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REVIEW

Metaplastic carcinoma of the breast, an unusual disease with worse prognosis: the experience of the European Institute of Oncology and review of the literature

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Abstract
Background Metaplastic carcinoma of the breast is a rare form of breast cancer and has an uncertain prognostic significance. The purpose of the present study was to compare the clinical course, and prognosis, between this type of tumor and poorly differentiated ductal carcinoma.
Patients and methods We analyzed 37 cases of metaplastic carcinoma of the breast treated at our institution (European Institute of Oncology in Milan, Italy) between 1997 and 2004, comparing them with 72 cases (control group) of poorly differentiated ductal carcinoma. All 109 patients had negative receptors and were G3 at final histology. The control cases were matched according to year of surgery, pT (pT1 vs. pT2/3/4), and pN (absent vs. present).
Results Of the 37 patients, eleven died from disease progression, eight developed metastatic disease and two experienced local recurrence. In the control group (72 patients) we observed three deaths due to disease progression, 13 distant metastases, and two local recurrences.
Conclusion The overall survival in the metaplastic carcinoma group was significantly worse than in the control group. As regards to disease-free survival, there was no statistically significant difference between the two groups.

Keywords Metaplastic carcinoma of the breast · Prognosis · Treatment · Review

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Introduction

Metaplastic carcinoma of the breast occurs in less than 5% of breast carcinoma patients [1] and has an uncertain prognostic significance. Tavassoli [2] reported an incidence of less than 1%, Pérez-Mies et al. [3] 0.3%, and Smith et al. [4] 0.02% for this type of tumor. Metaplastic breast carcinomas are currently considered as ductal carcinomas that undergo metaplasia into a glandular growth pattern [1, 5].

The definition of metaplastic carcinoma comprises a heterogeneous group of neoplasms. Wargostz et al. [6–10] suggested five variants of metaplastic carcinoma, including matrix-producing carcinoma, squamous cell carcinoma, spindle cell carcinoma, carcinosarcoma, and metaplastic carcinoma with osteoclastic giant cells. Oberman [1] suggested that all these tumors be categorized as metaplastic carcinoma of the breast, de-emphasizing whether the metaplastic component is of

mesenchymal or epithelial origin. Although these rare tumors show pathologic features of both carcinoma and sarcoma, metaplastic carcinoma with a sarcomatous component is a different entity from primary breast sarcoma. Günhan-Bilgen [5] believes that differentiation is sufficiently significant to characterize these tumors as distinct entities for purposes of diagnosis, treatment, and prognosis.

The purpose of this study was to compare the clinical course and prognosis between metaplastic breast carcinoma and poorly differentiated ductal carcinoma.

Patients and methods

Cases were selected from the files of the Pathology and Breast Surgery Departments at the European Institute of Oncology in Milan. We analyzed cases of metaplastic breast carcinoma treated in the Division of Breast Surgery of our institution between 1997 and 2004. The following parameters were recorded: age of patients, size of the primary tumor at presentation, presence or absence of positive lymph node or distant metastases, proliferation-associated antigen ki-67, treatment modality, and patient survival.

We found records of metaplastic carcinoma in 44 cases, but we excluded seven patients from the analysis because they were lost to follow-up. One of these excluded patients had also suffered from gastric carcinoma in 1992.

All 109 patients had Grade 3 tumors with negative receptors. The control cases (where possible we selected two control cases for every case) were individually matched with the cases of metaplastic carcinoma according to the year of surgery, pT (pT1 vs. pT2/3/4), and pN (absent vs. present).

We used the Student T and Chi-square tests (respectively in Tables 1 and 2) to assess differences between the two groups. The disease-free survival and the overall survival curves were plotted using the Kaplan–Meier method. The Log-rank test was used to assess survival differences between groups. Multivariate Cox proportional hazards regression models were used to assess the prognostic significance of metaplastic tumors after adjustment for tumor size (in cm) and age of patients.

Table 1 Mean age, tumor size and ki-67, and T test of the metaplastic breast carcinoma and control group patients

	Metaplastic (N = 37) Mean	Control (N = 72) Mean	T-test
Age	56.6	51.4	0.06*
Size	3.4	2.7	0.17*
Ki-67	50.7	48.8	0.68

Table 2 pT and pN in the metaplastic breast cancer group and control group

freq.	%	Metaplastic (N = 37)		Control (N = 72)		chi-square
		freq.	%			
Pt	pT1	9	24.3	18	25.0	0.96
	pT 2/3/4	26	70.3	51	70.8	
	Missing	2	5.4	3	4.2	
PN	Absent	22	59.5	44	61.1	0.94
	Present	10	27.0	20	27.8	
	missing	5	13.5	8	11.1	
totale		37		72		

Results

We analyzed 37 patients with metaplastic breast carcinoma (mean age 56.6 years, mean tumor size 3.4 cm, mean ki-67 50.7), and 72 patients in the control group (mean age 51.4, mean tumor size 2.7 cm, mean ki-67 48.8), affected by poorly differentiated ductal carcinoma (Table 1). Of those with metaplastic carcinoma we observed 17 (45.9%) matrix-producing carcinomas, 3 (8.1%) spindle cell metaplastic carcinomas, 9 (24.3%) carcinosarcomas, 7 (18.9%) squamous cell metaplastic carcinomas, and 1 (2.7%) metaplastic sarcoma with osteoclastic giant cells. About 18 tumors (48.6%) affected the right breast while the remaining tumors (51.3%), affected the left breast. All cases had negative hormonal receptors.

