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Atypical medullary breast carcinoma – the clinical picture and prognosis

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Summary

Purpose: The purpose of this paper was to present the clinical picture and the effectiveness of treatment patients with atypical medullary breast carcinoma (A-MBC). *Materials and Methods:* Sixty-five patients with A-MBC were treated between 1975 and 2005. More of them (70.2%) were in Stage I or II and had no expression of c-erb-B2 gene (81.5%), estrogen receptor (87.7%), and progesterone receptor (76.9%). Radical mastectomy was applied in 55 patients (84.6%) and remaining ten (15.4%) patients underwent breast conserving therapy. The treatment effectiveness was evaluated as ten-year disease-free survival (DFS) rate (Kaplan-Meier method). *Results:* The ten-year disease-free survival (DFS) rate was 61.5%. Only lymph nodal status was statistically significant prognostic factor. Ten–year DFS rate was 82.1% and 30.8% for pN0 and pN+, respectively. *Conclusion:* Although A-MBC has probably a slightly better prognosis than invasive ductal breast carcinoma, these patients should be treated according to the same rules as those with breast cancer of basal-like or triple-negative type.

Key words: Medullary breast cancer; Atypical medullary breast cancer; Triple-negative breast cancer.

Introduction

According to literature, medullary breast carcinoma (MBC) makes up 1-3% of malignant breast tumours [1-4]. MBC is more frequent in a population of patients who have breast cancer with a mutation in the suppressor BRCA1 gene. Moreover, patients with MBC more often have BRCA1 compared to other forms of breast cancer [2, 5-9]. MBC often shows images of basal-like type breast cancer and its immunohistochemical tests usually find negative estrogen receptors, the lack of progesterone receptors, and HER-2/neu. This qualifies the cancer for its inclusion in the "triple-negative" cancer group [1, 3-6, 10-12].

Currently, the World Health Organization (WHO) recommends the following categories of breast "carcinomas with medullary features": medullary carcinoma (MC), atypical MC, and a subset of invasive carcinoma of no special type (NST); the criteria used to define MC are as follows: the syncytial architecture in > 75% of the tumour mass, histological circumscription or pushing margins, the lack of tubular differentiation, prominent, and diffuse lymphoplasmacytic stroma infiltration, and round tumour cells with abundant cytoplasm and pleomorphic high–grade vesicular nuclei containing one or several nucleoli. The terms "atypical medullary carcinoma and carcinoma with medullary features" was proposed for tumours that do not fulfil all the criteria. The diagnosis of atypical medullary breast carcinoma (A-MBC) was made when the tumour had a predominantly (greater than 75%) syncytial growth pattern, with only three or four of the preceding five criteria [6]. The WHO criteria are similar to those presented by Ridolfi *et al.* in 1977 [13].

Undoubtedly, these diagnostic criteria are difficult to apply, which results in inter- and intra-observer reproducibility [8, 14-16]. This has led some authors to question the possibility and usefulness of distinguishing the atypical form of medullary cancer and combining it with invasive carcinoma NST with medullary features or with the typical form in the MBC group [3, 8, 12, 17-19]. WHO stresses that "studies with higher MBC prevalence are likely to include examples of atypical MBC and/or invasive carcinoma NST with medullary features" [6]. However, the vast majority of authors in their works differentiate the typical and atypical form of medullary cancer (medullary carcinoma and atypical carcinoma-WHO), while demonstrating important differences between them [1, 3, 17, 20-35].

The purpose of this work was to present the 30-year experience of the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Krakow Branch (CCIO) in the treatment of patients with A-MBC with special regard to its clinical picture, as well as to the effectiveness of treatment.

Materials and Methods

Sixty-five patients with A-MBC were treated in the CCIO between January 1975 and September 2005, and this group of pa-

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tients was the subject of this detailed analysis. The youngest patient was 27-years-old and the oldest 67-years-old; the mean age of patients was 51 years; 45 (69.2%) patients were 55-years- old or younger, 16 (24.6%) patients were nulliparous, 23 (35.4%) had one child, 26 (40.0%) had two or more children, 31 (47.7%) patients were before menopause, and 34 (52.3%) after menopause.

