

Medullary breast cancer is a predominantly triple-negative breast cancer – histopathological analysis and comparison with invasive ductal breast cancer

Michał P. Budzik¹, Maciej T. Sobieraj², Maria Sobol¹, Janusz Patera³, Aleksandra Czerw^{4,5}, Andrzej Deptała¹, Anna M. Badowska-Kozakiewicz¹

¹Department of Cancer Prevention, Medical University of Warsaw, Warsaw, Poland

²Public Central Teaching Clinical Hospital, Warsaw, Poland

³Department of Pathology, Military Institute of Health Services, Warsaw, Poland

⁴Department of Economic and System Analyses, National Institute of Public Health – NIH, Warsaw, Poland

⁵Department of Health Economics and Medical Law, Medical University of Warsaw, Warsaw, Poland

Submitted: 22 April 2019; **Accepted:** 31 May 2019

Online publication: 17 July 2019

Arch Med Sci 2022; 18 (2): 432–439

DOI: <https://doi.org/10.5114/aoms.2019.86763>

Copyright © 2019 Termedia & Banach

Corresponding author:

Anna M. Badowska-Kozakiewicz PhD
Department of Cancer Prevention
Medical University of Warsaw
81 Żwirki i Wigury St
02-091 Warsaw, Poland
Phone: +48 22 572 07 02
E-mail: abadowska@wum.edu.pl

Abstract

Introduction: Medullary breast cancer (Mdbc) is an uncommon type of breast cancer representing 1–7% of all cases. It is characterized by the occurrence of many histopathological features associated with a high grade of malignancy.

Material and methods: Twelve MdbcS chosen from a group of 1,122 women suffering from invasive breast cancer were analyzed. Histopathological examination and analysis of a basic molecular profile, i.e. estrogen (ER), progesterone (PR) and HER2 receptor expression, and their comparison with invasive ductal breast cancer (IDC), were performed.

Results: Mdbc accounted for 1.07% of all analyzed invasive breast cancer patients. All patients were female, with an average age of 58.54 years. The Mdbc group exhibited a larger median tumor diameter (2.05 vs. 1.89 cm), although $\geq T2$ tumors comprised 42% vs. 51% for IDCs. Women without regional lymph node involvement (pN0) (83%) formed the largest group. There was a statistically significant difference in the presence of nodal involvement between the studied groups ($p < 0.001$). Based on the histological grade of malignancy, the majority of Mdbc comprised grade II tumors (G2) (93%). In general, Mdbc showed statistically higher histologic grade (G1-G3) than IDC ($p = 0.003$). The 5-year overall survival rate of Mdbc patients was 91%. Most MdbcS (92%) were triple-negative, whereas the remaining 8% were HER2 positive.

Conclusions: Mdbc presented at a younger age than IDC, had a higher histological grade, larger median size and less frequent regional lymph node involvement. Most MdbcS were triple-negative, whereas IDCs were predominantly luminal. Despite numerous aggressive pathological features of Mdbc, its clinical outcome and overall prognosis are favorable.

Key words: HER2, progesterone receptor, estrogen receptor, carcinoma with medullary features.

Introduction

According to the prevalent epidemiological data, breast cancer (BC) is the most frequent female cancer worldwide. The multitude of clinical

and pathological cases considered in creation of the World Health Organization (WHO) classification of breast neoplasms shows the complexity of the medullary breast cancer (MdBc) issue. MdBc is one of the most uncommon BC subtypes, representing 1–7% of all cases [1]. Its absolute prevalence, reaching every year around 4,900 cases worldwide, makes it a considerable proportion of the general cancer cases. Recent findings show MdBc to be a heterogeneous, spectrum-based group of various lesions rather than one strictly classified pathological diagnosis, and these neoplasms (typical medullary, atypical medullary and medullary-like invasive ductal carcinoma) are classified together as “carcinoma with medullary features” or simply “medullary breast cancer” [2]. Many studies have confirmed MdBc to exhibit a triple-negative phenotype, lacking progesterone (PR), estrogen (ER) and HER2 receptor expression. Usually triple-negative phenotype is associated with an aggressive clinical course, and is considered to be more resistant to chemotherapy and more likely to metastasize than other molecular breast cancer types. Moreover, it is associated with a lower disease-free survival rate and shorter life expectancy [3]. METABRIC research, considered to be the largest global study on breast cancer molecular issues, showed a significantly elevated rate of *TP53* mutations in comparison to other triple-negative cancers as the only significantly feature shared by the whole range of MdBc tumors [4]. MdBcs are in general associated with histopathological features widely acknowledged as “aggressive” – high mitotic index, enriched cytoplasm, easy syncytia formation and a very high level of genome instability. What is more, MdBcs are usually made of poorly differentiated cells characterized by the presence of large nuclei and prominent nucleoli. Surprisingly, patients with MdBc present significantly longer 5- and 10-year survival than patients suffering from other BC types. Higher frequency of rearranged genes is believed to be responsible for such an outcome. While inconsiderable genetic shifts are essential for cancer cells to be promoted and to avoid an immune system response, greater accumulation of mutations allows tumor epitopes to differ from unaffected ones relevantly enough to be recognized, infiltrated and confined by immune cells. This is the reason why MdBc should not be evaluated in Scar-Bloom-Richardson system, and if it is, the clinical outcome hardly corresponds with the most commonly assessed high grade [1].

