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Medullary Carcinoma Of The Breast: Ten Year Clinical Experience Of The Kuwait Cancer Control Centre

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Abstract

Background

Medullary carcinomas of the breast account for fewer than 7% of all invasive breast cancers. Some investigators include medullary carcinomas in the favourable histologic subtype, despite its aggressive histologic appearance. However, others fail to confirm its favourable prognosis.

Methods

This was a retrospective analysis of sixty-one (61) cases of breast cancer cases diagnosed with Medullary Carcinoma, presenting to the Kuwait Cancer Control Center between 1995 and 2005.

Results

Median survival time was 122 months and the seven-year disease free survival was 82%. Overall survival rate was not assessed as no cases died during the study period. No cases were metastatic from the start and only eight cases developed metastases, local recurrence or contralateral breast primary. 68.8% of the cases were Stage I or IIA (i.e. no lymph node affection).

Conclusion

There is no overt favourable prognosis of medullary carcinoma when compared to invasive ductal carcinoma. Prognosis is more related to stage than histologic subtyping. The majority of cases were negative estrogen and progesterone receptor status and node negative.

Keywords

Breast, Medullary carcinoma, favourable histology

Introduction

Medullary carcinomas are a rare entity and account for fewer than 5% to 7% of all invasive breast cancers[1- 7]. They are considered to carry a more favourable prognosis than other subtypes of infiltrating ductal carcinoma by some investigators[8-10], while others have failed to confirm this favourable prognosis[11]. This is a biological paradox because its clinical behaviour contrasts with its anaplastic morphology[8]. They are diagnosed by an association of five morphological features, established by Ridolfi et al: a predominantly syncytial growth pattern, a circumscribed border, a moderate to marked lymphoplasmacytic infiltrate, poorly differentiated nuclear grade with high mitotic rate, and the absence of glandular features or any in situ component.[12] Carcinomas lacking one of these features have been termed 'atypical medullary carcinoma' by some, while others diagnose them instead as infiltrating ductal carcinoma. Despite these defined morphological features, reproducibility of diagnosis is only moderate. Therefore, more specific and new diagnostic criteria such as genetic features would be very helpful.

Very little is known about the molecular alterations involved in the development of medullary carcinomas. These cancers are typically negative for estrogen receptor (ER), frequently negative for HER2neu status, and frequently present a mutation of p53[13]. A high proportion of medullary carcinomas have BRCA1 mutations[14] and, reciprocally, an excess of medullary carcinoma is seen in BRCA1 mutation carriers[15], suggesting a common targeted pathway or cell lineage with BRCA1

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breast cancer. It is not clear whether medullary and ductal breast cancers represent molecularly distinct entities and what genes/proteins might account for their phenotypic differences. Finally, the cell of origin of medullary carcinoma remains unknown. Thus, our understanding of medullary carcinoma is poor and reliable diagnosis is difficult.

Patients with medullary carcinoma usually present at a relatively younger age than patients with other breast cancers, with a wide age range reported. Maternal breast carcinoma was reportedly more frequent among women with medullary carcinoma than among women with other types of carcinoma.[16]

The majority of patients with a palpable mass in the upper outer quadrant of the breast, it is common to find enlarged ipsilateral axillary lymph nodes in medullary carcinoma patients, even when there are no nodal metastases microscopically. This phenomenon, which may complicate clinical staging[17], may also be encountered in patients with ductal carcinomas with medullary features[18].

Materials and Methods

Patients:

We reviewed 61 cases of breast carcinoma defined as either medullary or atypical medullary carcinoma presenting to the Kuwait Cancer Control Center from January 1995 to December 2005. All cases were retrospectively reviewed by the same member of the team by reviewing case files. At the time of surgery, a frozen section examination was performed, and the maximum diameter of the tumor was measured. Systematic biopsies were performed radially from the tumor site as well as all in suspected areas of the mastectomy specimen including the nipple, or of the lumpectomy specimen. The locoregional lymph nodes were sliced into 2-mm sections and histologically evaluated. All cases were pathologically diagnosed using the Ridolfi criteria[12].