All of the pathological material from these patients was reviewed by senior pathologist using the WHO criteria which make the diagnosis of typical medullary breast carcinoma (T-MBC) and A-MBC [6].

In 36 (55.4%) patients, the tumour was located in the upper outer quadrant of the breast, in 23 (25.4%) patients in the other quadrants, and in six (6.2%) patients it was situated centrally. Five (7.7%) patients demonstrated Stage I (according to UICC, 1997), 41 (63.1%) Stage II, and 19 (29.2%) Stage III. In 13 (20.0%) patients the tumour (pT) in the breast had more than two cm in diameter in the examination of the surgical material, in 39 (60.0%) two to five cm, and in 13 (20%) patients there was more than five cm in diameter. The microscopic examination found metastasis to the axillary lymph nodes (pN) in 26 (40.0%) patients, including 19 (29.2%) in one to three lymph nodes and in more than three lymph nodes of seven (10.8%) patients; 39 (60.0%) patients had no metastasis to the axillary lymph nodes.

The expression of c-erb-B2 was reported in 12 (18.5%) patients and the lack of this expression in the remaining 53 (81.5%) patients. Fifty-seven (87.7%) patients had no estrogen receptor expression and 50 (76.9%) no progesterone receptor expression.

All patients from the study group were originally treated surgically. Radical mastectomy was applied in 55 patients (84.6%): 18 (27.7%) patients underwent radical mastectomy using the Halsted method (patients treated between 1975 and 1982), 37 (56.9%) patients underwent radical mastectomy using the Patey or Madden method (patients treated between 1983 and 2005, and the remaining ten (15.4%) patients underwent breast conserving therapy (treated between 1998 and 2005), which consists of tumorectomy and axillary lymphagiectomy, followed by radiotherapy. These patients had a tumour in the breast with dimensions not exceeding two cm. In the imaging studies, the lesions did not show characteristics of multifocality or clinical signs of metastasis to the axillary lymph nodes. Postoperative radiotherapy in this group of patients consisted of whole breast irradiation with a dose of 50 Gy given in 25 fractions over five weeks using photon beam. Additionally, all these patients received amended boost of ten Gy given in five fractions to the tumour bed.

In 29 (44.6%) patients treated with radical mastectomy, postoperative radiotherapy was indicated because of metastasis in the axillary lymph nodes and/or the size of the tumour in the breast exceeding five cm in diameter. The irradiation included mixed photon-electron beam which covered the chest wall with postoperative scar and regional lymph nodes, giving 50 Gy in 25 fractions over five weeks.

A six-month adjuvant chemotherapy according to CMF (cyclophosphamide, methotrexate, 5-fluorouracil) or FAC (5-fluorouracil, adriamycine, cyclophosphamide) regimen was applied in 26 (40.0%) patients with metastasis to the axillary lymph nodes (pN+), and hormone therapy was used in eight with expression of hormone receptor.

There were no significant complications of the treatment, either after surgery or after radiotherapy, except for two patients treated by the Halsted method which in the long-term follow-up suffered swelling of the upper limb on the operated side with medium intensity.

A ten-year disease-free survival (DFS) was the criterion used to assess the effectiveness of the treatment, counting from the day of operation. The survival probability was estimated using the Kaplan-Meier method [36]. The log-rank test was used by Peto *et al.* who found significant differences in the research material [37]. The influence of selected factors on patient survival time was evaluated using the Cox proportional hazards model [38]. A *p*-value of less than 0.05 was considered significant in all tests.