Typical medullary breast carcinoma, whose cells present all of the aforementioned MdBc features, occurs more commonly among patients with *BRCA1* mutation, but only about 13% of women with MdBc have this mutation. Recent studies

suggest that the phenomenon of gene methylation might be responsible for flawed *BRCA1* expression [4, 5].

The aim of this study was to revise the histological and pathological features of MdBc and to analyze ER, PR and HER2 expression in order to make a comparison to invasive ductal breast cancer (IDC), which comprises the vast majority of diagnosed BCs.

Material and methods

The material for the study was composed of histological preparations obtained from 1,122 females diagnosed and treated for invasive breast cancer. MdBc was identified in 12 out of 1,122 women diagnosed with invasive BC in our center between 2009 and 2011. Clinical and demographic characteristics of patients were retrieved from the patient files. The biological material for the study derived from excisional breast biopsies and radical mastectomies. Tumor samples were fixed in 10% phosphate buffered formalin. After 24 h, fixated samples were dehydrated in alcohols of gradually increasing concentrations (50, 60, 70, 80, 90, and 96%), followed by pure alcohol and xylene. Afterwards, tissues were embedded in paraffin. Paraffin blocks were cut into sections, with a thickness of 4 μm each. The acquired samples were stained with different histopathological methods. Preparations stained with hematoxylin and eosin were used to identify histological type of cancer (WHO classification), histological grade of malignancy, and intensity of divisions expressed as the mitotic index of cancerous cells (the average number of mitoses in cancerous cells counted in 10 fields of vision at 400 \times objective magnification (surface field 0.17 mm^2)) [6].

Routinely, patients had a basic molecular profile evaluated, i.e. ER, PR and HER2 expression. Immunohistochemical procedures recruited paraffin samples placed on glass slides covered with 2% silane (Merck, Darmstadt, Germany) and dried for 24 h at 42°C. Prior to initiating the immunohistochemical procedures, samples were dewaxed by placing them in a series of alcohols of gradually decreasing concentrations (96, 90, 80, 70, 60, and 50%), and subsequently washed in distilled water. Immunohistochemical assays were performed using the En-Vision complex HRP Cytomatic (DAKO, Santa Clara, United States) (En-Vision Dual Link System-HRP, DAB, Code: K4065).

In order to define the expression of receptors for steroid hormones (ER, PR), monoclonal antibodies against estrogen receptor (Monoclonal Mouse Anti-Human Estrogen Receptor alpha, 1 : 50 dilution, Clone: 1D5, Code: IR654, DAKO, Santa Clara, United States) and progesterone receptor (Monoclonal

Mouse Anti-Human Progesterone Receptor, 1 : 400 dilution, Clone: PgR636, Code: IR068, DAKO, Santa Clara, United States) were used [6]. Samples were incubated at 60°C and then dewaxed. Afterwards, the cancerous epitopes were revealed by warming samples in a buffer for 40 min. Next, preparations were left at room temperature for 20 min, followed by rinsing them in a buffer, and endogenous peroxidase was blocked in 3% hydrogen peroxide. Subsequently, preparations were incubated with a dedicated antibody. Afterwards, samples were rinsed in a buffer for 10 min and then incubated with the reagent (Visualization Reagent) for 0.5 h. After that, preparations were washed in TBS (Tris-Buffered Saline, Code: S1968), pH 7.6, for 10 min, and then incubated with 3,3'-diaminobenzidine (DAB) (Substrate-Chromogen Solution) for a further 10-minute period to evoke the color reaction. Finally, hematoxylin preparations were stained and preparations were immersed in Canadian balm. Afterwards, the color reactions were assessed in accordance with the scale that takes into account the extent and intensity of staining of cancer cells' nuclei. Nuclear staining in > 10% of cells was regarded as positive (+) for ER and PR [6].

HER2 expression was defined by using the Hercept Test (Code: K5204, Dako, Santa Clara, United States) utilizing a polyclonal antibody against HER2 (Rb A – Hu HER2 – Rabbit Anti-Human HER2 Protein). HER2 state was defined by evaluating its expression on the cancerous cell membranes using immunohistochemistry, and in some cases (2+) proved by estimating the number of HER2 gene copies employing fluorescence *in situ* hybridization (FISH). The HER2 expression rate was established based on the maximum surface staining intensity, as follows: prominent peripheral membranous staining > 30% of tumor cells was designated 3+; temperate peripheral membranous staining in ≥ 10% of cancer cells or prominent perimetric membranous staining in ≤ 30% of cells was graded as 2+; poor and incomplete

membranous staining was marked as 1+; and no staining was scored 0. Scores of 0 and 1+ were both regarded as negative for HER2 amplification. A score of 3+ was considered as positive. A score of 2+ was considered equivocal and FISH was applied for confirmation. HER2 was considered to be amplified if the median HER2 copy number was ≥ 6 signals/cell or the ER2/CEP17 ratio was ≥ 2 [7]. Positive and negative control preparations were determined beforehand using techniques mentioned above.

