Original Article

Medullary Breast Carcinoma and Invasive Ductal Carcinoma: A Review Study

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Abstract

Background: Medullary breast carcinoma (MBC) is a unique histological subtype of breast cancer. The present study aimed to evaluate the classic and non-classic characteristics of MBC and its differences with IDC. The present review study incorporates 22 years of practical experience from a breast disease research center-based series of cases.

Methods: Retrospectively, the medical records of 3,246 patients were reviewed in the Breast Disease Research Center, Shiraz University of Medical Science (Shiraz, Iran), from December 1993 to December 2015. The tumor size, lymph node metastasis, pathologic stage, nuclear and histological grade, hormonal receptor status, recurrence, disease-free, and overall survival were reviewed. Differences between medullary breast carcinoma and invasive ductal carcinoma were analyzed statistically using the Chi-square, Fischer, independent-sample t test, and Kaplan-Meier analysis (SPSS version 19.0). $P<0.05$ were considered statistically significant.

Results: A total of 179 patients were identified with MBC and 3,067 patients were identified with IDC. The MBC group had a significant association with a higher histological grade ($P<0.001$) as well as negative estrogen receptor ($P<0.001$), progesterone receptor ($P<0.001$), and HER-2 ($P=0.004$) status. The MBC patients predominantly had triple-negative breast cancer (TNBC) according to the molecular subtype ($P<0.001$). In local invasion, MBC was less invasive compared to IDC ($P<0.001$). The disease-free survival (DFS) and overall survival (OS) differed significantly between the MBC and IDC groups (5-year DFS: 94.2% vs. 86.3%, $P=0.008$; 5-year OS: 98.1% vs. 92.8%, $P=0.004$).

Conclusion: Despite the poor and aggressive pathological features of MBC, its clinical outcome is more favorable compared to IDC. Our findings can be useful in improvement of diagnosis and treatment of less known breast cancer subtypes, such as MBC.

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Keywords ● Carcinoma ● Medullary ● Carcinoma ● Ductal ● Breast ● Prognosis ● Survival

What's Known

•   Invasive ductal carcinoma (IDC) is the most common subtype of breast cancer and medullary breast cancer (MBC) is among the rare subtypes with some controversies about its histopathology and survival rate.

What's New

•   Despite the poor and aggressive pathological features of MBC (e.g. tumor grade and TNBC), its clinical outcome is more favorable compared to IDC.
•   The results demonstrate that the OS and DFS rates are more desirable in MBC than in IDC.

Introduction

Breast cancer is the most common neoplasm in females worldwide.[1-3] It has been estimated that 1,384,155 new cases and nearly 459,000 deaths occur annually.[4,5] From the histological

viewpoint, breast cancer is very heterogeneous; some cases have slow growth and a very good prognosis, while some other tumors can have a highly aggressive clinical course.[6] In the Middle East, breast cancer is the most common malignancy among women. In Iran, breast cancer is also the most common malignancy among women; comprising 21.4% of all malignancies in females.[2,7]

For the first time in 1977, Ridolfi et al. defined medullary breast carcinoma (MBC) as one of the invasive and malignant subtypes of breast cancer.[8] MBC is well circumscribed and soft in consistency with a homogeneous gray and moist cut surface, but hemorrhage and necrosis can be found in some cases. Histologically, tumors consist of large tumor cells. The characteristic feature of MBC is a dense lymphocytic infiltration of the tumor stroma.[9,10] Overall, it comprises about 3-6% of all breast cancer subtypes[10] and its frequency has been reported to be about 3.3% in Iran.[2] MBC is characterized by young age, large tumor size, and high nuclear grade. Some studies found that MBCs seemed to exhibit a significantly higher proportion of triple-negative phenotype (absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2)).[11]

Breast invasive ductal carcinoma (IDC) is a common breast malignancy and a major cause of cancer-related death in women worldwide.[12-14] According to some studies conducted on Iranian populations, IDC is the most common subtype of breast carcinoma and is responsible for significant breast cancer mortality.[2]

Recently, many studies have been conducted on MBC and its unique characteristics. Some studies have also focused on differences between MBC and other subtypes of breast carcinoma.[15] Considering the fact that IDC is the most common subtype of breast cancer and MBC is among the rare subtypes with some controversies about its histopathology and survival, more attention should be paid to these malignancies.