Table 1. — *The analysis of influence of demographic, clinical, and hormonal characteristics on treatment results in 65 patients with atypical breast carcinoma.*

Parameters	No. of patients	10-year disease-free survival [%] (Kaplan-Meier method)	*p* (log rank test)
Age (years):			
≤ 55	45	62.2	NS
> 55	20	60.0	
No. of parturitions:			
none	16	62.5	
1	23	60.9	NS
≥ 2	26	61.5	
Menopausal status:			
Premenopausal	31	61.3	NS
Postmenopausal	34	61.8	
Localisation of primary tumor:			
Upper outer quadrant	36	63.9	NS
Other parts of breast	29	58.6	
Stage (UICC 1997):			
I - II	46	67.4	NS
III	19	47.4	
Tumor size (pT):			
< 2 cm	13	69.2	
2-5 cm	39	61.5	NS
> 5 cm	13	53.8	
Lymph node status (pN):			
pN0	39	82.1	
pN+ (1-3)	19	31.6	< 0.05
pN+ (≥ 4)	7	28.6	
C-erbB2 expression:			
Positive	12	66.7	NS
Negative	53	60.4	
Estrogen receptor expression:			
Positive	8	62.5	NS
Negative	57	61.4	
Progesteron receptor expression:			
Positive	15	60.0	NS
Negative	50	62.0	
Surgery method			
Halsted	18	61.1	
Patey or Madden	37	62.2	NS
BCS	10	60.0	
Total	65	61.5	

NS: non-significant; BSC: breast conserving surgery.

Results

The ten-year DFS rate was 61.5%. Table 1 presents the influence of demographic, clinical and hormonal charac-

teristics on treatment results. Both multivariate analysis conducted using the Cox method found that only the microscopic state of the axillary lymph nodes (pN) was an independent predictor in the study group. A statistically significantly higher rate of ten-year DFS was achieved in patients without metastasis to the axillary lymph nodes (pN0) in comparison to pN+ (respectively 82.1% *vs*. 30.8%). Out of the 25 patients who died during a ten-year follow-up, three (4.6%) patients died without the signs of cancer due to cerebral embolism or hemorrhage, two (3.1%) patients died due to ductal invasive cancer of the contralateral breast in the third and seventh year after the A-MBC treatment. Twenty (30.8%) patients died due to A-MBC. In all of them, distant metastasis to the lungs, brain, liver, and bones were the only causes of death.

Table 2. — *The comparison of some demographic, clinical, and pathological characteristics in patients with atypical medullary breast carcinoma in presented group with literature.*

Parameters	Presented group	Data from literature	
Mean age (years)	51	48.2	Vong *et al.* [22]
		53.7	Yilmaz *et al.* [35]
		45	Orlando *et al.* [41]
Age ≤ 55 year	69.2%	88.3%	Zhang *et al.* [26]
Premenopausal status	47.7%	50%	Zhang *et al.* [26]
		67%	Orlando *et al.* [41]
Stage I and II	70.8%	82.4%	Zhang *et al.* [26]
Mean tumor size (pT)	2.8 cm	2.2 cm	Rakha *et al.* [17]
		2.47 cm	Vong *et al.* [22]
Tumor size ≤ 5 cm	80.4%	94.1%	Zhang *et al.* [26]
		100.0%	Orlando *et al.* [41]
pN0	60.0%	77.8%	Vong *et al.* [22]
		70.6%	Zhang *et al.* [26]