Statistical analysis

Statistical analyses were performed using the Statistica 13.1 package. Biographical information was condensed using descriptive statistics (mean, median, range and standard deviation). The chi-square (χ^2) test with Yates' correction or Fisher's exact test, when the predicted cell counts were < 5, were used to compare categorical variables. The obtained results were considered statistically significant if $p \leq 0.05$.

Results

We analyzed 12 MdBCs representing 1.07% of a total of 1,122 females suffering from invasive BC qualified for the study. The mean age of the studied group of patients was 58.54 years (range: 30–70 years). Patients were divided into 7 age groups: ≤ 30; 31–40; 41–50; 51–60; 61–70; 71–80; and ≥ 81 years (Figure 1). Among all 1,122 investigated invasive BCs, a wide range of histological subtypes was found. IDC comprised the largest subgroup (76.29% of cancers) (Figure 2), followed by lobular (14.08%) and mixed ductal and lobular cancers (3.65%). Metaplastic, mucinous, tubular, medullary and micropapillary cancers were much less frequent (Table I). Clinicopathological findings of all MdBC cases are summarized in Table II. The average diameter of the primary MdBC foci was 2.05 cm (range: 1.2–3.5 cm). The MdBC group

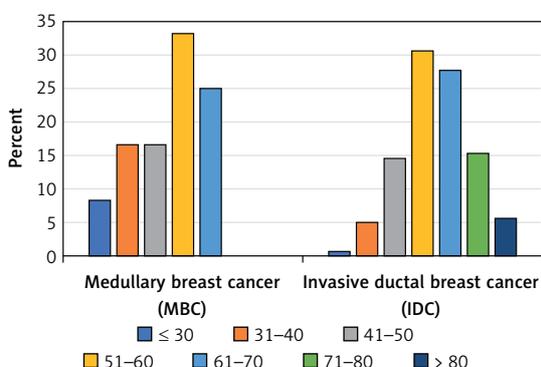


Figure 1. Age distribution in the medullary breast cancer (MdBC) group and the invasive ductal breast cancer (IDC) group of patients

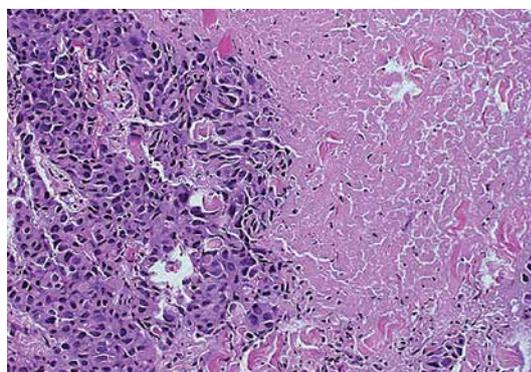


Figure 2. Histopathological image of invasive ductal breast carcinoma (IDC) with central necrosis, grade 3 (400x magnification)

demonstrated a larger median tumor diameter than the IDC group (2.05 cm vs. 1.89 cm), although $\geq T2$ tumors comprised 42% vs. 51%, respectively. The right breast was involved in 5 patients, the left one in 7. All analyzed MdBCs were unifocal. Most patients (58%) had T1c disease (which means tumor > 10 mm but ≤ 20 mm in the greatest dimension). In the study we also assessed the regional lymph nodes status, finding that in both examined BC groups (MdBC, IDC) women without regional lymph node involvement (pN0) (83%; 57%, respectively) comprised the largest group. Postoperative microscopic examination proved regional lymph nodes metastasis only in 2 (17%) MdBC cases. The present study shows a statistically significant difference in the presence of nodal involvement between MdBC and IDC groups ($p < 0.001$).

Depending on the histological grade of malignancy, MdBC showed a statistically higher grade of histological malignancy (G1–G3) ($p = 0.003$) compared to IDC (Figure 3). Most MdBC cases were grade II tumors (G2) (93%), similarly to the IDC cluster, in which G2 tumors accounted for 59%. A significant difference can also be found when analyzing highly differentiated tumors. 9% of IDCs were assessed as G1 tumors, while there were non-differentiated (G1) tumors among MdBCs. The same disproportion was found in the group of undifferentiated tumors (G3), in which 32% of IDCs and 42% of MdBC were found.

