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ORIGINAL ARTICLE

Metaplastic carcinoma of the breast: Clinicopathological features and immunohistochemical analysis

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Summary

Purpose: *Metaplastic breast carcinoma (MBC) is a rare and heterogeneous group of neoplasms characterized by a mixture of spindle, squamous and/or mesenchymal cells. The purpose of this study was to assess the immunohistochemical features, biological characteristics and myoepithelial differentiation of a series of MBC patients.*

Methods: *The archival pathological material from 33 MBC patients was evaluated. Analysed were patient characteristics, pathological and immunohistochemical features and their relevance as prognostic factors of patient survival.*

Results: *The median patient age was 44 years (range 17-82), and the median tumor size 5 cm (range 0.5-17.0). The majority of patients (n=29; 87.8%) were treated by modified radical mastectomy, 1 (3%) patient had breast-conserving surgery and another 1 (3%) had latissimus dorsi flap reconstruction. Metastasis to axillary lymph nodes was found in 14 (42.4%) patients, 18 (54.5%) patients were triple negative, and 22 (66.7%) were epidermal growth factor receptor (EGFR) positive. The 5-year event-free survival was 25.9%, whereas the 5-year overall survival was 27.5%. Immunohistochemical analysis showed the following: vimentin positivity in 31 (93.9%) patients, high molecular weight cytokeratin (HMWCK) positivity in 31 (93.9%), CK5/6 positivity in 28 (84.8%), P63 positivity in 19 (57.6%) and calponin positivity in 18 (54.5%) patients. Two particularly interesting findings were noted, namely, myoepithelial differentiation in the carcinomatous and sarcomatous elements of MBC, and EGFR immunopositivity.*

Conclusion: *Immunohistochemistry has an important role to play in the diagnosis and treatment decision of MBC. This report presents findings related to a broad panel of immunohistochemical markers for a large series of metaplastic cases, which indicate poor prognosis for this tumor.*

Key words: epidermal growth factor receptor, immunohistochemistry, metaplastic breast cancer, myoepithelial markers, prognostic factors

Introduction

MBC is a general term that refers to a heterogeneous group of neoplasms characterized by an intimate admixture of adenocarcinoma, with dominant areas of spindle, squamous and/or mesenchymal differentiation [1]. Mesenchymal areas may include chondroid, osseous and other types of mesenchymal tissue [2].

MBC is a rare malignancy of the breast and accounts for <1% of all breast cancers [1,2]. It can be classified into broad subtypes according to the phenotypic appearance [1]. With regard to diverse cell differentiation, these tumors can be classified into monophasic spindle or sarcomatoid carcinoma; biphasic carcinosarcoma; and divergent stromal differentiation including chondroid, osseous and rarely rhabdoid metaplasia, as well as adenosquamous and pure squamous cell carcinoma [2]. Recent studies have shown myoepithelial differentiation to include both carcinomatous and sarcomatous elements, indicating MBC to be highly aggressive, with a high rate of extranodal metastases [3-5].

This study assessed the immunohistochemical features, biological characteristics and myoepithelial differentiation of a series of MBC cases, including examples of each of the different subtypes. It also examined prognostic factors and outcomes related to patient survival.

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Methods

This retrospective review examined 33 MBC patients treated at the Ankara Oncology Education and Research Hospital between 1998-2007. The following parameters were recorded: patient age, patient complaints, family history of breast cancer, menopausal status, size of primary tumor at presentation, lymph node status, distant metastasis, stage, treatment protocol, time of locoregional recurrence, time of distant metastasis and time of death. Initial diagnosis of all patients was through mammograms and breast ultrasonography of both breasts. Disease stage was recorded based on anterior-posterior chest radiography, whole body bone scans and abdominal ultrasonography; thorax computed tomography was subsequently performed in those patients diagnosed with T4 tumors.

Following surgical and post-surgical treatment protocols such as chemotherapy and radiotherapy, patients were followed-up every 3 months for 2 years and at 6-month intervals thereafter. Follow-up consisted of physical examination, mammogram and liver function tests as well as abdominal ultrasonography, computed tomography scans and whole body bone scans, as necessary.

Histopathological examination

Formalin-fixed and paraffin-embedded pathology slides were reviewed by two of the authors and confirmed or reclassified the pathological diagnosis in line with WHO 2003 criteria [1].