About 17 patients were treated with breast conservative surgery, 19 with mastectomy, and for two patients there was no record regarding the type of surgery.

Two patients developed local recurrence during follow-up, and 8 had distant metastases, and 11 died (from lung and bone metastasis). About 34 patients had received surgery as primary therapy, while three had received neoadjuvant systemic therapy.

Of the 37 patients analyzed 9 (24.3%) had pT1, 26 (70.3%) pT2/3/4, and for 2 (5.4%) patients, data for pT were missing. About 22 cases (59.5%) were pN0, 10 (27%) had positive lymph nodes and 5 (13.5%) were missing (Table 2).

Overall survival was significantly worse in metaplastic carcinoma (long rank $P < 0.0001$ and adjusted HR = 5.0(1.3;20.0) (Fig. 1a). With regards to the disease-free survival curves, there were no statistically significant differences between the two groups (long rank $P = 0.053$ and adjusted HR = 0.9(0.4;2.1), even

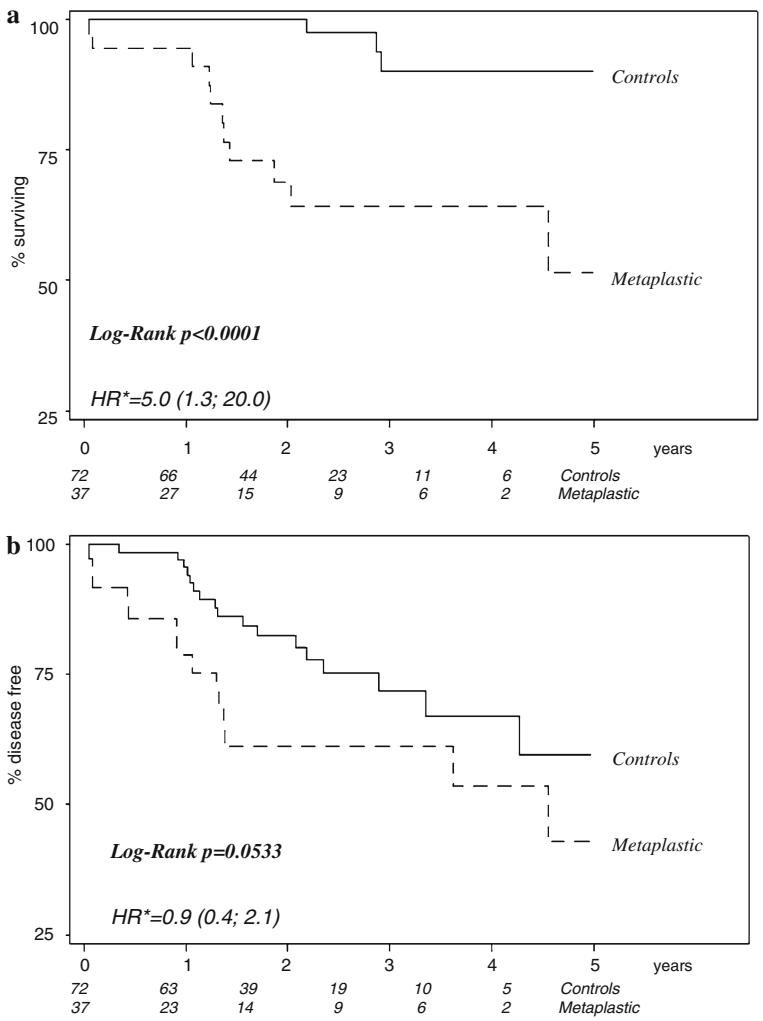

Fig. 1 (**a**) Overall survival between control group and metaplastic, (**b**) Disease free survival between control group and metaplastic carcinomas

though the metaplastic carcinoma group experienced more events.

Discussion

Metaplastic carcinomas of the breast are a heterogeneous group of neoplasms which exhibit varied patterns of metaplasia and differentiation along multiple cell lines. This group of neoplasms includes matrix-producing carcinoma, squamous cell carcinoma, spindle cell carcinoma, carcinosarcoma, and metaplastic carcinoma with osteoclastic giant cells [6–10]. The matrix-producing carcinoma is a distinct form of metaplastic carcinoma that consists of overt carcinoma with transition to an abundant cartilaginous and/or osseous stromal matrix in the absence of an intervening spindle cell component [6]. Wargotz and Norris suggested the cumulative 5-year survival rate for patients with matrix producing carcinoma is relatively more favorable than previous reports suggest [6].