Most MdBC tumors (92%) were triple-negative, and 8% were HER2 positive (Figure 4). There were no ER and/or PR positive (luminal) BCs found in the studied group (Figure 5). The MdBC group included significantly more tumors with steroid hormone receptor negativity and no HER2 overex-

Table I. Distribution of histological types in the group of 1,122 patients with invasive breast cancer

Type	No.	%
Invasive ductal carcinoma	856	76.29
Invasive lobular carcinoma	158	14.08
Mixed ductal and lobular invasive carcinoma	41	3.65
Metaplastic carcinoma	13	1.16
Mucinous (colloid) carcinoma	19	1.69
Tubular carcinoma	14	1.25
Carcinoma with medullary features	12	1.07
Invasive micropapillary carcinoma	9	0.81
Total	1,122	100.00

pression/gene amplification in contrast to the IDC group (ER-, 100% vs. 26%, $p < 0.001$; PR-, 100% vs. 29%, $p < 0.001$; HER2 0/1+, 92% vs. 82%, $p = 0.004$) (Table III, Figure 2). Data analysis showed that the highest percentage of IDC (68%) presented prominent steroid hormone receptor expression simultaneously demonstrating HER2 negativity (ER+, PR+, HER2 0/1+) (Figure 6).

According to the TNM staging criteria, in both investigated groups (MdBC, IDC), stage II tumors comprised the largest group (75%; 43%, respectively). Despite the presence of many features associated with histological malignancy, MdBCs were assessed only as stage II (75%) and III (25%) tumors. Among IDCs, 27% of tumors were assessed as stage I, 43% as stage II, 14% as stage III, and 16% were staged IV. A statistically significant difference was observed between distribution of clinical stages in both investigated groups ($p < 0.001$).

Table II. Clinicopathological features of 12 medullary breast cancer (MdBC) cases

No.	Age	Material	Side	Max diameter [cm]	pT	pN	M	Grade	Lymph nodes	ER	PR	HER2
1	56	Postoperative material	L	3.0	2	0	x	3	0/13	-	-	0
2	37	Postoperative material	L	1.7	1c	0	x	2	0/20	-	-	0
3	59	Postoperative material	L	1.5	1c	0	x	2	0/8	-	-	0
4	49	Postoperative material	R	1.2	1c	1	x	2	1/20	-	-	0
5	43	Postoperative material	R	2.0	1c	1	x	3	1/8	-	-	0
6	65	Postoperative material	R	1.7	1c	0	x	3	0/1	-	-	0
7	54	Postoperative material	L	2.8	2	0	x	3	0/13	-	-	0
8	30	Postoperative material	R	2.5	2	0	x	2	0/20	-	-	0
9	57	Intraoperative assessment of the margin	L	1.4	1c	0	x	2	0/13	-	-	0
10	70	Postoperative material	R	3.5	2	0	x	2	0/13	-	-	0
11	63	Postoperative material	L	1.3	1c	0	x	3	0/12	-	-	1+
12	34	Postoperative material	L	2.0	2	0	x	2	0/20	-	-	3+

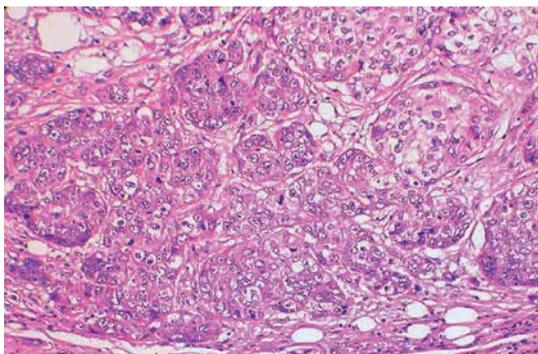


Figure 3. Histopathological image of medullary breast carcinoma (MdBc), grade 2 (200× magnification)

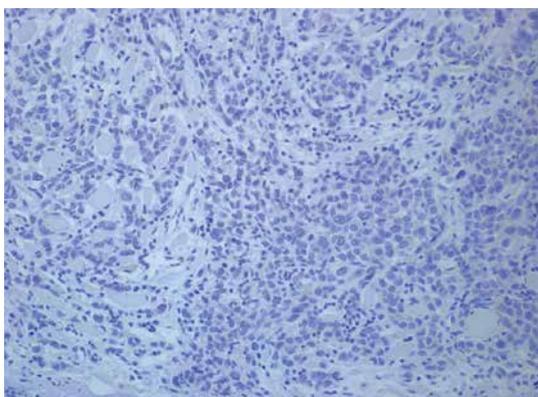


Figure 4. Example of immunohistochemical HER2 staining of triple-negative breast cancer, scored 0 (stained cells accounted for less than 10% of total tumor cells); the micrograph was taken with objective 20×



Figure 5. ER-negative medullary breast carcinoma (MdBc) (200× magnification)

In order to determine overall MdBc prognosis, a 5-year follow-up of patients was conducted. In the present study we observed a 91% 5-year overall survival rate for MdBc patients.