Discussion

The analysis included a group of 65 patients with A-MBC treated in the CCIO in the years 1975-2005. This represented 0.62% of all women with breast cancer treated during this period. Presented in literature groups of patients with A-MBC have various numbers: 273 cases of A-MBC were diagnosed (4.3%) in the material from the protocol of the National Survival Adjuvant Breast and Bowel Project (NSA BP), presented by Fisher *et al.*, in a group of 6,404 patients with Stage I-II breast cancer [20]. Between 1987 and 1988 in Nottingham, UK, 2.3% of patients with invasive breast cancer suffering from A-MBC were accounted for in a group of 2,304 patients [1]. The patients with A-MBC accounted for 15.89% in a group of 428 patients with triple- negative breast cancers as presented by Zhang *et al.* [26]. It should be stressed that the literature usually presents groups of patients from a population of only several, or a dozen or so, for instance Vu-Nishino *et al.* (seven patients), Matkovic *et al.* (nine patients), Vong *et al.* (nine patients), Orlando *et al.* (nine patients), Lim *et al.* (12 patients), Cheung *et al.* (12 patients), Tamiolakis *et al.* (15 patients), Xu *et al.* (13 patients), Yilmaz *et al.* (18 patients), and Rubens *et al.* (21 patients) [12, 21, 22, 24, 31, 34, 35, 39-41]. The groups of patients with A-MBC counting several dozen cases were presented by Zhang *et al.* (68 patients), Ridolfi *et al.* (79 patients), Reinfuss *et al.* (84 patients), and Rakha *et al.* (88 patients) [13, 17, 26 28]. The literature also presents isolated cases of A-MBC e.g. with atypical diagnostic or clinical features (unusual sonographic findings, gastric metastasis, oral cavity metastases, etc.) [23, 42-44].

The population, microscopic, clinical, and immunohistochemical characteristics of the study group are as follows: mean age 51 years and 69% were younger than 55 years, 25% of patients were nulliparous, the tumour in 55.4% of patients was located in the upper outer quadrant of the breast, 70.8% of patients was in Stage I or II of disease, in 80.4% of patients, the breast tumour (pT) did not exceed five cm, 40% of patients had metastasis to the axillary lymph nodes, including 10.8% with lesions in more than three nodes, absence of expression: c-erb-B2 gene (81.5% patients), and estrogen receptor (87.7%), progesterone receptor (76.9%).

The comparison of these characteristics with the observations of other authors is difficult because the literature contains few studies concerning A-MBC patients only, and those that are available often present a numerically small group of patients and only selected features of A-MBC [17, 22, 26, 28, 35, 41, 45, 46]. The analysis indicates both similarities and significant differences between the groups of patients with A-MBC presented in the literature; differences in the assignment of patients to the A-MBC group are probably the main reasons for this. However, data concerning T-MBC, both those presented in Table 2 and contained in the literature, indicate that the clinical picture of A-MBC and T-MBC differ significantly and that the clinical manifestation of A-MBC is close to the image of invasive ductal carcinoma (IDC). Compared with T-MBC, the group of patients with A-MBC had a higher percentage of subjects with advanced cancer (Stage III) - 30% *vs*. 10% in breast tumours (pT) exceeding five cm in diameter, 20% *vs*. 5-10% with metastasis to the axillary lymph nodes, 30-40% *vs*. 10-20% with metastasis in more than three lymph nodes, 10% *vs*. 0-3% in positive hormone receptor lesions and the expression of c-erb B2- 20% *vs*. 5-10% [2, 10, 12, 47-50].

In the presented group, a ten-year DFS rate was 61.5%. This survival rate in the literature ranged from 62% to 74% in the material studied by Ridolfi *et al.* (74%) [13], Rapina *et al.* (62%) [19], and Reinfuss *et al.* (63.1%) [28]. Zhang *et al.* reported DFS rate of 80.9% in the group of 68 patients with A-MBC, with a follow-up of 70.6 months. It must be emphasized that the number amounted to 92.3% in the group of 26 patients with T-MBC; relapse rates were

5.8% for T-MBC, 19.1% for A-MBC, and 26.7% for IDC [26]. The vast majority of authors quite unambiguously confirm that the prognosis of patients with A-MBC is worse than in patients with TMBC [3, 13, 19, 20, 21, 28, 32, 35, 40]; the survival of patients with A-MBC was comparable to patients with IDC in the group presented by Fisher *et al.* [20]; the analysis of Ridolfi *et al.* shows a statistically better ten-year DFS survival in the group of patients with T-MBC - 100% *vs*. A-MBC - 43%, and IDC-43% [13], according to Pedersen *et al.* 75%, 33%, and 43% [51], and Tavassoli 100%, 56%, and 43%, respectively [52].

