined subgroup in neoadjuvant studies and responses were not infrequently reported to be poor (Rayson et al., 1999).

Adjuvant chemotherapies are not also successful in case series in MpBC in the long-term (Al Sayed et al., 2006). Bae et al. reported no survival advantage of adjuvant chemotherapies in 42 of 47 patients with

MpBC (Bae et al., 2011). Another study confirmed the ineffectiveness of adjuvant chemotherapy on disease-free survival during 3 to 9 years of follow-up in MpBC (Chao et al., 1999). In contrast, Gutman et al found both disease-free and overall survival benefit with adjuvant chemotherapy in stage 1 and 2 MpBC patients (Gutman et al., 1995). Because of the heterogeneity and sarcomatous features of MpBC, different chemotherapy regimens and dose schedules would be more appropriate. The dosage of anthracycline in MpBC studies might not be enough for the sarcomatous tumor nature of MpBC. This might partly explain the common treatment failure in MpBC. In contrast to other series, a better but statistically insignificant outcome in carcinosarcoma group was observed in the current study. This better outcome might be speculated to be the result of cisplatin containing regimens unlike other studies. Galebarman et al. reported one such strategy is used of ifosfamide and etoposide for carcinosarcoma variant of MpBC (Galebarman et al., 2010). Chien et al reported near complete response with bevacizumab/doxorubicin/dacarbazine containing neoadjuvant regimens in sarcomatous subgroup in MpBC [Chien T et al, 2010]. In another case series; patients received liposomal doxorubicin and bevacizumab but developed disease progression (Moulder et al., 2011). Alternative chemotherapy regimens might improve response and prognosis in MpBC subgroups.

The prognosis of MpBC is reported to be worse than breast adenocarcinoma (Sarah et al., 2012). The worse prognosis of MpBC can not only be explained by greater tumor size but also with histopathological tumor heterogeneity, higher proliferation index and poorer differentiation although less incidence of axillary lymph node involvement in comparison to breast adenocarcinomas. This may also be explained by frequent triple negative feature and lack of effectiveness of targeted therapies against this tumor.

Toumi et al. reported DFS and OS in MpBC were to be 42-84% and 64-83% respectively, during 5 years follow-up period (Toumi et al., 2011). In another study reported DFS and OS was found to be higher (81% and 93% respectively) in 5 years of follow-up (Park et al., 2010). However, Al Sayed et al. reported an event free survival and OS of 15% and 48%, respectively during 3 years of follow up (Al Sayed et al., 2006). In the current series, 3 year PFS and OS were 33% and 56%, respectively. Lower DFS and OS might partly be explained by higher involvement of axillary lymph nodes, aggressiveness of tumor pathologies and inclusion of limited number of MpBC patients.

MpBC is a rare disease entity and consists of different heterogeneous subgroups. There is no specific treatment guidelines for MpBC and subgroup. Subgroup-specific and more courageous treatment approaches are required to improve survival rates. The addition of platinum to the chemotherapy regimen for squamous and triple negative subgroups, or high dose anthracycline regimen for sarcoma subgroup may be suitable alternatives. Since MpBC has a poor prognosis and aggressive nature, studies to evaluate different treatment alternatives for different subgroups may yield better treatment choices, in the future.

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