Statistical methods:

Statistical package for social sciences (SPSS) version 14 was used to construct a database and for data analysis. Quantitative variables were summarized using mean ± standard deviation, median, and qualitative variables were summarized using frequency and percentage. Disease free survival (DFS) was measured from the date of surgery until the date of any relapse of breast cancer (local or distant), a new breast cancer or other type of cancer, or last patient contact. It was estimated by Kaplan Meier's method and survival curves were compared using Log rank test. Significance level of 0.05 was set for this study. No Overall Survival was estimated as no patients were reported to have died within the study period.

Results

Frequency:

61 patients were diagnosed with medullary carcinoma of the breast from 2,475 patients diagnosed with breast cancer in the Kuwait Cancer Control Center during the 10-year period from January 1995 to December 2005 (2.46%). All the patients were female. Of the 61 patients, 46 (75%) were of Arab origin and 15 (25%) were

	No	%
Nationality		
- Arab origin	46	75
- Asian descent	15	25
Age:		
- 20-30 years	6	10
- 31-40 years	17	28
- 41-50 years	28	46
- 51-60 years	7	11
- Above 60 years	3	5
Menopausal Status:		
- Premenopausal	44	72
- Postmenopausal	17	28
Family History of Cancer:		
- Positive	25	41
- Negative	36	59
Laterality:		
- Right Breast Cancer	31	51
- Left Breast Cancer	30	49
Surgical Treatment:		
- Conservative Surgery	29	47.5
- MRM	32	52.5

Table 1 : Patient Characteristics (n=61)

Tumor Size (T Stage):		
- T1	19	31
- T2	36	59
- T3	6	10
- T4	0	0
Nodal Stage (N)		
- Nx	1	2
- N0	45	74
- N1	13	21
- N2	0	0
- N3	2	3
Pathological Stage:		
- Stage I	18	30
- Stage II	40	65
- Stage III	3	5
- Stage IV	0	0
Tumor Grade:		
- Unknown	33	54
- Grade I	1	2
- Grade II	6	10
- Grade III	21	34
Mitotic Index:		
- Unknown	25	41
- Low	3	5
- Moderate	4	7
- High	29	47
Lymphoplasmic Infiltration:		
- Unknown	22	36
- Positive	35	57
- Negative	4	7
Lymphovascular Permeation:		
- Unknown	13	21
- Positive	39	64
- Negative	9	15
Hormonal status:		
ER:		
- Unknown	10	16
- Positive	12	20
- Negative	39	64
PR:		
- Unknown	10	16
- Positive	5	8
- Negative	46	76
Her-2-neu Status by IHC:		
- Unknown	28	46
- 0 or 1+	25	41
- 2+	3	5
- 3+	5	8
Ki67 score:		
- Unknown	39	64
- Positive	13	21
- Negative	9	15
Site of Failure:		
- Local recurrence	3	5
- Distant metastasis	6	10
- Contralateral carcinoma	2	3

Table 2 : Tumor Characteristics (n=61)

of Asian descent. The ages ranged between 22 and 75 years with the median age being 42 years. 17 patients (27.8%) presented between 31 and 40 years, 6 patients (10%) presented between 20 and 30 years, 28 patients (46%) presented between 41 and 50 years, 7 patients (11.5%) presented between 51 and 60 years and 3 patients (5%) presented between 61 and 75 years. (Table 1)

72.1% (44) of the cases were pre-menopausal and only 27.9% (17) were post-menopausal. Only 19 patients (31.1%) gave a history of contraceptive pill use and 32 patients (52.5%) gave a history of breast feeding their children while 44.3% (27%) did not. 25 patients (41%) gave a positive family history of different malignancies. However, there are no facilities for evaluation of the BRCA genes. 49 patients have a positive parity history (78.4%).