Shiraz is a referral center for breast cancer in southern Iran. To the best of our knowledge, no studies have been conducted on this topic in this region. Subsequently, the present study aimed to evaluate the classic and non-classic characteristics of MBC and its differences with IDC. Additionally, considering all characteristics of these tumors, we attempted to identify which of the two has a better survival. The present review study incorporates 22 years of practical experience from a breast disease research center-based series of cases.

Patients and Methods

Retrospectively, the medical records of 3,246 patients were reviewed in the Breast Disease Research Center, Shiraz University of Medical Science (Shiraz, Iran), from December 1993 to December 2015. A complete history and physical examination, bilateral mammography, chest radiology, and routine blood and biochemical tests were required for all patients prior to surgery. The patients with distant metastasis at diagnosis, those with ductal carcinoma in situ, and the patients who had received neoadjuvant chemotherapy were excluded. The patients with occult breast cancer presenting with axillary node metastasis and those with a history of ipsilateral or contralateral breast cancer were excluded too.

In the present study, MBC was defined according to the strict criteria of Ridolfi et al.[8] and only typical MBC was included. The clinicopathologic features, including tumor size, lymph node (LN) metastasis, pathologic stage, nuclear and histological grade with immunohistochemical findings, such as ER, PR, and HER2 status, recurrence and disease-free and overall survival were reviewed retrospectively. Demographic information, such as sex, age, case number, and operation date was gathered using a data collecting form. Eventually, the difference between the IDC and MBC groups regarding the clinicopathological factors was evaluated using the Chi-square test, t test, Fischer, and Kaplan-Meier analysis. All analyses were performed using the SPSS statistical software (version 19.0) and $P<0.05$ was considered statistically significant.

Results

The MBC group included 179 patients between 30 and 86 years old, with the mean age of 54.24 years. On the other hand, the IDC group contained 3,067 patients between 25 and 103 years old, with the mean age of 54.81 years. Although the mean age of the MBC group was lower compared to the IDC group, the difference was not statistically significant ($P=0.83$). The tumor size ranged from 0.5 to 9 centimeters in the MBC group, but from 0.5 to 15 centimeters in the IDC group. Nevertheless, the mean of tumor size was similar in both groups (mean=2.8, $P=0.53$).

The expression of ER was lower in the MBC group than in the IDC group (30.2% vs. 75%, $P<0.001$). PR expression was also lower in the MBC group in comparison to the IDC group (24.9% vs. 69.3%, $P<0.001$). Thus, hormone

receptor (HR) expression was lower in the MBC group compared to the IDC group. Regarding HER-2 status, the frequency of HER-2 negative cases was higher in the MBC group compared to the IDC group (82.2% vs. 70.2%, P=0.004). In molecular subtypes, four categories were defined (table 1). HR+/HER2- subtype was detected in 24.5% of the cases in the MBC group and 58.2% of those in the IDC group (P<0.001). The frequency of HR+/HER2+ molecular subtype was also lower in the MBC group compared to the IDC group (7.5% vs. 18%, P<0.001). In addition, HR-/HER2+ subtype was observed in 10.4% of the cases in the MBC group, but 11.7% of those in the IDC group (P=0.18). Considering the triple-negative breast cancer (TNBC), the MBC patients predominantly had TNBC according to the molecular subtype (P<0.001). In axillary node involvement, 30.6% of the cases in the MBC group and 53.4% of those in the IDC group were positive (P<0.001). To evaluate local invasion, lymphatic, vascular, perineural, and lymphovascular invasions were taken into account. In all these subcategories, IDC was more invasive compared to MBC (P<0.001 for all the four subcategories).