Immunohistochemistry

Antigen retrieval was performed with the avidin-biotin method using a pressure cooker for the following antibodies:

1) Cytokeratin (CK) 7, Neomarkers, 1/100 dilution
2) Cytokeratin (CK) 20, ImmunoVision, 1/100 dilution
3) Vimentin, Neomarkers, 1/50 dilution
4) High molecular weight cytokeratin (HMWCK), Neomarkers, 1/50 dilution
5) Cytokeratin (CK) 5/6, Neomarkers, 1/10 dilution
6) p63, Neomarkers, 1/100 dilution
7) Calponin, Neomarkers, 1/400 dilution
8) S100 (in matrix producing areas)
9) Estrogen receptor (ER), Neomarkers, 1/250 dilution
10) Progesterone receptor (PR), Neomarkers, 1/500 dilution
11) HER-2, Neomarkers, 1/800 dilution
12) HER-1, Neomarkers, 1/25 dilution

For each case, immunohistochemical analysis was performed on representative sections of the carcinomatous and sarcomatous areas. CK 5/6, p63, and calponin were used for myoepithelial differentiation, and Hercep tests were used to determine HER-2 positivity. Quick scores indicated ER positivity in up to 10% of all cells and PR positivity in up to 5% of all cells [6].

Statistical analyses

All statistical analyses were performed using the SPSS software program (version 10.0, Statistical Software, Chicago, USA). Event-free survival (defined as the period of time between diagnosis and local relapse or metastasis) and overall survival (defined as the period of time between diagnosis and time of death or last control) curves were plotted using the Kaplan-Meier method. A log-rank test model was used to assess the effects of patient age, tumor size, lymph node status, hormone receptors status, HER-2, EGFR, triple negativity and immunohistochemical positivity on overall and event-free survival.

Results

Clinical characteristics of patients are summarized in Tables 1 and 2. All patients were females presenting at a median age of 44 years (range 17-82). The most common symptom was a mass in the breast, which was present in 26 patients (79%). Other symptoms included pain in one patient (3%) and nipple discharge, edema, ulceration and skin involvement in 3 (9%) patients. Three (9%) patients were asymptomatic. Twenty (60.6%) patients were premenopausal, whereas 13 (39.4%) were peri- or post-menopausal. Thirty patients (90.9%) had no family history of breast cancer, but 3 (9.1%) had a family history of breast cancer. The median tumor size at presentation was 5 cm (range 0.5-17).

According to the American Joint Committee on Cancer (AJCC) staging, 2 (6%) patients presented with stage I, 18 (55%) with stage II, 11 (33%) with stage III and 2 (6%) with stage IV. Metastasis to axillary lymph nodes was found in 14 (42.4%) patients at the time of diagnosis, and metastasis to the bone and lung was found in the 2 (6%) stage IV patients.

Chemotherapy included taxane-based regimens administered to the 2 (6%) stage IV patients and preoperative anthracycline-based regimens administered to 5 (15.1%) patients. Partial clinical response was observed in 5 patients.

Surgical treatment consisted of modified radical mastectomy in 29 (87.8%) patients, breast conserving

Table 1. Patient and tumor characteristics

Characteristics	*n (%)*
Age (years)	
Median (range)	44 (17-82)
Family history	
Yes	3 (9.1)
No	30 (90.9)
Menopausal status	
Pre-menopausal	20 (60.6)
Peri- postmenopausal	13 (39.4)
Breast involved	
Right	7 (25.9)
Left	20 (74.1)
Presenting signs	
Mass only	26 (79)
Nipple discharge	3 (9)
Pain	1 (3)
Edema	3 (9)
Ulceration	3 (9)
Skin involvement	3 (9)
Tumor size (cm)	
Median (range)	5 (0.5-17)
<2	3 (9.1)
2-5	16 (48.5)
>5	14 (42.4)
Type of operation	
MRM	29 (87.8)
MRM with latissimus dorsi flap	1 (3)
BCS	1 (3)
Biopsy only	2 (6)
Stage	
I	2 (6)
II	18 (55)
III	11 (33)
IV	2 (6)
Lymph node metastasis	
Present	14 (42.4)
Absent	19 (57.6)

MRM: modified radical mastectomy, BCS: breast conserving surgery

surgery and axillary dissection in 1 (3%) patient and modified radical mastectomy with latissimus dorsi flap reconstruction in 1 (3%) patient, whereas only biopsies were performed in the 2 (6%) stage IV patients.

Adjuvant postoperative anthracycline-based chemotherapy was administered to 29 patients. Only 2 patients were treated with hormonal therapy alone. Adjuvant postoperative radiotherapy was administered to 15 patients. Ten patients received hormonotherapy as adjuvant treatment.

MBC subtypes, according to WHO (2003) classifications, consisted of 13 epithelial and adenosquamous cases (39.4%), 12 biphasic (adenosquamous) cases (36.4%) and 8 monophasic (squamous) cases (24.2%). The biphasic cases included high-grade carcinomatous components.