All patients have an immunohistochemical diagnosis of medullary carcinoma which included typical and atypical entities. 33 patients (54.1%) did not have known differentiation, only 1 patient (1.64%) had Grade I differentiation. 6 patients (9.8%) have moderate differentiation (Grade II) and 21 patients (34.4%) have poor differentiation (Grade III). 25 patients (41%) did not have mitotic index mentioned within the pathology report. Only 3 patients (5%) have a low mitotic index and 4 patients (6.5%) have a moderate mitotic index while 29 patients (47.5%) have a high mitotic index. (Table 2)

Lymphoplasmic infiltration was found in 35 patients (57.4%) and was negative in 4 patients (10.3%). However, 22 patients (36%) did not have actual status of the lymphoplasmic infiltration stated within the pathology report. 13 patients (21.3%) did not have status of lymphovascular permeation reported. 39 patients (63.9%) were negative for lymphovascular permeation and 9 patients (14.8) were found positive.

Most of the patients have a negative hormonal receptor status. 39 patients (63.9%) were negative for Estrogen Receptor (ER) and 46 patients (75.4%) were negative for Progesterone Receptor (PR). 12 patients (19.7%) were positive for ER and 5 patients (8.2%) were positive for PR. 10 patients (16.4%) have unknown receptor status. Of the 28 patients evaluated for HER2neu

status, most were negative. 25 patients (41%) have a negative score of either '0' or '1+'. Only 3 patients (5%) have a strongly positive score of '3+' and 5 patients (8%) have a moderately positive score of '2+'. Only 22 patients were evaluated for ki67: 9 patients (15%) were negative and 13 patients (21%) were positive.

The cases were almost equally divided between left and right breast presentation, i.e. 30 patients (49%) and 31 patients (51%) respectively. 42 patients (69%) have the tumour arising in the UOQ.

19 patients (31.1%) have a T1 lesion, 36 patients (59%) have a T2 lesion, and 6 patients (9.8%) have a T3 lesion. 45 patients (73.8%) have

