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MEDULLARY CARCINOMA BREAST A CLINICOPATHOLOGIC CORRELATIVE STUDY

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ABSTRACT

Medullary carcinoma of breast is an uncommon distinct type of ductal carcinoma with unique morphological, immunohistochemical and prognostic features. An intriguing feature of this subtype is the relatively better prognosis compared to invasive ductal carcinoma, despite the high-grade histological appearance. This necessitates the precise recognition of this entity. A review of the 411 breast carcinoma cases reported in the Department of Pathology, Sri Ramachandra Medical College & Research Institute from 2008 to 2013, revealed 10 cases to be medullary carcinoma. The morphological, immunohistochemical findings, clinical features, treatment history and prognosis were procured and analyzed. The most common age group noted in our series of medullary carcinoma was the 7th decade with a mean age of 53 years. The most common location was upper and inner quadrant, as against upper and outer quadrant in IDC NOS. The mean tumor size was 3.25cm in greatest diameter. Seventy percent of medullary carcinomas presented in pT2 N0 cM0. In our study all the cases were of triple negative molecular subtype. Follow up data was available in 50% of the cases. None of them showed recurrence or metastasis.

INTRODUCATION

Medullary carcinoma of breast is an uncommon distinct type of ductal carcinoma. It derives it's name from medulla, that is Latin for marrow, owing to the similar gross appearance. It represents about 5% of all breast carcinomas. An intriguing feature of this subtype is the relatively better prognosis compared to invasive ductal carcinoma, despite the high grade histological appearance (Emad A Rakha *et al*., ? and Huober *et al*., 1977). Owing to these contradicting qualities these carcinomas appear to present a biological paradox. In our study we compared the clinicopathological profile of medullary carcinoma with the most commonly encountered invasive ductal carcinoma, not otherwise specified (NOS).

MATERIALS AND METHODS

All breast carcinoma cases reported in the department of pathology, SRMC&RI from 2008-2013 were reviewed. The haematoxylin and eosin stained slides along with the ER, PR, Her2/neu immunostained slides were retrieved from the archives and reviewed to confirm the diagnosis.

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The clinical data for these cases was collected from the medical records. Several simplified criteria of medullary phenotype have been proposed in order to increase reproducibility. The Ridolfi criteria (Ridolfi *et al*., 1977) remains the most generally accepted. We followed this histologic criterion that included, syncytial architecture of the tumor cells, pushing margins, absence of glandular/tubular structures, a diffuse lymphoplasmacytic infiltrate, tumor cells with a vesicular nuclei and a prominent nucleoli. The treatment history was procured for all these cases. This data was compared with invasive ductal carcinoma NOS and analyzed.

RESULTS

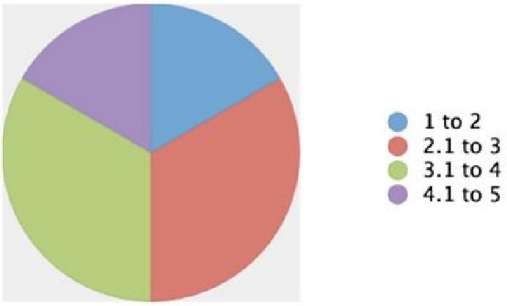
Of the 411 cases of breast carcinoma reported, 10 were medullary carcinomas. Five of these patients presented in the seventh decade. Five of the ten tumors were seen in the upper inner quadrant of the breast, which was the most common location in our study. Size of the tumors ranged from 1.5cm to 4.5cm (in greatest dimension) with a mean size of 3.25cm. Except for a single case that presented at stage one (according to pathologic TNM staging), all other cases presented as stage 2. Only one of these showed nodal metastasis. None of our cases showed distant metastasis. Apart from the above analysis, molecular sub typing of all the cases showed a triple

negative/ basal phenotype. Out of the 10 medullary carcinoma cases, follow up data was available for 5 cases. These patients received varying cycles of chemo and radiotherapy post mastectomy**.** Three patients after two years and two patients at the end of one year of surgery and chemotherapy showed no metastasis or recurrence.