The study presented in 1995 by Reinfuss *et al.*, which included 184 cases originally diagnosed as medullary carcinoma treated at the present CCIO in the years 1952-1983, showed a ten-year DFS survival in 84.6% (44/52) of patients with T-MBC, 63.1% (53/84) with A-MBC, and 45.8% (22/48) with non-medullary carcinoma [28]. Thus, the present study and numerous literature data clearly demonstrate that A-MBC has a worse prognosis than T-MBC, though perhaps better than IDC.

The concept of A-MBC was introduced into the literature in 1977 by Ridolfi *et al.* [13]. It was reinforced by the studies of Jacquemier *et al.* and Harris and Lessellsa [45, 46]. In 1988, Rapin *et al.* proposed to use the term MBC only for T-MBC and to eliminate other forms, such as A-MBC or non-medullary carcinoma from this terminology; the authors presented a ten-year DFS in 92% of patients with T-MBC and 53% in those with A-MBC [19]. In 1988, Wargotz and Silverberg suggested to not distinguish the term A-MBC [18]. In later years, some authors followed their footsteps and decided not to recognize A-MBC, justifying their decision by significant differences in the microscopic image and especially in the prognosis between A-MBC and IDC (Fisher *at al.* in 1990, Pedersen *et al.* in 1991, Tavassoli in 1992, Rigaud *et al.* in 1993, Gaffey *et al.* in 1995, Pedersen *et al.* in 1995, Jensen in 1997, and Orlando *et al.* in 2005) [3, 14, 15, 20, 41, 51-53]. However, many authors recognized the clinical importance of the criteria created by Ridolfi *et al.* and are still distinguishing A-MBC (Ponsky *et al.* in 1984, Reinfuss *et al.* in 1995, Yilmaz *et al.* in 2002, Rakha *et al.* in 2009, and Zhang *et al.* in 2013 [17, 26, 28, 35, 54]. The authors emphasize two features of A-MBC: higher growth dynamics than in T-MBC, larger breast tumours, metastasis to the axillary lymph nodes, and a worse prognosis; in their opinion, these features are approaching A-MBC to IDC. At the same time, although the diagnosis of A-MBC may be useful prognostic information for a clinician, the emphasis is that it has no significant influence on the choice of treatment.

Conclusion

Although A-MBC has probably a slightly better prognosis than IDC, there is no doubt that patients with breast cancer should be treated according to the same rules as those suffering from IDC (as type of basal-like or triple-negative).

References

[1] Weigelt B., Geyer F.C., Reis-Filho J.S.: "Histological types of breast cancer: how special are they?" *Mol. Oncol.*, 2010, *4*, 192.

[2] Bertucci F., Finetti P., Cervera N, Charafe-Juffret E, Mamessier E, Adelaide J.. *et al.*: "Gene expression profiling shows medullary breast cancer is a subgroup of basal breast cancers". *Cancer Res.*, 2006, *66*, 4636.

[3] Jensen M.L., Kiaer H., Andersen J., Jensen V., Melsen F. Prognostic comparison of three classifications for medullary carcinomas of the breast. *Histopathology*, 1997, *30*, 523.

[4] Rakha E.A., Reis-Filho J.S., Ellis I.O.: "Basal-like breast cancer: a critical review". *J. Clin. Oncol.*, 2008, *26*, 2568.

[5] Marginean F., Rakha E.A., Ho B.C, Ellis I.o, Lee A.H.: "Histological features of medullary carcinoma and prognosis in triple-negative basal-like carcinomas of the breast". *Mod. Pathol.*, 2010, *23*, 1357.

[6] Jacquemier J., Reis-Filho J.S., Lakhani S.R., Rakha E.: "Carcinomas with medullary features. WHO classification of tumours of the breast". 4th ed. Lyon: International Agency for Research on Cancer, 2012, 46.

[7] Vargas A.C., Da Silva L., Lakhani S.R.: "The contribution of breast cancer pathology to statistical models to predict mutation risk in BRCA carriers". *Fam. Cancer*, 2010, *9*, 545.

