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Typical medullary breast carcinoma: clinical outcomes and treatment results

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Typical medullary breast carcinoma (T-MBC) accounts for less than 1% of all malignant breast neoplasms, and immunohistochemically is characteristic of "triple-negative" breast carcinoma. The purpose of this study was to describe the clinical characteristics and treatment results for patients with T-MBC treated at a single institution, and discuss the controversial aspects of this very rare form of breast cancer. Analyses was performed in 120 patients with T-MBC who were treated between 1970 and 2005. These cases represent 1.1% of all (11 270) patients treated for breast cancer during this period. According to TNM classification, 26 patients (21.6%) were in stage I, 80 patients (66.7%) in stage II and 14 (11.7%) in stage III of clinically advanced breast cancer. Involved axillary lymph nodes occurred in just 10 (8.3%) of the patients, and in all cases metastases were observed in 1–3 lymph nodes. All the patients underwent primary surgery. Radical mastectomies were performed on 98 (81.6%) patients, while the other 22 (18.4%) underwent breast-conserving surgery (BCS). Radiotherapy was performed in 36 patients (22 after BCS and 14 after mastectomy). Patients with nodal involvement (10 patients) received adjuvant chemotherapy, and 8 patients with hormone receptor expression received hormonotherapy with tamoxifen. The 10-year DFS rate was 90%. Out of 120 patients with T-MBC, only 4 (3.3%) died from this cancer. We showed that none of the population, neither clinical nor microscopic, had a statistically significant influence on the 10-year disease-free survival rate. Our results are similar to others presented in literature.

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Key words: breast cancer, typical medullary carcinoma, outcome, treatment results

Introduction

According to the WHO classification, medullary carcinoma is a well-circumscribed tumour (with pushing margins), composed of poorly differentiated cells with scant stroma and prominent lymphoplasmacytic infiltration. The cells of classic medullary carcinoma are characterised by abundant cytoplasm and pleomorphic high-grade vesicular nuclei. They are arranged in syncytial structures which constitute

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at least 75% of histologically sampled areas. What is more, the histological texture of medullary carcinoma lacks tubular differentiation [1]. The above-mentioned criteria are similar to those presented by Ridolfi et al. in 1977 [2]. Tumours displaying all these definitive characteristics are classified as (classic) medullary carcinomas. When most, but not all, of these necessary histological features are present, the latest edition of the WHO classification recommends that the tumour be classified as invasive carcinoma NST with medullary features.

According to WHO, medullary breast carcinoma (classic, typical) accounts for less than 1% of all malignant breast neoplasms, and the higher incidence of this carcinoma reported by many authors is due to the inclusion of NST with medullary features among patients with invasive carcinoma [1, 3, 4] Typical medullary breast carcinoma (T-MBC) occurs more frequently in patients with mutations of the suppressor gene *BRCA-1* present. The mutation of this gene is more frequently observed [1, 5–11] in patients with T-MBC. Immunohistochemically T-MBC is usually characterised by features typical of basal-like carcinomas; they do not express oestrogen, progesterone and HER 2/neu receptors. Hence, they were included in so-called "triple-negative" breast carcinomas [1, 5–7, 12–21].

The purpose of this study was to describe the clinical characteristics and treatment results for patients with T-MBC treated at a single institution in Poland, and discuss the controversial aspects of this very rare form of breast cancer.

Patients and methods

Between January 1970 and December 2005, 120 women with T-MBC were treated at the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Kraków (MSCCCIO). These cases represent 1.1% of all (11 270) patients treated for breast cancer during this period. All the histologic slides were re-examined, and a diagnosis of T-MBC was made according to WHO criteria [1]. The stage of cancer was determined using the recently adopted UICC TNM classification for breast cancer at the treatment planning stage. All the patients received initial surgical treatment at the MSCCCIO, and they underwent all other therapeutic procedures, such as postoperative radiotherapy, adjuvant chemotherapy and hormonotherapy in the same institution.

The clinopathological characteristics of patients with T-MBC is presented in Table I.