Immunohistochemical analysis is provided in

Table 2. Pathological characteristics

Characteristics	*n (%)*
Subtypes	
Epithelial	13 (39.4)
Biphasic	12 (36.4)
Monophasic	8 (24.2)
Hormone receptor positivity	
ER	3 (9.1)
PR	9 (27.3)
ER and/or PR	10 (30.3)
C-erbB2 positive	6 (18.2)
Triple negative (ER, PR and C-erbB2 negative)	18 (54.5)
Immunohistochemistry results	
Vimentin	31 (93.9)
HMWCK	31 (93.9)
CK5/6	28 (84.8)
P63	19 (57.6)
Calponin	18 (54.5)
EGFR	22 (66.7)

ER: estrogen receptor, PR: progesterone receptor, HMWCK: high molecular weight cytokeratin

Table 3. Myoepithelial differentiation was evaluated according to 3 markers: CK5/6, P63 and calponin. Immunoreactivity was positive for CK5/6 in 28 (84.8%) cases, for p63 in 19 (57.6%) cases and for calponin in 18 (54.5%) cases. Positivity in all cases was observed in both carcinomatous and sarcomatous areas. In 2 (6%) cases, positivity was observed for only one marker (CK 5/6), whereas in the majority of cases positivity was observed for 2 markers (CK5/6 and P63: 18 cases, 54.5%; CK5/6 and calponin: 16 cases, 48.4%; p63 and calponin: 13 cases, 39.3%) and in 13 cases (39.3%), positivity was present for all 3 markers.

ER positivity was observed in 3 cases (9.1%), PR positivity in 9 cases (27.2%) and both ER and/or PR positivity in 10 cases (30.3%). HER-2 positivity (score 3) was seen in 6 (18.2%) cases, EGFR positivity in 22 (66.6%) cases, and both HER-2 and EGFR positivity in 4 (12.1%) cases. In total, 18 (54.5%) patients were triple-negative.

Table 3. Immunohistochemistry results in MBC patients by subtype

	Monophasic N=13	*Biphasic N=12*	*Epithelial N=8*
ER +	2	0	1
PR+	3	4	2
ER and/or PR+	4	4	2
Vimentin	11	12	8
HMWCK	12	12	7
Ck 5/6	12	10	6
P63	6	9	4
Calponin	7	5	6
EGFR	8	8	6
C-erbB2	3	2	1
Triple negative	6	7	5

For abbreviations see footnote of Table 2

EGFR immunoreactivity was seen in the metaplastic areas of 12 (36.3%) triple negative cases, whereas no EGFR positivity was observed in any of the triple-positive cases.

The follow-up period ranged from 6 to 120 months (median 30). At the end of follow-up, 22 (66.6%) patients were alive with no metastasis or locoregional recurrence, whereas locoregional recurrence was observed in 4 (12.1%) patients within 5-19 months, distant metastasis was observed in 9 (27.2%) patients within 6-49 months, and 8 (24.2%) patients died of disease. The overall 5-year survival rate and event-free 5-year survival rate were 27.5 and 25.9%, respectively (Figures 1,2). No differences in overall or event-free survival rates were observed by any of the parameters assessed (age, tumor size, estrogen receptor, HER-2, EGFR, triple negativity).

Discussion

MBC is a heterogeneous group of neoplasms characterized by an admixture of adenocarcinoma with areas of spindle, squamous, osseous, and/or chondroid cells [2,7,8]. MBC subtypes are classified by cell differentiation as either monophasic (spindle or sarcomatoid carcinoma), biphasic (carcinosarcoma and adenocarcinoma, with divergent stromal differentiation, including chondroid, osseous, and rarely rhabdoid (metaplasia) as well as adenosquamous and pure squamous carcinomas [2,9]. The monophasic variants appear purely mesenchymal, but epithelial components were only demonstrable by immunohistochemistry for cytokeratins [10].

Whereas MBC usually presents in women in their 50s and 60s [11-13], in the present study the median patient age was 44 years (range 17-82), with 2 patients under 30 years. In most cases, the patient complaint was of a mass in the breast. Radiographic assessment in some cases resulted in a mistaken diagnosis of a benign neoplasm. Most tumors were large, with a median size at diagnosis of 5 cm (range 0.5-17). In 14 patients, the mass was > 5 cm, which is larger than in previous reports [13,14]. In line with the literature, the clinical characteristics in this series of patients included a rapidly growing mass, nipple discharge and edema. Due to the large size at presentation, surgery tended to be radical, with modified radical mastectomies performed in 87.8% of the patients. This ratio was higher, however the tumor size was smaller in these series compared to our patients [13,14].

Although axillary metastasis is rarer in patients with MBC than in patients with infiltrative ductal carcinoma, the metastatic potential is higher and prognosis is much poorer in MBC patients. In our series, axillary nodal disease was seen in 14 patients (42.4%). This rate is higher than in most previous reports, with the exception of Sayed et al., who reported a rate of 53% [12,13,15].