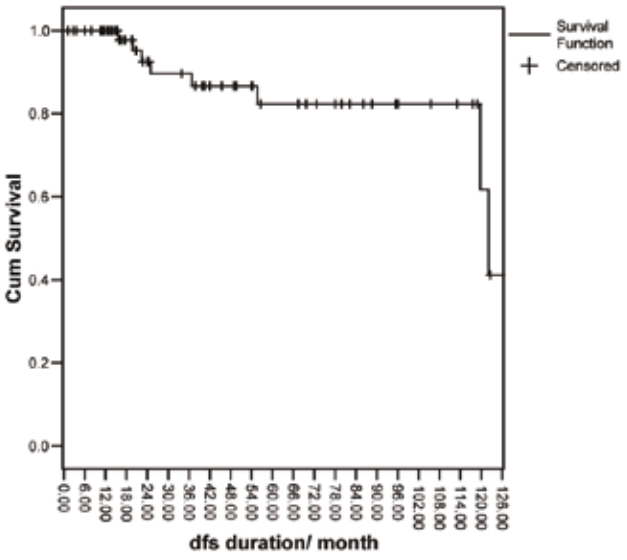

Fig. 1: Disease free survival curve for all cases

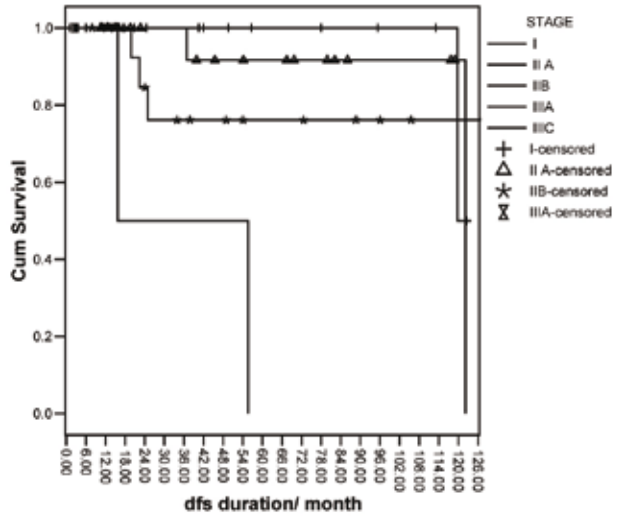

Fig. 1(a): Disease free survival curves for the different stages

no staging, 13 patients (21.3%) have N1 staging, no patient had a N2 staging and only 2 patients (3.3%) have a N3 staging. One case does not have N staging as no axillary dissection was done. 18 cases were staged Stage I (29.5%), while 24 cases were Stage IIA (39.3%), therefore 68.8% of the cases were without nodal affection. 16 cases were staged Stage IIB (26.2%), 1 case was Stage IIIA (1.63%), and 2 cases were Stage IIIC (3.3%). No cases were metastatic from the start but eventually 9 cases (14.75%) metastasized. 3 patients (5%) have local recurrence, 6 patients (9.8%) have distant metastases and 2 patients (3.3%) developed carcinoma in the contralateral breast.

29 patients (47.5%) underwent conservative surgery and 32 patients (52.5%) underwent MRM. Subsequent adjuvant treatment in the form of radiation therapy, hormonal therapy and chemotherapy was given according to indication.

Disease Free Survival rates:

The estimated DFS rates at 10 years was 61%, however, the DFS at 7 years was 82% (95% CI, 117.3 to 126.87 months). The median survival time was 122 months.

T-staging was found to have a statistically significant negative relationship with survival. Disease free survival was found to decrease with increasing tumour size where the 7-year disease free survival was 100%, 80.38% and 37.5% for T1, T2 and T3 respectively ($p = 0.0283$).

When assessing the Nodal status as either negative or positive, there was an insignificant negative relationship with the negative nodal group having a 7-year disease free survival of 87% and 67.53% for the positive group ($p = 0.6526$). However, when the nodal status was assessed as separate entities, there was a statistically significant negative association with a decrease in disease free survival with increasing nodal affection. The 7-year disease free survival for the N0, N1, and N3 groups was 87%, 90% and 0% respectively ($p = 0.0005$).

The difference in disease free survival was significant with the different stages, ($p = 0.0003$) with a decrease with increasing stage. Stage I had a 7-year disease free survival of 100%, Stage

II was 83.71%, and Stage III was 0%.

Although not statistically significant, an increase in mitotic index revealed a decrease in disease free survival, (p = 0.0656) where the 7-year disease free survival for low and moderate mitotic index was 100% and 63.92% for those with high mitotic index.

Survival was found to be negatively associated with lymphovascular permeation, but insignificant (p = 0.6528) with the 7-year disease free survival decreasing from 84.33% to 66.67% with permeation.

Survival was found to be positively associated, although insignificant, with positive estrogen and progesterone receptor status. The 7-year disease free survival was 100% for both positive estrogen and progesterone receptor status. This decreased to 86.63% and 88.71% for negative estrogen and progesterone receptor status (p = 0.1679 and p = 0.5531 respectively). Ki67 also had an insignificant positive relationship with the disease free survival (p = 0.105) being 100% for those positive for ki67 and 66.67% for those not.

Other factors examined including menstrual history, contraceptive history, breast feeding history, family history, lymphoplasmic infiltration, HER2neu status and the different treatment modalities used were not predictive of survival in univariate analysis.

Discussion

Medullary carcinoma of the breast demonstrates distinct pathological features, described in detail by Moore and Foote in 1949,[19] with unique biological and clinical characteristics. Its clinico-pathologic character has various implications that may dictate diagnostic and therapeutic approaches. The purpose of this retrospective study was to compare epidemiological, clinical and pathological characteristics and outcome of medullary carcinoma.

Medullary carcinoma has been reported by some investigators to have a better prognosis than other histologic subtypes, particularly invasive ductal carcinoma.[20-24] Moore and Foote[19] have even stated that only 11.5% of their patients with medullary carcinoma died of the tumour within 5 years. So while presenting with less favourable clinical and pathologic characteristics, some have found these patients to show improved long-term distant relapse-free survival. Local control rates have also been found to be comparable with patients with invasive ductal carcinoma. These findings may suggest that these patients are appropriate candidates for more conservative treatment with lumpectomy and radiation therapy and are associated with favourable prognosis in long-term outcome.[25]