Discussion

Breast cancer is one of the most prevalent female cancers worldwide. Even though the mortality

rate decreases each year owing to earlier diagnoses and increasingly effective treatment, it remains the most common cause of cancer-related death in women [8]. It comprises many diverse subgroups, containing cancers with varying histopathological characteristics and clinical course. One of them is MdBc, seen rarely, but known for a favorable prognosis. It was defined for the first time in 1977, by Ridolfi *et al.* [9]. MdBc represents 1% to 7% of all diagnosed invasive BCs, which corresponds to the present study, which showed that MdBc comprises 1.07% of all invasive breast cancers. BC with medullary features is a histological diagnosis characterized by syncytial growth, well-circumscribed borders, and dense lymphocytic infiltration. MdBc usually has a soft consistency with a homogeneous gray and dense cut surface, but hemorrhage and central necrosis can be found in some cases. Histologically, medullary tumors consist of large cells. Most MdBcs, despite their worrisome cytologic and histologic features, triple-negativity, and high mitotic activity, have a favorable prognosis [10]. Invasive ductal breast carcinoma stands in contrast to MdBc. Invasive ductal subtype of BC is the most prevalent histological subtype BC in the Polish and European population as well, and is responsible for significant breast cancer mortality [11]. Considering the fact that IDC is the most frequent type of breast malignancy while MdBc is among the rarest subtypes, it is essential to provide a comparison of these breast cancers, especially focused on histopathological features and patients' overall survival.

The average age of MdBc patients in the present study was 54.5 years, which is slightly more than in available analyses (usually patients' mean age ranges from 45 to 54 years) [12]. Women under 40 years of age are generally defined as young in the contemporary reports, and those under 35 years of age as very young. The proportion of very young patients (< 35 years old) was 16.7% in the present study, similarly to results of a study conducted by Park *et al.* which revealed that 13.5% of analyzed patients were under 35 [12]. That fact proves that MdBc is especially a problem in the youngest group of patients, and that MdBc patients are usually younger than those who suffer from different types of BC, including IDC [13]. The average age of IDC patients in the present study was 60.5 years, which corresponds to the available data. It has also been proven that occurrence of BC at earlier ages is usually related to *BRCA1* and/or *BRCA2* mutations [13, 14]. According to the published data, MdBc more often can be found in African-American and Japanese women compared to women of the white race. Moreover, MdBc diagnosis is extremely rare in males, representing less than 0.5% of even such rare male breast cancer [15].

Table III. Comparison of invasive ductal breast cancer (IDC) and medullary breast cancer (MDBC)

Parameter	IDC (n = 856)	MdBC (n = 12)	P-value
Mean age [years]	60.5	51.4	–
Mean tumor size [cm]	1.89	2.05	–
Side:			
Right breast	404 (47.2)	5 (41.67)	0.703
Left breast	452 (52.8)	7 (58.33)	
Tumor size (T-stage):			
T1a	19 (2.21)	–	< 0.001*
T1b	72 (8.41)	–	
T1c	332 (38.79)	7 (58.33)	
T2	354 (41.36)	5 (41.67)	
T3	26 (3.04)	–	
T4	53 (6.19)	–	
Lymph nodes (N-stage):			
pN0	489 (57.13)	10 (83.33)	< 0.001*
pN1	233 (27.21)	2 (16.67)	
pN2	95 (11.10)	–	
pN3	39 (4.56)	–	
Tumor grade:			
G1	73 (8.53)	–	0.003*
G2	507 (59.23)	7 (58.33)	
G3	276 (32.24)	5 (41.67)	
Molecular subtypes:			
Luminal	641 (74.88)	–	< 0.001*
Triple negative	99 (11.57)	11 (91.67)	
HER2 overexpression	116 (13.55)	1 (8.33)	
Estrogen receptor status:			
ER–	219 (25.58)	12 (100)	< 0.001*
ER+	637 (74.42)	–	
Progesterone receptor status:			
PR–	245 (28.62)	12 (100)	< 0.001*
PR+	611 (71.39)	–	
HER2 status:			
HER2 0/1+	702 (82)	11 (91.67)	0.004*
HER2 2+	51 (5.96)	–	
HER2 3+	103 (12.04)	1 (8.33)	
TNM staging:			
I	236 (27.57)	–	< 0.001*
II	365 (42.64)	9 (75.0)	
III	121 (14.14)	3 (25.0)	
IV	134 (15.64)	–	

*Statistically significant results $p \leq 0.05$.

Previous studies presented controversial results regarding MdBC tumor size. Flucke *et al.* and Wang *et al.* reported smaller tumor diameter in MdBC compared to the IDC [16, 17]. On the other hand, Oh *et al.* found that MdBC had larger tumor size than IDC ($p < 0.001$) [18]. The present study showed that MdBCs are slightly larger than IDC tumors (2.05 cm vs. 1.89 cm, respectively) (Table III).