Regarding tumor cell differentiation, three grades were defined.[16] According to the results, 55.3% of the cases in the MBC group and only 18.3% of those in the IDC group were grade III. Hence, it seems that the poorly differentiated tumor cells were higher in MBC than in IDC (P<0.001). Furthermore, 35% of the cases in the MBC group and 25.8% of those in the IDC group were in stage I at the time of diagnosis (P=0.003). However, IDC had a more aggressive manner in stages II, III, and IV (table 1). Based on the results, 16.3% of the IDC cases in comparison to 8% of the MBC ones were in stage III (P=0.011). Moreover, recurrence was detected in 8.4% of the MBC patients and 15.8% of the IDC ones (P=0.03).

The surgical management of the breast was also evaluated in all patients. Accordingly, breast conserving surgery (BCS) was performed in 64.2% of the MBC patients and 46.4% of the IDC ones (P<0.001). Besides, 98.4% of the patients with MBC and 97.5% of those with IDC received chemotherapy (P=0.4). In addition, the rate of radiotherapy was 83.5% and 81% in the MBC and IDC groups, respectively (P=0.3). Moreover, 79.5% of the IDC cases and 43.2% of the MBC ones underwent hormonal therapy (HT) (P<0.001). It should be noted that right breast involvement was observed in 52.8% of the MBC cases and 48.1% of the IDC ones (P=0.12).

The results of Kaplan-Meier analysis showed a significant difference between the MBC and IDC groups with respect to the overall survival

(OS) rate (P=0.004). The five-year OS rates were 92.8% and 98.1% for IDC and MBC, respectively (figure 1). The results of Kaplan-Meier analysis also indicated a difference between the two groups concerning the disease-free survival (DFS) rate (P=0.008). The five-year DFS rates were 86.3% and 94.2% for IDC and MBC, respectively (figure 2).

Discussion

MBC is one of the invasive and malignant subtypes of breast cancer that usually has unique demographic and clinicopathological characteristics. Considering the fact that IDC is the most common subtype of breast cancer and MBC is among the rare subtypes with some controversies about its histopathology and survival, more attention should be paid to these malignancies. The present study evaluated the
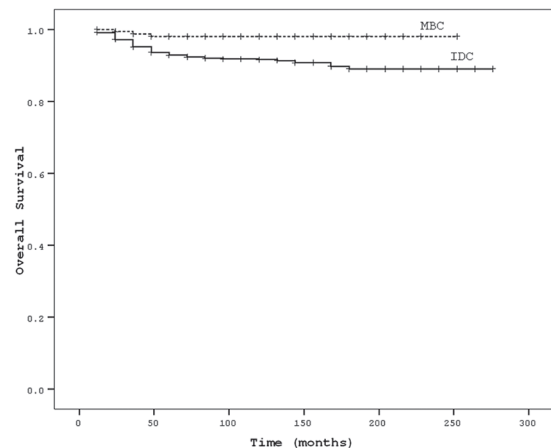
Figure 1: The five-year overall survival rates were 92.8% and 98.1% for IDC and MBC, respectively (P=0.004). MBC: Medullary breast carcinoma; IDC: Invasive ductal carcinoma.
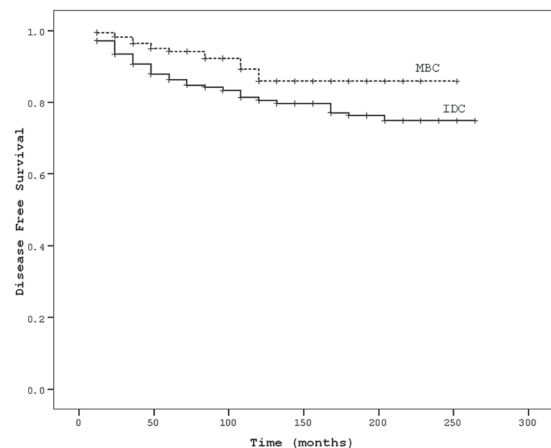
Figure 2: The five-year disease-free survival rates were 86.3% and 94.2% for IDC and MBC, respectively (P=0.008). MBC: Medullary breast carcinoma; IDC: Invasive ductal carcinoma.