[8] Kleer C.G.: "Carcinoma of the breast with medullary-like features: diagnostic challenges and relationship with BRCA1 and EZH2 functions". *Arch. Pathol. Lab. Med.*, 2009, *133*, 1822.

[9] Lakhani S.R., Van De Vijver M.J., Jacquemier J.: "The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2". *J. Clin. Oncol.*, 2002, *20*, 2310.

[10] Jacquemier J., Padovani L., Rabayrol L., Lakhani S.R., Penault-Llorca F., Denoux Y., *et al.*: "Typical medullary breast carcinomas have a basal/myoepithelial phenotype. J Pathol. 2005,207,260-268.

[11] Rakha E.A., Ellis I.O. Triple-negative/basal-like breast cancer: review". *Pathology*, 2009, *41*, 40.

[12] Vu-Nishino H., Tavassoli F.A., Ahrens W.A., Haffty B.G.: "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.

[13] Ridolfi R.L., Rosen P.P., Port A., Kinne D., Miké V.: "Medullary carcinoma of the breast: a clinicopathologic study with 10 year follow-up". *Cancer*, 1977, *40*, 1365.

[14] Gaffey M.J., Mills S.E., Frierson H.F.Jr., Zarbo R.J., Boyd J.C., Simpson J.F., Weiss L.M.: "Medullary carcinoma of the breast: interobserver variability in histopathologic diagnosis". *Mod. Pathol.*, 1995, *8*, 31.

[15] Rigaud C., Theobald S., Noël P., Badreddine J., Barlier C., Delobelle A., *et al.*: "Medullary carcinoma of the breast. A multicenter study of its diagnostic consistency". *Arch. Pathol. Lab. Med.*, 1993, *117*, 1005.

[16] Pedersen L., Holck S., Schiødt T., Zedeler K., Mouridsen H.T.: "Inter- and intraobserver variability in the histopathological diagnosis of medullary carcinoma of the breast, and its prognostic implications". *Breast Cancer Res. Treat.*, 1989, *14*, 91.

[17] Rakha E.A., Aleskandarany M., El-Sayed M.E., Blamey R.W., Elston C.W.: "The prognostic significance of inflammation and medullary histological type in invasive carcinoma of the breast". *Eur. J. Cancer*, 2009, *5*, 1780.

[18] Wargotz E.S., Silverberg S.G.: "Medullary carcinoma of the breast: a clinicopathologic study with appraisal of current diagnostic criteria". *Hum. Pathol.*, 1988, *19*, 1340.

[19] Rapin V., Contesso G., Mouriesse H., Bertin F., Lacombe M.J., Piekarski J.D., *et al.*: "Medullary breast carcinoma. A reevaluation of 95 cases of breast cancer with inflammatory stroma". *Cancer*, 1988, *61*, 2503.