In the previous studies, regional lymph nodes metastasis was not observed in most of the MdBC patients. In the present analysis the majority of patients (83%) were assessed as pN0 and the remaining 17% of patients were pN1. High lymph node involvement (pN3, pN4) has not been observed, which reflects positively on the overall survival (OS) and recurrence-free survival (RFS) time [12, 19–22]. The incidence of nodal metastasis is usually lower than in other BCs, especially IDC [21]. Taking into account local invasion, it seems that IDC tumors are more aggressive than MdBC. Flucke *et al.* also proved that MdBC patients had a notably higher node-negative rate compared to those with IDC (75% vs. 48%, respectively; $p = 0.0014$) [16]. This conclusion may be related to the histopathological characteristics of MdBC, which include pronounced lymphocytic infiltration particularly with CD3, CD8, granzyme-B positive and TIA-1 lymphocytes. The other explanation may be the fact of a dissimilar immune response to cancer cells in MdBC than in other tumors, such as the presence of IgG, the absence of IgA, dense infiltration of plasma cells, and expression of tumor-specific antigens, e.g. HLA-DR, ganglioside D3, and β -actin [12, 23, 24]. These processes might be engaged in the tumor spread control and general invasiveness. By blocking the metastatic potential they improve the MdBC prognosis. Rare regional lymph node metastasis is not only a characteristic feature of MdBC, but seems to be the crucial prognostic factor and a sign of a cancer invasiveness too. The essential importance of lymph

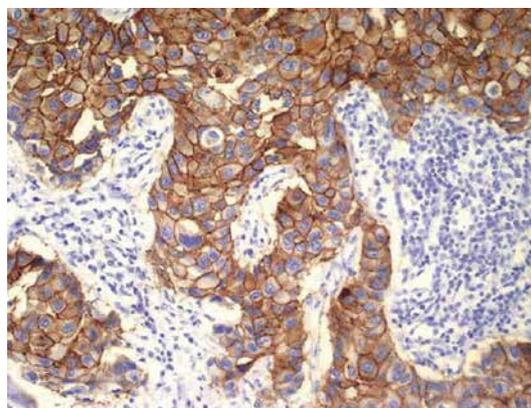


Figure 6. Strong, circumferential HER2 staining in > 30% of invasive ductal carcinoma (IDC) cells (3+) (original magnification, 20 \times)

node involvement in MdBC has been reported in numerous studies [14, 25, 26]. Martinez *et al.* reported that 10-year survival rates in MdBC with and without regional lymph node involvement were 67.5% and 81.9%, respectively [14]. Furthermore, Ridolfi *et al.* reported that patients with regional lymph node metastasis to < 3 lymph nodes did not die significantly earlier from the disease [9]. In the present study, the 5-year survival rate was 91%, and a significant difference between pN0 and pN1 MdBCs was not observed.

Hormonal receptor expression profile (ER, PR, and HER2) is widely known as a predictive prognostic factor. Hormonal status also implies the choice of the therapeutic strategy. It is also proven that MdBC is characterized by a lower incidence of ER, PR and HER2 expression. In the present study all MdBCs were ER- and PR-negative, whereas 92% of them were HER2-negative (HER2 0/1+). Therefore it was observed that the vast majority (92%) of MdBCs showed triple-negativity, similarly to the previous studies [1, 14, 27]. As mentioned above, the molecular subtype of BC is one of the most significant factors influencing the clinical course. It is widely known that both triple-negative and HER2 overexpressing subtypes predict a serious prognosis. In the present study, patients with a triple-negative disease were younger at the time of the primary diagnosis compared to those with other molecular BC types. When comparing all breast cancer histological subtypes, the same observation can be made. MdBC patients were on average at least 5 years younger than patients with any other histological type of BC. In the present analysis, the triple-negative breast cancer ratio was significantly higher in the MdBC compared to the IDC group ($p < 0.001$).

Many analyses have reported a much more favorable prognosis for MdBC patients compared to those suffering from IDC [28]. Xue *et al.* reported that the 2-year RFS and OS rates for triple-negative IDCs were 79% and 82%, respectively [29]; whereas Zhaohui *et al.* reported that the 2-year RFS and OS rates for triple-negative MdBC were 98.2% and 99.1%, respectively [28]. A statistically significant difference was also detected between MdBC and IDC patients with respect to the 5-year RFS (94.2% vs. 86.3%, $p = 0.008$) [18]. Several years later Cao *et al.* concluded that MdBC in Chinese women was characterized by a less aggressive clinical outcome and a better prognosis than IDC also after 10 years of follow-up [30]. Huober *et al.* reported that 14-year distant RFS and OS percentages for MdBC and IDC tumors were 76%, 64% and 66%, 57%, respectively [31]. In other words, although the MdBC patients predominantly exhibit a triple-negative molecular phenotype, their clinical outcome is better compared to the

IDC patients [32, 33]. This finding proves that the triple-negative molecular phenotype of BC is an insufficient factor for predicting overall prognosis as it had been thought for many years. The favorable overall prognosis for MdBC patients might be clarified through gene expression profiling. Vincent-Salomon *et al.* reported that cytokeratin 5/6 was expressed significantly more strongly in MdBC than in any other breast cancer histological subtype [34, 35]. Moreover, Bertucci *et al.* observed an extremely effective host immune response, upregulated expression of metastasis-inhibiting agents, and enhanced cancer cell apoptosis as histological features associated with better prognosis [36]. High frequency of remarkable inflammation and uncommon fibrosis regions are also biological features associated with a good prognosis [37, 38].