The youngest patient in the study group was 26 years old and the oldest was 72: the mean age of the patients was 51 and the median age was 52. A total of 94 of the patients (78.3%) were aged between 35 and 64; 10 (8.3%) of the patients were aged below 35 and 16 (13.3%) were aged above 64. On the other hand, 58 patients (48.3%) were younger than 51 and 62 (51.7%) were older than 51 years. A total of 26 patients (21.6%) were diagnosed with stage I clinically advanced cancer according to the TNM UICC classification, while 80 patients (66.7%) were diagnosed with stage II and 14 (11.7%) with stage III. An examination of the post-surgical material revealed that the breast tumour was less than 2 cm in diameter in 45 of the patients (37.5%), ranged between 2 and 5 cm in 70 patients (58.3%), and was more than 5 cm in diameter in 5 patients (4.2%). Microscopy revealed that metastases in the axillary lymph nodes occurred in just 10 (8.3%) of the patients, while in all cases metastases were observed in 1–3 lymph nodes. The analysis revealed no expression of oestrogen receptors (ER) in 112 patients (93.3%), no expression of progesterone receptors (PgR) in 115 patients (95.8%), and expression absence of HER2/neu receptors in 105 (87.5%) patients. The treatment methods used for patients with T-MBC are presented in Table II.

All the patients underwent primary surgery. Radical mastectomies (Halsted during the period 1970–1982, Patey or Madden in 1883–2005) were performed on 98 (81.6%) patients, while the other 22 (18,4%) patients treated between 1995 and 2005 underwent breast-conserving surgery (BCS). All those patients who underwent BCS received adjuvant radiotherapy. A dose of

Table I. The clinicopathological characteristics of patients with T-MBC

Characteristics	No. of patients	%
Age (years)		
< 51	58	48.3
≥ 51	62	51.7
Stage (TNM)		
I	26	21.6
II	80	66.7
IIIA	14	11.7
Tumour size (pT)		
< 2 cm (pT1)	45	37.5
2–5 cm (pT2)	70	58.3
> 5 cm (pT3)	5	4.2
Lymph node status (pN)		
pN0	110	91.7
pN+ (1–3)	10	8.3
pN+ (≥ 4)	–	–
ER status:		
Positive	8	6.7
Negative	112	93.3
PgR status:		
Positive	5	4.2
Negative	115	95.8
HER 2/neu status:		
Positive	15	12.5
Negative	105	87.5
Total	120	100.0

Table II. The treatment methods delivered in the presented group of patients with T-MBC

Treatment method	No. of patients	%
Surgery		
Mastectomy	98	81.6
Breast-conserving surgery (BCS)	22	18.4
Radiotherapy		
Yes	36	30.0
No	84	70.0
Chemotherapy		
Yes	10	8.3
No	110	91.7
Hormonal therapy		
Yes	8	6.7
No	112	93.3
Total	120	100.0

50 Gy administered in 25 fractions was delivered over the course of 5 weeks to the whole breast using the two tangential fields technique. This was followed by a boost (10 Gy administered in 5 fractions) to the tumour bed. After mastectomy procedures, 14 of the 98 patients (with pN+, and/or pT > 5 cm) received adjuvant radiotherapy at a dose of 50 Gy in 25 fractions administered to the chest wall with scar and regional (axillary, internal mammary and supraclaviculor) lymphatic areas. Patients with nodal involvement received adjuvant chemotherapy according to a CMF (cyclophosphamide, methotrexate, and 5- fluorouracil) schedule. Endocrine therapy with tamoxifen was administered to 8 (6.7%) patients with PgR and/or ER expression.

Treatment efficacy was measured on the basis of 10--year disease-free survival (DFS) rates. The Kaplan-Meier estimation was used for this purpose. The long rank test was applied to evaluate the significance of the results. The statistical significance level was established at $p \leq 0.05$.

Results

All the patients were followed up for a period of at least 10 years (or until their deaths). The median follow-up time was 14 years. The 10-year DFS rate was 90%.

The relationship between the results of treatment and population, clinical and microscopic characteristics, expression of the *c-erb-B2* gene and the presence of hormone receptors are presented in Table III.

As shown in Table III, it was not confirmed in the patient study group whether any of the studied population, clinical and microscopic factors, or any factors analysed immunohistochemically, had a statistically significant influence on the 10-year disease-free survival rate.

The patients' follow-up and the causes of treatment failure are presented in Table IV.