Table 1.

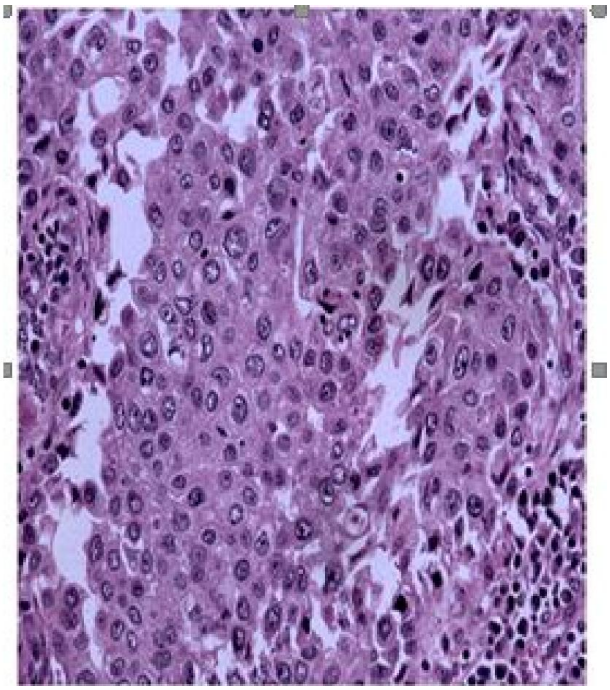
S.N0	AGE	SIZE(cm)	LOCATION	pTNM
1	68	3.5	LOQ	pT2NOcM0
2	47	2.5	LQ	pT2NOcM0
3	32	4.5	OQ	pT2NOcM0
4	62	1.5	UIQ	pT1cNOcM0
5	65	4	LOQ	pT2NOcM0
6	60	4	UIQ	pT2NOcM0
7	39	4.5	CENTRAL	ypT2N1acMx
8	69	3.5	UOQ	pT2NOcMx
9	42	2.5	UIQ	pT2NOcM0
10	45	2	-	-

Medullary carcinoma cases reported from 2008 to 2013



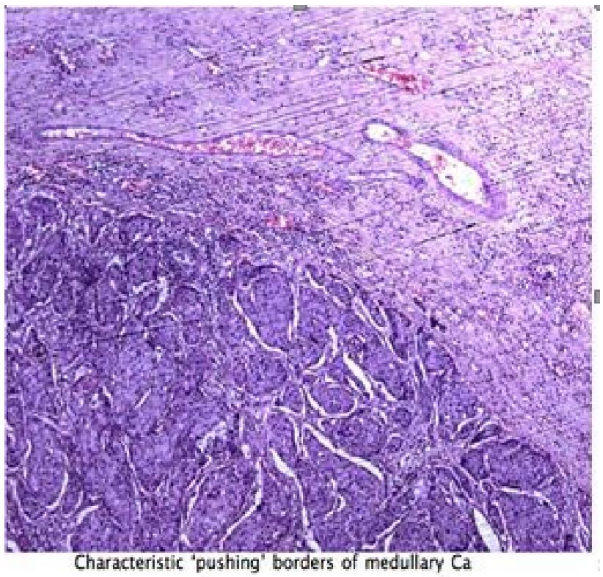
Size wise distribution of all medullary carcinoma cases (cms)

Figure 1.