Immunohistochemical analysis examined a panel of 11 antibodies, as follows: CK7, CK20, vimentin, high molecular weight cytokeratin, CK5/6, p63, calponin, ER alpha, PR, HER-2, and EGFR. Two interesting points emerged in this area, namely myoepithelial differentiation in carcinomatous and sarcomatous elements of MBC tumors and EGFR immunopositivity.

Some authors have observed a strong and diffuse p63 expression in the nuclei of normal myoepithelial cells in lobules and ducts, myoepithelial tumors and monophasic sarcomatoid/metaplastic carcinomas of the breast. The presence of p63 immunoreactivity seems to point towards myoepithelial/basal cell histogenesis differentiation in some types of these tumors [16]. In our cases, 3 markers (CK5/6, p63, calponin) were used to evaluate myoepithelial differentiation. It is better to evaluate with 2 or 3 markers than 1 marker.

Myoepithelial markers have been shown to play a

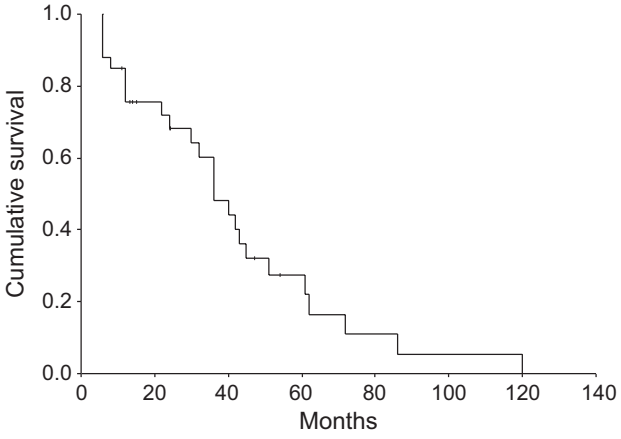

Figure 1. Overall survival rates in metaplastic breast carcinoma patients.

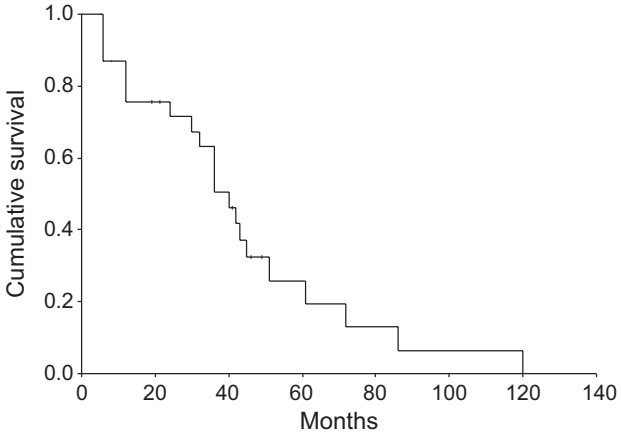

Figure 2. Disease-free survival rates in metaplastic breast carcinoma patients.

major role in the diagnosis of MBC [16]. Moreover the findings warrant that the role of p63 pathway should be investigated in neoplasms showing a basal/myoepithelial cell immunophenotype [17]. It seems that tumors with a basal cell phenotype are associated with an aggressive behavior [17]. The mesenchymal components (heterologous metaplasia) suggest development of this type of tumor by transformation of carcinoma cells into sarcoma with cells detection of epithelial features in sarcomatous cells by immunohistochemistry [18].

The level of hormone receptors in metaplastic carcinomas and the expression of HER-2 oncogene are usually low [5]. Only 10 (30.3%) patients were ER and/or PR positive in our series, which is similar to other series [18-21]. This contrasts the general impression that high-grade MBC may be biologically different from high-grade invasive ductal carcinoma [5]. The absence of hormone receptors and HER-2 oncoprotein may further limit the oncological treatment options [5].

While 70-80% of mammary metaplastic carcinomas overexpress EGFR, gene amplification of EGFR can be found in about one-third of these tumors [22]. In our series, EGFR was immunoreactive in 18 (58.0%) cases, 4 (12.9%) of which also expressed HER-2 immunoreactivity.

Whereas EGFR immunoreactivity was seen in 11 (35.4%) triple-negative cases, no EGFR immunoreactivity was observed in triple-positive cases. This finding may be useful for targeting therapies.

Age, duration of symptoms, prior estrogen use, TNM stage, tumor size and axillary nodal status have all been reported as prognostic factors for MBC [12,15,21]. In general, discussions of MBC in the literature indicate that prognosis is worse for MBC than for invasive ductal carcinoma. Luini et al. reported a lower 5-year survival rate for MBC than for invasive ductal carcinomas with the same characteristics [14]. A Swedish series reported a survival rate similar to ours, although the average tumor size (2.5 cm) was smaller than in our study [20].

We conclude that immunohistochemistry has an important role in the diagnosis and treatment decision of MBC. The report presented here provides an evaluation of a large series of metaplastic carcinomas using a wide range of immunohistochemical markers.

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