In conclusion, the low level of MdBC diagnosis is suspected to be caused by the absence of unequivocal histological and immunohistochemical diagnostic criteria. There are some features making MdBC recognition easier, such as syncytial pattern of tumor growth, lymphocyte infiltration, absence of tubular structures, infrequent necrosis foci, high mitotic rate, enriched cytoplasm and a very high level of genome instability, but they are not specific enough. Despite many aggressive pathological features of MdBC, its clinical outcome is much more favorable than for any other breast cancer type. This study proves that IDCs and MdBCs are completely different and independent types of the breast malignancy. In the vast majority of cases, MdBC diagnosis is associated with the triple-negative phenotype. It should be remembered that triple-negativity is usually associated with poor prognosis, but the MdBC group seems to be an important exception. Since triple-negativity can be related to both IDC and MdBC tumors, it is necessary to describe new markers and prognostic factors for this rare type of BC in order to enhance the accuracy of the diagnoses made and the effectiveness of oncological treatment.

Conflict of interest

The authors declare no conflict of interest.

References

1. Romaniuk A, Lyndin M, Sikora V, Lyndina Y, Panasovska K. Histological and immunohistochemical features of medullary breast cancer. *Fol Med Cracov* 2015; 52: 41-8.
2. Provenzano E, Ulaner GA, Chin SF. Molecular classification of breast cancer. *PET Clin* 2018; 13: 325-38.
3. Badowska-Kozakiewicz AM, Budzik MP, Liszcz A, et al. Clinicopathological factors associated with novel prognostic markers for patients with triple negative breast cancer. *Arch Med Sci* 2018. DOI: <https://doi.org/10.5114/aoms.2018.79568>.