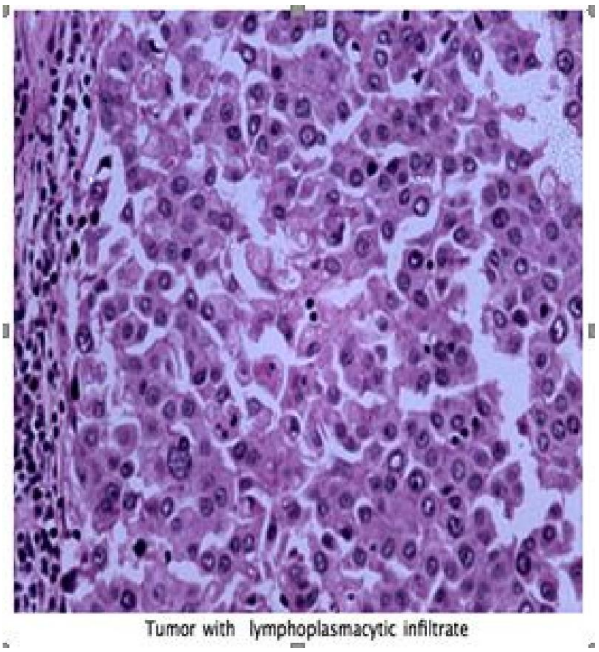
tumor cells with a prominent nucleoli

Figure 2.



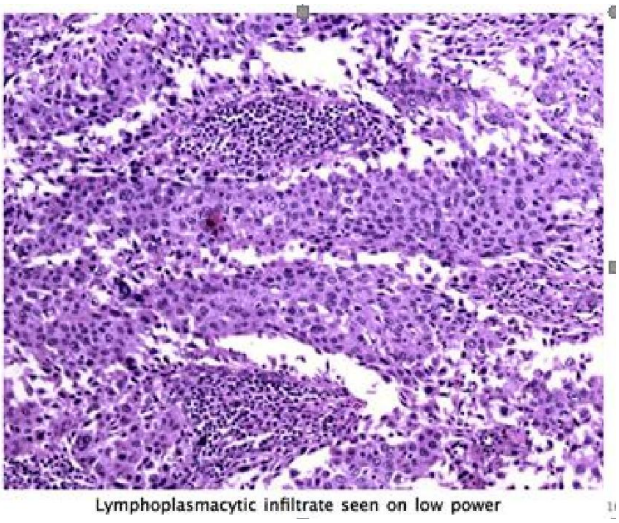
Characteristic 'pushing' borders of medullary Ca

Figure 3.



Tumor with lymphoplasmacytic infiltrate

Figure 4.



Lymphoplasmacytic infiltrate seen on low power

Figure 5.

DISCUSSION

Medullary carcinoma is a rare variant of breast carcinoma with a reported incidence of 1-7% (Rapin *et al*., 1988). Out of the 411 cases of breast carcinomas received, the number of medullary carcinomas was 10 amounting to 2.5% of all cases. This is in concurrence with reports in the literature (Rapin *et al*., 1988). Pederson *et al*. (1995) and Rapin *et al*. (1988) in their study reported the mean age of women with medullary carcinomas ranging from 45-52 years. In our series age range for medullary carcinoma was 32-69 years with a mean age of 53 years. Anatomic distribution of medullary carcinomas is not reported to differ significantly from other invasive carcinomas. However five of the ten tumors were seen in the upper inner quadrant of the breast in our study, whereas IDC NOS occurs most commonly in the upper outer quadrant (Haagensen, 1986). Ridolfi *et al*. (1977) found median diameter of medullary carcinomas to vary from 2-2.9 cm. In our study tumors ranged from 1.5 to 4.5 cm in greatest dimension with a mean size of 3.25 cm, which was larger than reports in previous studies.

In our study 90% of the cases presented at stage 2 (according to pathologic TNM grading) and 10% at stage 1. This was in concurrence with the previous literature (Ridolfi *et al*., 1977). None of the cases showed nodal metastasis except for one case in our series. This was in concurrence with the study by Jensen *et al*. (?) and Rapin *et al*. (1988) in which they found less than 10% of medullary carcinomas present with nodal metastasis. Francis Bertuci *et al*. (2006) using wide genome oligonucleotide microarrays found that invasive ductal carcinomas may present as various molecular subtypes (luminal A, luminal B, her2neu and basal) whereas 95% of medullary carcnomas show a basal phenotype. Katrina Bauer *et al*. (?) and Vinayaka *et al*. (2011) found 12.5% and 19.9% of their IDC NOS cases to be of triple negative subtype respectively. In comparison to IDC NOS the percentage of triple negative molecular subtype in medullary carcinomas was significantly higher. All of the cases in our series belonged to the triple negative category.