[20] Fisher E.R., Kenny J.P., Sass R., Dimitrov N.V., Siderits R.H., Fisher B.: "Medullary cancer of the breast revisited". *Breast Cancer Res. Treat.*, 1990, *16*, 215.
[21] Xu R., Feiner H., Li P., Yee H., Inghirami G., Delgado Y., Perle M.A.: "Differential amplification and overexpression of HER-2/neu, p53, MIB1, and estrogen receptor/progesterone receptor among medullary carcinoma, atypical medullary carcinoma, and high-grade invasive ductal carcinoma of breast". *Arch. Pathol. Lab. Med.*, 2003, *127*, 1458.
[22] Vong J.S., Yu A.M., Ng D.C.H., Lui P.C.W., Law B.K.B., Chau H.H.L., *et al.*: "Reduced numbers of regulatory T cells in breast carcinoma with medullary features". Histopathology. 2011,59,345-349
[23] Kroupis C., Lianidou E., Goutas N., Ladopoulou A., Konstantopoulou I., Pantazidis A., *et al.*: "Atypical medullary breast carcinoma in a family carrying the 5382insC BRCA-1 mutation". *Breast J.*, 2003, *9*, 260.
[24] Matkovic B., Juretic A., Separovic V., Novosel I., Separovic R., Gamulin M., Kruslin B.: "Immunohistochemical analysis of ER, PR, HER-2, CK 5/6, p63 and EGFR antigen expression in medullary breast cancer". *Tumori*, 2008, *94*, 838.
[25] Shousha S.: "Medullary carcinoma of the breast and BRCA1 mutation". *Histopathology*, 2000, *37*, 182.
[26] Zhang J., Wang Y., Yin Q., Zhang W., Zhang T., Niu Y.: "An associated classification of triple negative breast cancer: the risk of relapse and the response to chemotherapy". *Int. J. Clin. Exp. Pathol.*, 2013, *6*, 1380.
[27] Rodríguez-Pinilla S.M., Rodríguez-Gil Y., Moreno-Bueno G., Sarrió D., Martín-Guijarro M.C., Hernandez L., Palacios J.: "Sporadic invasive breast carcinomas with medullary features display a basal-like phenotype: an immunohistochemical and gene amplification study". *Am. J. Surg. Pathol.*, 2007, *31*, 501.
[28] Reinfuss M., Stelmach A., Mituś J., Ryś J., Duda K.: "Typical medullary carcinoma of the breast. A clinical and pathological analysis of 52 cases". *J. Surg. Oncol.*, 1995, *60*, 89.
[29] Ashida A., Fukutomi T., Tsuda H., Akashi-Tanaka S., Ushijima T.: "Atypical medullary carcinoma of the breast with cartilaginous metaplasia in a patient with a BRCA1 germline mutation". *Jpn. J. Clin. Oncol.*, 2000, *30*, 30.
[30] Marcus J.N., Watson P., Page D.L., Narod S.A., Lenoir G.M., Tonin P., *et al.*: "Hereditary breast cancer: pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage". *Cancer*, 1996, *77*, 697.
[31] Tamiolakis D., Simopoulos C., Cheva A., Lambropoulou M., Kotini A., Jivannakis T., Papadopoulos N.: "Immunophenotypic profile of tumor infiltrating lymphocytes in medullary carcinoma of the breast". *Eur. J. Gynaecol. Oncol.*, 2002, *23*, 433.
[32] Nurlaila I., Telisinghe P.U., Ramasamy R.: "CD8+ lymphocytes and apoptosis in typical and atypical medullary carcinomas of the breast". *Immunol. Lett.*, 2013, *156*, 123.
[33] Chu Z., Lin H., Liang X, Huang R, Zhan Q, Jiang J, Zhou X.: "Clinicopathologic characteristics of typical medullary breast carcinoma: a retrospective study of 117 cases". *PLOS One*, 2014, *9*, e111493.
[34] Cheung Y.C., Chen S.C., Lee K.F., Wan Y.L., Ng S.H.: "Sonographic and pathologic findings in typical and atypical medullary carcinomas of the breast". *J. Clin. Ultrasound*, 2000, *28*, 325.
[35] Yilmaz E., Lebe B., Balci P., Sal S., Canda T.: "Comparison of mammographic and sonographic findings in typical and atypical medullary carcinomas of the breast". *Clin. Radiol.*, 2002, *57*, 640.
[36] Kaplan E.L., Meier P.: "Nonparametric estimation from incomplete observation". *J. Am. Stat. Assoc.*, 1958, *53*, 457
[37] Peto R., Pike M.C., Armitage P., Breslow N.E., Cox D.R., Howard S.V., *et al.*: "Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples". *Br. J. Cancer*, 1977, *35*, 1.