4. Curtis C, Shah SP, Chin SF, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature* 2012; 486: 346-52.
5. Parise C, Caggiano V. The role of histology on survival of triple negative breast cancer. *J Clin Oncol* 2018; 36: DOI: 10.1200/JCO.2018.36.15_suppl.e12590.
6. Budzik MP, Patera J, Sobol M, et al. Clinicopathological characteristics of metaplastic breast cancer – analysis of the basic immunohistochemical profile and comparison with other invasive breast cancer types. *Breast* 2019; 43: 135-41.
7. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology e College of American Pathologists (ASCO/CAP) clinical practice guideline update. *J Clin Oncol* 2013; 31: 3997-4013.
8. Hao J, Zhang Q, Zhou Y, Chen L, Wu P. Association between circulating leptin concentration and G-2548A gene polymorphism in patients with breast cancer: a meta-analysis. *Arch Med Sci* 2018; 15: 275-83.
9. Ridolfi RL, Rossen PP, Port A, et al. Medullary carcinoma of the breast: a clinicopathologic study with 10 year follow-up. *Cancer* 1977; 40: 1365-85.
10. Geyer FC, Pareja F, Weigelt B, et al. The spectrum of triple-negative breast disease. High- and low-grade lesions. *Am J Pathol* 2017; 187: 2139-51.
11. Razeq AA, Gaballa G, Denewer A, et al. Invasive ductal carcinoma: correlation of apparent diffusion coefficient value with pathological prognostic factors. *NMR Biomed* 2010; 23: 619-23.
12. Park I, Kim J, Kim M, et al. Comparison of the characteristics of medullary breast carcinoma and invasive ductal carcinoma. *Breast Cancer* 2013; 16: 417-25.
13. Mateo AM, Pezzi TA, Sundermayer M, et al. Atypical medullary carcinoma of the breast has similar prognostic factors and survival to atypical medullary breast carcinoma: 3,967 cases from the National Cancer Data Base. *J Surg Oncol* 2016; 114: 533-6.
14. Martinez SR, Beal SH, Canter RJ, et al. Medullary carcinoma of the breast: a population-based perspective. *Med Oncol* 2011; 25: 738-44.
15. Li Cl. Risk of mortality by histologic type of breast cancer in the United States. *Horm Cancer* 2010; 1: 156-65.
16. Flucke U, Flucke MT, Hoy L, et al. Distinguishing medullary carcinoma of the breast from high-grade hormone receptor-negative invasive ductal carcinoma: an immunohistochemical approach. *Histopathology* 2010; 56: 852-9.
17. Wang XX, Jiang YZ, Liu XY, et al. Difference in characteristics and outcomes between medullary breast carcinoma and invasive ductal carcinoma: a population based study from SEER 18 database. *Oncotarget* 2016; 7: 22665-73.
18. Oh JW, Park S, Kim JH, et al. Clinical analysis of medullary carcinoma of the breast. *Breast Cancer* 2009; 12: 47-53.
19. Aksoy A, Odabas H, Kaya S, et al. Hormone receptor status and survival of medullary breast cancer patients. *Saudi Med J* 2017; 38: 156-62.
20. Lim S, Park SH, Park HK, et al. Prognostic role of adjuvant chemotherapy in node-negative (NO), triple-negative (TN), medullary breast cancer (MBC) in the Korean population. *PLoS One* 2015; 10: e0140208.
21. Chu Z, Lin H, Liang X, et al. Clinicopathologic characteristics of typical medullary breast carcinoma: a retrospective study of 117 cases. *PLoS One* 2014; 9: e111493.
22. Vu-Nishino H, Tavassoli FA, Ahrens WA, et al. Clinicopathologic features and long-term outcome of patients with medullary breast carcinoma managed with breast-conserving therapy (BCT). *Int J Radiat Oncol Biol Phys* 2005; 62: 1040-7.
23. Malyuchik SS, Kiyamova RG. Medullary breast carcinoma. *Exp Oncol* 2008; 30: 96-101.
24. Kuroda H, Tamaru J, Sakamoto G, et al. Immunophenotype of lymphocytic infiltration in medullary carcinoma of the breast. *Virchows Arch* 2005; 446: 10-4.
25. Foschini MP, Eusebi V. Rare (new) entities of the breast and medullary carcinoma. *Pathology* 2009; 41: 48-56.
26. Reinfuss M, Stelmach A, Mitus J, et al. Typical medullary carcinoma of the breast: a clinical and pathological analysis of 52 cases. *J Surg Oncol* 1995; 60: 89-94.
27. Shokouh TZ, Ezatollah A, Barand P. Interrelationships between Ki67, HER2/neu, p53, ER, and PR status and their associations with tumor grade and lymph node involvement in breast carcinoma subtypes retrospective-observational analytical study. *Medicine (Baltimore)* 2015; 94: e1359.
28. Zhaohui C, Hao L, Xiaohu L, et al. Clinicopathologic characteristics of typically medullary breast carcinoma: a retrospective study of 117 cases. *PLoS One* 2014; 9: e111493.
29. Xue C, Wang X, Peng R, et al. Distribution, clinicopathologic features and survival of breast cancer subtypes in Southern China. *Cancer Sci* 2012; 103: 1679-87.
30. Cao AY, He M, Huang L, et al. Clinicopathologic characteristic at diagnosis and the survival of patients with medullary breast carcinoma in China: a comparison with infiltrating ductal carcinoma-not otherwise specified. *World J Surg Oncol* 2013; 11: 91.
31. Huober J, Gelber S, Goldhirsch A, et al. Prognosis of medullary breast cancer: analysis of 13 International Breast Cancer Study Group (IBCSG) trials. *Ann Oncol* 2012; 23: 2843-51.
32. Zangouri V, Akrami M, Tahmasebi S, et al. Medullary breast carcinoma and invasive ductal carcinoma: a review study. *Iran J Med Sci* 2018; 43: 365-71.
33. Nowikiewicz T, Wnuk P, Matkowski B, et al. Application of artificial neural networks for predicting presence of non-sentinel lymph node metastases in breast cancer patients with positive sentinel lymph node biopsies. *Arch Med Sci* 2016; 13:1399-407.
34. Vincent-Salomon A, Gruel N, Lucchesi C, et al. Identification of typical medullary breast carcinoma as a genomic sub-group of basal-like carcinomas, a heterogeneous new molecular entity. *Breast Cancer Res* 2007; 9: R24.
35. Maeda T, Nakanishi Y, Hirofumi Y, et al. Immunohistochemical co-expression status of cytokeratin 5/6, androgen receptor, and p53 as prognostic factors of adjuvant chemotherapy for triple negative breast cancer. *Med Mol Morphol* 2016; 49: 11-21.
36. Bertucci F, Finetti P, Cervera N, et al. Gene expression profiling shows medullary breast cancer is a subgroup of basal breast cancers. *Cancer Res* 2006; 66: 4636-44.
37. Liao HY, Zhang WW, Sun JY, et al. The clinicopathological features and survival outcomes of different histological subtypes in triple-negative breast cancer. *J Cancer* 2018; 9: 296-303.
38. Marginean F, Rakha EA, Ho BC, et al. Histological features of medullary carcinoma and prognosis in triple-negative basal-like carcinomas of the breast. *Mod Pathol* 2010; 23: 1357-63.