On the other hand, many have questioned this belief and several investigators have failed to find a more superior prognosis for this rare pathological entity.[11, 26] Ellis et al,[27] evaluated 1,621 women with various types of invasive breast cancer. 44 patients had medullary carcinoma and 76 patients had atypical medullary carcinoma and they showed no survival benefit when compared to the invasive ductal carcinoma of no special type group (p = 0.3 and p = 0.1 respectively). Thurman et al[28] found no statistically significant difference in the site of first failure between patients with medullary, mucinous, or tubular carcinoma and patients with invasive ductal carcinoma following breast-conservative therapy. However, although not statistically significant, they found that there was a trend toward a lower long-term rate of disease-free survival in patients with invasive ductal carcinoma.

Over 100 factors have been identified as having prognostic significance in breast cancer, but only a few remain significant when subjected to a multivariate analysis. The most important prognostic factors include: presence and number of positive lymph nodes; tumour size; microscopic grade; and presence of lymphovascular invasion. Other parameters studied such as hormone receptor status and HER2neu have more of a predictive than prognostic value and may reflect possible response to specific forms of therapy.

The extent of axillary lymph node involvement by breast cancer remains the dominant prognostic indicator for later systemic disease.[29] Our study confirmed this finding but it should be mentioned that almost 70% of the cases did not have nodal

affection. Xu et al[30] found that even patients with favourable breast cancer subtypes have a significant rate of axillary nodal metastasis. Axillary nodal staging remains important in such patients; SLN biopsy is an ideal method to obtain this staging information. Reinfuss et al,[23] studied 52 women diagnosed with typical medullary breast carcinoma and concluded the only prognostic factor to be the microscopical axillary lymph nodes status. In the group of pN0 patients, 97.1% survived 10 years, pN+ 58.8% only. The sole causes of unsuccessful treatment were distant metastases to lungs, liver and bones. Typical medullary carcinoma is a favourable histological type of breast carcinoma with very good prognosis for pN0 patients.

Tumour size is still considered the second factor to predict outcome from disease.[31] This study also confirms this fact with significances proving disease free survival decreases with increase of tumour size ($p = 0.0283$). It is known that histological grading has clear prognostic significance in a tertiary role [32]; however, we could not signify this in our study. We can, however, observe that most cases were found to have poor differentiation. Patient age is considered to be an independent prognostic factor and very young women diagnosed with breast cancer do have a poorer prognosis. [33] The median age for the study's population was found to be 42 years which coincides with expected age incidence for medullary carcinoma. It is appropriate to state that histological subtyping has not been documented as an independent prognostic factor.

Estrogen and progesterone receptor status were found to be mainly negative as well as HER2neu status. These factors are generally considered to be predictive factors. Yakirevich et al [8] compared medullary, atypical medullary and high grade invasive ductal carcinomas as regards the different markers. They found that none of the medullary cases showed HER2neu amplification or overexpression. Immunostaining for ER/PR was rarely positive in either medullary or atypical medullary groups, and there were no significant differences of expression of ER/PR between these 2 lesions ($P > .05$). However, the expression rate of ER/PR (31%/44%) in high grade invasive ductal carcinoma was higher than in both medullary ($P = .05$) and atypical medullary ($P = .01$) carcinomas. These differences were found to possibly account for the different clinical and biological behaviours, and may potentially aid in diagnosis and management of these groups of patients.

One study concluded that medullary breast cancer patients benefited from the use of adjuvant chemotherapy, however due to limited patient numbers, no comment was given for the use of adjuvant hormones. They found that tumours less than 1cm were most favourable as were those without nodal metastases. They found that patients with positive nodes and tumour size greater than 1 cm had prognosis similar to that ascribed to invasive ductal carcinoma numbers and may benefit from systemic regimens. [34]

Conclusion

We conclude that there is no favourable prognosis of medullary carcinoma when compared with other histologic subtypes of breast cancer, mostly invasive ductal carcinoma. Therefore it should not be considered as a prognostic factor. Prognosis was found to be more related to stage. It is essential to state that the majority of the cases were found to have negative estrogen and progesterone receptor status as well as node negative disease. However, larger data sets should be examined to further clarify therapy recommendations.

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