[38] Cox D.R.: "Regression models and life-tables". *J. R. Stat. Soc. Series B. Stat Methodol.*, 1972, *34*, 187.
[39] Rubens J.R., Lewandrowski K.B., Kopans D.B., Koerner F.C., Hall D.A., McCarthy K.A.: "Medullary carcinoma of the breast. Overdiagnosis of a prognostically favorable neoplasm". *Arch. Surg.*, 1990, *125*, 601.
[40] Lim K.H.J., Telisinghe P.U., Abdullah M.S., Ramasamy R.: "Possible significance of differences in proportions of cytotoxic T cells and B-lineage cells in the tumour-infiltrating lymphocytes of typical and atypical medullary carcinomas of the breast". *Cancer Immunity*, 2010, *10*, 3.
[41] Orlando L., Renne G., Rocca A., Curigliano G., Colleoni M., Severi G., *et al.*: "Are all high-grade breast cancers with no steroid receptor hormone expression alike? The special case of the medullary phenotype". *Ann. Oncol.*, 2005, *16*, 1094.
[42] Sobrino-Mota V., Lagarejos-Bernardo S., Varela-Mezquita B., Castro Y., Segura-González C., Pérez-Milán F.: "Unusual sonographic findings in a case of atypical medullary inflammatory carcinoma of the breast". *J. Clin. Ultrasound*, 2008, *36*, 166.
[43] Jin B., Liu Y.P., Wang H.J., Wang Q.S.: "Gastric metastasis of atypical medullary carcinoma from breast: a case report". *Chin. Med. Sci J.*, 2012, *27*, 121.
[44] McCarty M.J., Vukelja S.J.: "Atypical medullary carcinoma of the breast metastatic to the oral cavity". *Am. J. Otolaryngol.*, 1994, *15*, 189.
[45] Jacquemier J., Robert-Vague D., Torrente M., Lieutaud R.: "Mise en evidence des immunoglobulines lymphoplasmocytaires et epitheliales dans les carcinomes infiltrans á stroma lymphoide et les carcinomes médullaires du sein". *Arch. Anat. Cycol. Path.*, 1983, *31*, 296.
[46] Harris M. Lessells A.M.: "The ultrastructure of medullary, atypical medullary and non-medullary carcinomas of the breast". *Histopathology*, 1986, *10*, 405.
[47] Cao A.Y, He M., Huang L., Shao Z.M., Di G.M.: "Clinicopathologic characteristics 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.
[48] Zhang J., Wang Y., Yin Q., Zhang W., Zhang T., Niu Y.: "An associated classification of triple negative breast cancer: the risk of relapse and the response to chemotherapy". *Int. J. Clin. Exp. Pathol.*, 2013, *6*, 1380.
[49] Flucke U., Flucke M.T., Hoy L., Breuer E., Goebbels R., Rhiem K., *et al.*: "Distinguishing medullary carcinoma of the breast from high-grade hormone receptor-negative invasive ductal carcinoma: an immunohistochemical approach". *Histopathology*, 2010, *56*, 852.
[50] Thurman S.A., Schnitt S.J., Connolly J.L., Gelamn R., Silver B., Harris J.R, Recht A.: "Outcome after breast-conserving therapy for patients with stage I or II mucinous, medullary, or tubular breast carcinoma". *Int. J. Radiat. Oncol. Biol. Phys.*, 2004, *59*, 152.
[51] Pedersen L., Zedeler K., Holck S, Schiodt T, Mouridsen H.T.: "Medullary carcinoma of the breast, proposal for a new simplified histopathological definition". *Br. J. Cancer*, 1991, *63*, 591.
[52] Tavassoli F.A.: "Infiltrating carcinomas, common and familiar special types: medullary carcinoma". *In:* Tavassoli F.A. (ed). *Pathology of the breast.* Norwalk, Connecticut: Appleton and Lange, 1992, 333.
[53] Pedersen L., Zedeler K., Holck S., Schiodt T., Mouridsen H.T.: "Medullary carcinoma of the breast. Prevalence and prognostic importance of classical risk factors in breast cancer". *Eur. J. Cancer*, 1995, *31A*, 2289.
[54] Ponsky J.L., Gliga L., Reynolds S.: "Medullary carcinoma of the breast: an association with negative hormonal receptors". *J. Surg. Oncol.*, 1984, *25*, 76.

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