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Characteristics	N (%)		P value
	Medullary	**Invasive ductal carcinoma**	
Sex			-
Female	179 (100)	3,067 (100)	
Male	0	0	
Breast			0.13
Right	94 (52.8)	1,462 (48.1)	
Left	84 (47.2)	1,576 (51.9)	
Operation			<0.001
Quadrantectomy	115 (64.2)	1,409 (46.4)	
Mastectomy	64 (35.8)	1,627 (53.6)	
Chemotherapy			0.40
Yes	121 (98.4)	2,114 (97.5)	
No	2 (1.6)	55 (2.5)	
Radiotherapy			0.30
Yes	91 (83.5)	1,620 (81.1)	
No	18 (16.5)	377 (18.9)	
Hormonal therapy			<0.001
Yes	48 (43.2)	1,720 (79.5)	
No	63 (56.8)	444 (20.5)	
Recurrence			0.03
Yes	14 (8.4)	448 (15.8)	
No	152 (91.6)	2,379 (84.1)	
5-years DFS rate±SEM	94.2±0.01	86.3±0.007	0.008
5-years OS±SEM	98.1±0.01	92.8±0.005	0.004
Grade			<0.001
I	7 (18.4)	629 (23.2)	
II	10 (26.3)	1,583 (58.4)	
III	21 (55.3)	496 (18.3)	
Lymphatic invasion			<0.001
No	131 (73.2)	1,529 (49.9)	
Yes	48 (26.8)	1,538 (50.1)	
Vascular invasion			<0.001
No	147 (82.1)	2,019 (65.8)	
Yes	32 (17.9)	1,048 (34.2)	
Perineural invasion			<0.001
No	167 (93.3)	2,355 (76.8)	
Yes	12 (6.7)	712 (23.2)	
Lymphovascular invasion			<0.001
No	122 (68.2)	1,433 (46.7)	
Yes	57 (31.8)	1,634 (53.3)	
Axillary node involvement			<0.001
Positive	53 (30.6)	1,566 (53.4)	
Negative	120 (69.4)	1,368 (46.6)	
ER			<0.001
Positive	51 (30.2)	2,205 (75)	
Negative	118 (69.8)	737 (25)	
PR			<0.001
Positive	42 (24.9)	2,034 (69.3)	
Negative	127 (75.1)	900 (30.7)	
HER-2			0.004
1+, Negative, FISH-	88 (82.2)	1,555 (70.2)	
FISH+, 3+	19 (17.8)	660 (29.8)	
Breast cancer subtypes			<0.001
HR+/HER2-	26 (24.5)	1280 (58.2)	
HR+/HER2+	8 (7.5)	395 (18)	
HR-/HER2+	11 (10.4)	257 (11.7)	
TNBC	61 (57.5)	266 (12.1)	
TNM staging			<0.001
I	48 (35)	567 (25.8)	
II	70 (51.1)	902 (41)	
III	11 (8)	359 (16.3)	
IV	8 (5.8)	373 (16.9)	
Age (years) Mean (max-min)	54.24±11.40 (30-86)	54.81±11.85 (25-103)	0.83
Tumor size (centimeters) Mean (max-min)	2.80±1.44 (0.5-9)	2.82±1.55 (0.5-15)	0.53

Table 1: The comparison of medullary carcinoma and invasive ductal carcinoma

TNBC: Triple-negative breast cancer; HR: Hormonal receptor; ER: Estrogen receptor; PR: Progesterone receptor; HER-2: Human epidermal growth factor receptor 2; FISH: Fluorescence in situ hybridization; DFS: Disease-free survival; OS: Overall survival; SEM: Standard error of mean; TNM: Tumor size, lymph node, metastasis

clinical features and unique characteristics of MBC and its differences with IDC.