In our study follow up data was available for 5 cases. None of these patients presented with recurrence or metastasis. Marginear *et al*. (?) and Huober *et al*. (1977) found medullary carcinomas to have a fairly good prognosis despite their lack of expression of ER, PR, Her2neu (triple negative status). In comparison patients of IDC NOS showed a 35-50% survival rate after 10 years (Ellis *et al*., 1992). Medullary carcinoma is more common in Japanese women (Eisinger *et al*., 1977; Ellis *et al*., 1993 and Marcus *et al*., 1996) and tends to occur only in one breast. But approximately 3-18% patients may develop bilateral tumours and rarely these maybe metachronous (Maier *et al*., 1977 and Wargotz and Silverberg, 1988). At Memorial hospital in New York city these tumors were termed bulky adenocarcinomas until the name medullary was proposed in the 1940s (Foote and Stewart, 1946 and Moore and Foote, 1949). Mammographically all these lesions are typically well circumscribed and appear firm in consistency and may be confused with a benign lesion such as a fibroadenoma (Markovitz *et al*., ? and Meyer *et al*., 1989). Cut surface has a distinct margin which outlines the tumor and distinguishes it from the surrounding breast tissue. Despite this deceptively benign appearance these tumors are malignant in their behavior. The role of a pathologist is indispensable in making an accurate diagnosis. Histological examination of this subtype of breast carcinoma cases have showed that most of these have a syncytial growth pattern, high histologic grade with a high mitotic count, and a prominent lymphocytic infiltrate (Cook and Weaver, 1995 and Horsfall *et al*., 1986). The histologic criteria has been modified over the years to decrease interobserver variability. The initial criteria introduced by Foot and Stewart (1946) and later by Moore and Foot (1949) were further altered by Ridolfi *et al*. (1977). The presence of an abundant lymphoplasmacytic infiltrate in medullary carcinoma is similar to lymphoepithelial carcinoma arising at other sites. This along with other features has suggested that Epstein Barr virus might play a role in the pathogenesis of this entity, however there is no reported study showing evidence of EBV (Lespagnard *et al*., 1995). Apart from these histologic similarities, clinical features also showed similarities in our study. These were presentation as stage 2, an average size of 3.25cm, most common location in the upper inner quadrant and presentation more commonly in the 60-70 year age group. Tumors not showing the typical histological features but only 2 or 3 of the other usual criteria are referred to as atypical medullary carcinoma which exhibit a poorer prognosis compared to the usual medullary carcinomas (Ridolfi *et al*., 1977). Our cases were also triple negative, as reported in the literature.

A high frequency of medullary carcinomas have been reported in patients with BRCA1 germ line mutation[1,2,3] An association with an alteration in the TP53 gene has also been noticed. Although no specific type of TP53 mutation was found to be characteristic of medullary carcinomas, over staining maybe interpreted as a biological marker (doi: 10.1093/jnci/91.7.641). Alterations in theses genes (BRCA1 and TP53) principally involved in DNA repair mechanisms along with a high proliferation rate may be the cause of the high sensitivity of medullary carcinomas to radio/ chemotherapy. Medullary breast carcinomas have been shown to overexpress multiple pluripotent genes (François Bertucci *et al*., 2006) located on the short arms of chromosomes 6 and 12 such as IL27RA, IL15RA and IL12RB1. Few genes encoding transcription factors responsible for differentiation of Th1 subset of T lymphocytes including STAT1 and genes encoding IFN regulation such as IRF1 and IRF7 were seen to be over expressed. Genes associated with apoptosis such as those encoding for TNF receptors were also seen to be up regulated. Genes under expressed include those involved with maintainence of the architecture and cytoskeleton for example, those coding actin (ACTG2, ACTA2), myosin light chain (MYL9) and beta tropomyosin (TPM2).