Table III. Treatment results in 120 patients with T-MBC in relation to population, clinical, microscopic and immunohistochemically characteristics

Characteristics	No of patients	10-year disease-free survival	
		No. of patients	%
Age			
< 51	58	52	89.7
≥ 51	62	56	90.3
TNM stage			
I	26	24	92.3
II	80	72	90.0
IIIA	14	12	85.7
Tumour size (pT)			
< 2 cm	45	41	91.1
2–5 cm	70	63	90.0
> 5 cm	5	4	80.0
Node status (pN)			
pN0	110	102	92.7
pN+ (1–3)	10	6	60.0
ER status			
Positive	8	7	87.5
Negative	112	101	90.2
PgR status			
Positive	5	4	80.0
Negative	115	104	90.4
HER 2/neu status			
Positive	15	13	86.7
Negative	105	95	90.5
Total	120	108	90.0

Three patients died from myocardial infarction, two from haemorrhage, one from acute pancreatitis, one from lung cancer and one from infiltrating ductal carcinoma of the second breast. The other patients died as a result of distant T-MBC metastases in the bones, the lungs, the brain and the liver.

Table IV. The follow-up and patterns of treatment failure in 120 patients with TMBC

Follow-up and causes of death	No. of patients	%
10-year DFS	108	90.0
Cause of death:		
Distant metastases of T-MBC	4	3.3
Other	8	6.7
Total	120	100.0

DFS — disease-free survival

To sum up, out of a total of 120 patients with T-MBC in the study group, only 4 (3.3%) died from this cancer; in all these patients a microscopy revealed metastases in the axillary lymph nodes. None of the 110 patients with T-MBC without lymph node metastases died of the disease; hence all the patients who underwent breast-conserving treatment survived for 10 years disease-free.

Discussion

In this study we presented the clinical characteristics and treatment results for patients with T-MBC at the same institution and we discussed the controversial problems relating to adjuvant systemic treatment of this rare breast cancer.

Clinicopathologic characteristics

Our analysis proved that in patients with T-MBC:

— the mean age was 51 years (26–72), median — 52 years;
— the percentage of patients with stage I–II TNM was almost 90%;
— the percentage of patients with pT ≤ 5 cm and pN0 was above 90%;
— ER and PgR negative status was observed in more than 90% of the patients;
— HER-2/neu negative status was observed in almost 90% of the patients.

Similar population, microscopic and clinical characteristics, as well as immunohistochemically studied factors can be found quite often in the literature, obviously in varying frequency and intensity [1, 2, 15, 17, 18, 21–30]. However, it is important to stress that making strict comparisons between the present study group of patients and groups presented by other authors is very difficult and remains a questionable approach, since a T-MBC diagnosis itself is problematic and controversial. It is important to bear in mind the inconsistencies pointed out in the literature when it comes to assessing the type of cancer (T-MBC vs invasive carcinoma NST with medullary features) between pathologies (interobserver), as well as inconsistencies in assessing the same pathology (intraobserver). The WHO itself has stressed the difficulties involved in applying in practice strict T-MBC criteria [1]. Some authors have discussed an overall group of patients with T-MBC, so-called atypical MBC — A-MBC, and even with invasive NST carcinoma with medullary features; some publications from the 1960s and 1970s are in this respect difficult to verify.

Age of patients

The mean age of patients in the study group was 51 years; similar values have been reported by Vong et al. [31] — 51.7, Wong et al., [29] — 51.0 and Martinez et al. [27] — 50 years; meanwhile, lower values have been reported by Khomsi et al. [23] — 47.5, Vu — Nishino et al. [16] — 47.5, Yilmaz et al. [32] — 48.3, Wargotz & Silverberg [24] — 45 years, Thurman et al. [22] — 44 years, and Vo et al., which noted a mean survival of as low as 39.2 years [30]. The vast majority of researchers stress that the percentage of cases of MBC is higher among young patients with lung cancer than it is in older patients [1, 22, 16–18, 28, 33–35]. A study conducted by CASH (Cancer and Steroid Hormone Study) noted that the higher the age, the lower the percentage of patients with MBC; it was highest in the 20–29 and 30–39 age brackets, while among patients aged 40–49 and 50–54, it was still higher than in older patients [33, 34]. In 1995 Berg and Hunter observed a high percentage of MBC in young patients, highest among patients aged < 30; among patients aged 30–34 it was confirmed in 8% of cases, among patients aged 45–49 it was present in only 3% of cases, and in the 75–79 age group — 1.5% [35].