In the present study, although MBC involved patients in younger ages, its difference with IDC was not statistically significant (table 1). This finding is in contrast with similar studies. For instance, Wang et al. reported that the MBC group presented a younger age at diagnosis (P<0.001).[11] Also, Park et al. (2013) reported that MBC occurred at a younger age in comparison to IDC.[15] The difference between the results might be justified by the larger sample size in the above-mentioned studies. Ethnic variations could also play a role in such differences.

The previous studies revealed controversial results regarding tumor size. For example, Flucke et al.[17] found smaller tumor size in the MBC group than in the IDC group. Wang et al. also reported larger tumor size in the IDC group.[11] In contrast, Vo et al.[18] demonstrated that the MBC group had larger tumors in comparison with the IDC group (P<0.001). However, the findings of our study showed no significant difference between the two groups concerning the tumor size (table 1).

Considering local invasion, it seems that IDC has a more aggressive manner compared to MBC. Flucke et al.[17] also showed that patients with MBC had a higher node-negative rate compared to those with IDC (75.0% vs. 47.9%, P=0.0014). In 2005, Ha Vu-Nishino et al. disclosed that despite the poor clinicopathological features of MBC, local control rates of the patients with MBC and IDC were comparable. These findings suggested that the patients diagnosed with medullary carcinoma were appropriate candidates for BCS.[19] This can justify our findings that MBC had a less aggressive manner in the 4 subcategories of local invasion (lymphatic, vascular, perineural, and lymphovascular invasions).

The results of the current study showed a significant difference between the IDC and MBC groups regarding the 5-year OS rate (92.8% vs. 98.1%, P=0.004). A significant difference was also observed between the two groups with respect to the 5-year DFS rate (86.3% vs. 94.2%, P=0.008). In 2009, Oh et al. reported that in spite of MBC's aggressive pathological features, its clinical outcome was favorable. They also revealed a difference between the Korean female patients with typical MBC and IDC concerning the 10-year OS rate (86.0% vs. 74.7%).[20,21] In 2013, A-Yong Cao et al. concluded that MBC in Chinese women demonstrated less aggressive behavior and a better prognosis than IDC after 10 years.[21] In contrast, some other studies, including the one performed by

Fisher et al.,[22,23] showed no significant difference between MBC and IDC regarding OS rate.[23-26]

Triple-negative breast cancers are defined as lack of ER, PR, and HER2. These types of cancer are associated with aggressive clinical behavior and poor prognosis.[26,27] In the present study, the rate of TNBC was significantly higher in the MBC group compared to the IDC group (P<0.001). Supporting our finding, Wang et al. indicated that 56% of the cases in the MBC group and 13.2% of those in the IDC group were triple-negative (P<0.001).[11] In 2008, Mersin et al. mentioned that TNBC is not uncommon and tends to display a more aggressive clinical course, as HER2-positive breast carcinoma. They also stated that tumor subtype, triple-negative or non-triple-negative, was an independent predictor of DFS.[27] Based on the results of our study and similar studies,[19,20,28-30] OS and DFS rates were more favorable in MBC than in IDC. In other words, although the MBC patients predominantly had TNBC,[31] their clinical outcome was better compared to the patients with IDC. This finding can arise the challenge that the triple negativity of breast cancer as the only factor is not sufficient for predicting prognosis.

Inevitably, our study had some limitations. The sample size of the MBC group was small and in the terms of tumor size and age, our findings were different in comparison with similar studies. We could not perform multivariate analysis to identify prognostic factors in the MBC group because of the small sample size and rare recurrences. In terms of the follow-up data, patient compliance was poor in some cases and, consequently, they were omitted from the study.

Conclusion

Despite the poor and aggressive pathological features of MBC (e.g. tumor grade and TNBC), its clinical outcome was more favorable compared to IDC. In other words, although TNBC patients should display a more aggressive clinical course and poor prognosis, our results demonstrated that the OS and DFS rates were more desirable in MBC than in IDC. Overall, our findings can be useful in improvement of diagnosis and treatment of less known breast cancer subtypes, such as MBC.

Acknowledgement

Conflict of Interest: None declared.

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