Spindle cell carcinoma is a rare neoplasm in which a spindle cell component predominates, resembling a low-grade sarcoma or a reactive process such as fascitis or granulation tissue, with a cumulative 5-year survival rate of 64%, which contrasts with the lower survival rate for metaplastic carcinoma overall [7].

Carcinosarcoma is a generic term for biphasic neoplasms having both malignant epithelium (carcinoma) and malignant stroma (sarcoma), with a 5-year survival of 49% [8].

Squamous cell carcinoma of ductal origin is identified by the presence of infiltrating carcinoma which is exclusively squamous; there is no involvement of the overlying skin or intraductal carcinoma, which is also exclusively squamous. It has a disease-related 5-years cumulative survival rate of 63% [9]. Metaplastic carcinoma with osteoclastic giant cells is an intraductal or infiltrating carcinoma contiguous or admixed with a

bland-appearing spindle cell or sarcomatous stroma within which osteoclastic giant cells are mixed.The cumulative 5-years survival rate for Wargotz is 68% [10].

Metaplastic carcinomas are usually seen in women who are over 50 years of age [5–10]. The ages of our patients ranged between 22 and 91 years (mean 56.6 years); 11 patients were less than 50 years old. The clinical behavior of metaplastic carcinomas is poorly documented. They often manifest as a rapidly growing, palpable mass with a high density on mammography and which may be microlobulated on sonography. Complex echogenicity with solid and cystic components may be observed sonographically and is related to necrosis and cystic degeneration found histopathologically [5, 11, 12]. In FNA smears, only 57% of cases show ductal carcinoma and metaplastic components. Thus, in almost one half of cases, the diagnosis is not possible by FNA [13–18]. The diagnosis of metaplastic breast carcinoma often requires immunohistochemistry with a cytokeratin panel to distinguish such cases from phyllodes tumors, primary sarcomas, and fibromatoses [19]. Wargotz [7] reported a mean size tumor of 4.4 cm. Our tumors were slightly smaller (3.4 cm). Tumor size appears to be important, and it has also been suggested that these tumors have a high potential for distant metastases although they are frequently lymph node-negative [1, 7, 20–23].

Metaplastic carcinomas are usually not associated with estrogen or progesterone receptors, as was the case in all patients reported here. Axillary lymph node involvement is reported in, 6% [8], 26% [7], and 25–30% [11] of cases. In our cases we reported 27%. As with other breast carcinomas, these tumors have a high metastatic potential despite frequently negative lymph nodes, as observed in this and in other studies [6, 7, 24, 25] (Table 2). More than 50% of these tumors are associated either with local or distant metastases (or both) [11] within 5 years, with recurrence indicating very poor prognosis. Christensen reported that metaplastic carcinoma gave rise to distant metastases in 50% of cases but no local recurrences [24]. Most published data on metastases of metaplastic carcinoma have shown haematogenous (lung and bone) metastases rather than lymphatic spread [1, 7, 8, 22]. We observed 3 cases of local recurrence versus 8 cases of distant metastases.

The precise histogenesis and prognosis of metaplastic carcinomas is still poorly understood, although some studies have shown a good prognosis in a relatively short follow-up period [26–29] Chao et al. [26] reported that duration of symptoms, TNM stage, tumor size, and axillary nodal status were significant prognostic factors of survival. However, a Mayo Clinic study showed that only age and prior estrogen use were found to be significantly associated with either free or overall survival [25]. Women older than 60 years at diagnosis were found to have an increased disease-free survival time compared to those less than 60 years old, but no difference in overall survival was found [25].

Rayson et al. reported the median survival from detection of metastasic disease as 8 months, using systemic treatment [25]. Although experience with systemic therapy for metastasic disease is not particularly extensive, it appears that metaplastic breast carcinomas are less responsive to therapy with the conventional regimens used for typical adenocarcinoma of the breast. Wargotz et al. [8], also found no survival advantage for patients treated either by chemotherapy or radiation for distant metastases. These data suggest that patients with metastasic metaplastic breast carcinoma may be candidates for innovative chemotherapeutic regimens as first-line therapy for metastatic disease.

Wargotz [8] and Rayson [25] suggest that metaplastic carcinoma prognosis is worse than that of typical breast carcinoma; we observed that the overall survival curves for those groups were significantly worse for metaplastic carcinomas. However, it appears that more events occur in metaplastic carcinomas, but the difference in disease-free survival was not statistically significant between the two groups.

In conclusion, our findings suggest that when compared with typical breast carcinoma, metaplastic carcinomas have a worse disease-free survival, and a significantly decreased overall survival.

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