Stage of disease

A total of 88.3% of the patients in the study group were diagnosed with stage I or II of the disease according to the TMN classification. This result is in accordance with the observations of many authors who emphasis that patients with this advanced stage of the disease clearly predominate in percentage terms [2, 10, 18, 21, 22, 24, 25, 28–30]. According to certain authors, patients with stages I and II° of the disease represent more than 90% of the total. For example, Cao et al. report a figure of 94.6%, Anz et al. — 92.3%, and Zhang et al. — 96.2% [18, 28, 36].

Size of tumour in the breast

In more than 95% of patients in the study group, the breast tumour (pT) did not exceed 5 cm. Bertucci et al. [6] and Vo et al. [30] reported exactly the same percentage of pT1 and pT2 tumours. Hang et al. reported that tumours < 5 cm accounted for 92.3% [28] of the total, while Cao et al. gave a figure of 97.4% [18] and Flucke et al. — 98.2% [17]. Meanwhile both Wang et al [29] and Vu-Nishino et al. [16] reported that such tumours accounted for approximately 100% of their cases.

Microscopic state of axillary lymph nodes

Micropscopy revealed the absence of metastases in the axillary lymph nodes of 91.7% of the patients in the study group; in the remaining 8.3% of cases, metastases were identified in 1–3 lymph nodes. Patients with T-MBC tend to have a lower overall frequency of ALN (axillary lymph node) metastases than patients with invasive ductal carcinoma with medullary features or usual invasive ductal carcinoma [2, 16, 17, 21, 22, 24, 25, 27–29, 31, 37–40]. Martinez et al. [27] identified pN0 in 71.7% of patients, Flucke et al. [17] — 75%, Vo et al. [30] — 76.7%, Khomsi et al. [9] — 78.8%, Thurman et al. — 90% [22] and Zhang et al. [28] — 92.3%. When nodal metastases are present, they typically involve

no more than three lymph nodes [18, 22, 24, 25, 37, 40–42]. Cao et al reported the following observations: 70.2% of patients with pN0, 23.9% pN+ (1–3) and 5.9% pN+ (> 3), while Thurman et al. noted 90% of patients with pN0 and 10% with pN+ (1–3) [22].

Oestrogen and progesterone receptors and c-erb B2 gene expression

The general view is that T-MBC indicates negative progesterone and oestrogen receptors as well as an absence of *c-erbB2* gene expression [1, 5, 6, 12, 1, 16–19, 27, 30, 31, 37, 42–45], while no progesterone receptors were identified in 95.8% of cases and *c-erb B2* gene expression was only noted in 12.5% of cases. Bertucci et al. described a group of patients, in 100% of whom there were no oestrogen receptors and in 96% no progesterone receptors [6]. Jacquemier et al. presented a study in which they identified negative oestrogen receptors in 89.5% of patients and negative progesterone receptors in 48.7% [5]; Matkovic et al. reported percentages of 94.0% and 83%, respectively [44]. In an analysis of 13 controlled clinical studies, Huober et al. observed negative oestrogen and progesterone receptors in 81% of patients [26]. The *c-erb B2* gene expression was shown to be absent in 100% of the patients observed by Bertucci et al. [6] and Vang et al. [31], in 94.4% of the patients studied by Jacquemier et al. [5] as well as in 93.4% of cases in a study conducted by Flucke et al. [17].

Efficacy of treatment for patients with T-MBC

Of the 120 patients with T-MBC comprising the study group, a total of 108 (90%) survived disease-free for 10 years. Only 4 (3.3%) of the patients died as a result of T-MBC, all with metastases occurring in the axillary lymph nodes 91-3N+). None of the 110 patients with T-MBC, in whom no metastases occurred in the axillary lymph nodes, died of the disease.

Table V shows the treatment results for MBC according to the data from the literature. According to Table V and other data from the literature, the 10-year survival rate for patients with MBC varies between 63% and 94.9%, while the 5-year survival rate ranges from 70% to 92.3%; these significant differences mainly result from differences in the clinical and microscopic composition (T-MBC vs invasive carcinoma NST with medullary features) of the groups of patients being compared [16, 18, 21, 22, 24–27, 29, 39, 45]. The vast majority of the researchers stress that the prognosis for patients with MBC is good or even very good, especially in the case of T-MBC, and is significantly better than among patients with invasive ductal carcinoma [2, 5–7, 11, 13, 14, 16–18, 21–23, 25–28, 37, 40, 42, 45–48]. Koerner provided an analysis of five series, which included a pathologic review of cases recorded as medullary carcinoma (MBC) or as invasive ductal carcinoma with medullary features [37]; fewer than 50% of the lesions were accepted as MBC, and the remaining cases were diagnosed as invasive ductal carcinomas with medullary features or invasive ductal carcinomas [2, 24, 25, 40, 42]. Patients with MBC proved to have a statistically significant more favourable prognosis than those in either of the other two groups [37].

Table V. Treatment results in patients with T-MBC

Author, reference, year of publication	Survival rates	
	10-year	5-year
Rapin V et al. [24] 1988	92.0%	–
Reinfuss M et al. [39] 1995	–	78.0%
Thurman SA et al. [21] 2004	63.0%	
Vu-Nishino H et al. [16] 2005	94.9%	–
Gjerstorff MF et al. [45] 2006	84.0%	–
Khomsi F et al. [22] 2007	–	85.0%
Vo T et al. [29] 2007	79.5%	89.0%
Martinez SR et al. [26] 2011	78.0%	–
Huober J et al. [25] 2012	66.0% (14-year)	–
Zhang J et al. [27] 2013	–	92.3% (6-year)
Cao AY et al. [18] 2013	91.0%	–
Stelmach A et al. [present] 2016	90.0%	–

A study conducted by Cao et al. showed the following 10-year overall survival rates: 91% for patients with BM and, 81% for patients with invasive ductal carcinoma. Gjerstorff reported results of 84% and 63%, respectively [18, 45]. Meanwhile, Martinez et al. observed 14-year survival rates of 66% and 57%, respectively, including, 80% and 73% for pN0 patients, respectively and 63% and 49% for pN+ patients, respectively [27]. Undoubtedly surprising is the fact that the prognosis for T-MBC, despite its "triple negative breast cancer" features, is good or even very good, indeed significantly better than it is for infiltrate ductal breast carcinoma. Most authors think that this is due to the presence of abundant lymphoplasmacytic infiltration that is inseparably associated with this cancer [49, 50]. Jacquemier et al. as well as Bertucci et al. suggest that this may partly be a result of myoepithelial differentiation T-MBC [5, 6].

Treatment of T-MBC

The current treatment of choice for patients with T-MBC is breast conserving therapy (BCT) supplemented with radiotherapy. This is particularly the case with patients with breast tumours not exceeding 3 cm; sentinel lymph node mapping is an appropriate procedure for staging axillary lymph nodes [37]. It should be stressed that the prognosis for patients with small, node-negative T-MBC is particularly favourable with a 10-year DFS rate of 90% or better [2, 24].

In the study group, all 22 patients treated with BCT survived for 10 years disease-free.

Adjuvant chemotherapy can probably be omitted in patients with T1 N0 M0 TMBC; the indications for systemic adjuvant therapy in other patients are similar to those for non-medullary invasive duct carcinoma.

Conclusions

1. The population, microscopic and clinical characteristics as well as selected immunohistochemically assessed features of T-MBC are:
   - a mean age of 51 years;
   - almost 90% are stage I or II patients;
   - more than 90% patients had breast tumours (pT) not exceeding 5 cm;
   - more than 90% of the patients had negative axillary lymph nodes;
   - no patients developed metastases in more than 3 axillary lymph nodes;
   - absence of progesterone and oestrogen receptors expression in more than 90% of the patients;
   - absence of *c-erb B2* expression was observed in more than 90% of the patients.
2. The 10-year disease-free survival rate for the author's own material was 90%. Only 3.3% of the patients (4/120) died from T-MBC, all of them from metastases in the axillary lymph nodes (N+ 1–3). None of the 110 patients with no metastases in the axillary lymph nodes (N0) died from T-MBC.
3. The surgical procedure of choice for patients with T-MBC, is, with the right indications, breast conserving therapy (BCT). Of the 22 patients who underwent BCT from the author's own material, all survived for 10 years disease-free.
4. T-MBC patients with no metastases in the axillary lymph nodes require no adjuvant chemotherapy.

Conflict of interest: none declared

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