Conclusion

Medullary carcinomas of breast are unique and histopathology remains the gold standard for identification of these tumors. Molecular work up is essential as most of these belong to the triple negative molecular subtype inspite of their fairly good prognosis.

REFERENCES

Eisinger, F., Jacquemier, J., Guinebretiere, JM., Birnbaum, D. and Sobol, H. 1997. p53 involvement in BRCA1-associated breast cancer. *Lancet*, 350: 1101.

Ellis, IO., Galea, MH., Locker, A., Roebuck, EJ., Elston, CW., Blamey, RW. and Wilson, ARM. 1993. Early experience in breast cancer screening: Emphasis on development of protocols for triple assessment. *Breast,* 2: 148-153.

Marcus, JN., Watson, P., Page, DL., Narod, SA., Lenoir, GM., Tonin, P., Linder-Stephenson, L., Salerno, G., Conway, TA. and Lynch, HT. 1996. Hereditary breast cancer: pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. *Cancer*, 77: 697-709.

Pedersen, L., Zedeler, K., Holck, S., Schiodt, T. and Mouridsen, HT. 1995. Medullary carcinoma of the breast. Prevalence and prognostic importance of classical risk factors in breast cancer. *Eur J Cancer,* 31A:2289-2295.

Rapin, V., Contesso, G., Mouriesse, H., Bertin, F., Lacombe, MJ., Piekarski, JD., Travagli, JP., Gadenne, C. and Friedman, S. 1988. Medullary breast carcinoma. A reevaluation of 95 cases of breast cancer with inflammatory stroma. *Cancer*, 61: 2503-2510

Felicia Marginean, Emad A Rakha, Bernard C Ho, Ian O Ellis and Andrew HS Lee, Histological features of medullary carcinoma and prognosis in triple-negative basal-like carcinomas of the breast, Department of Histopathology, Nottingham University Hospitals, Nottingham, UK

Huober, J., S. Gelber, A. Goldhirsch, A. S. Coates, G. Viale, C. Öhlschlege,, K. N. Price, R. D. Gelber, M. M. Regan and B. Thürliman, Prognosis of medullary breast cancer: analysis of 13 International Breast Cancer Study Group (IBCSG) trials.

Ridolfi, RL., Rosen, PP., Port, A., Kinne, D. and Mike, V. 1977. Medullary carcinoma of the breast: a clinicopathologic study with 10 year follow-up. *Cancer*, 40: 1365-1385

Dixon, JM. and Sainsbury, JRC. 1998. Handbook of Diseases of the Breast. 2nded. Churchill Livingstone: Edinburgh

Haagensen, CD. 1986. Diseases of the Breast. 3rd ed. WB Saunders: Philadelphia

Cook, DL. and Weaver, DL. 1995. Comparison of DNA content, S-phase fraction, and survival between medullary and ductal carcinoma of the breast. *Am J Clin Pathol,* 104: 17-22.

Horsfall, DJ., Tilley, WD., Orell, SR., Marshall, VR. and Cant, EL. 1986. Relationship between ploidy and steroid hormone receptors in primary invasive breast cancer. *Br J Cancer*, 53: 23-28.

Foote FW Jr and Stewart FW. 1946. A histologic classification of carcinoma of the breast. *Surgery*.

Moore OS Jr and Foote FW Jr. 1949. The relatively favorable prognosis of medullary carcinoma of the breast. *Cancer*.

Markovitz, P., Contesso, G., Sarrazin, D. *et al*. ?. Le carcinome medullaire du sein. tude clinique et anatomo-radiologique propos de 56 observations.

Meyer, JE., Amin, E., Lindfors, KK. *et al*. 1989. Medullary carcinoma of the breast: Mammographic and US appearance. *Radiology*.

Maier, WP., Rosemond, GP., Goldman, LI. *et al*. 1977. A 10-year study of medullary carcinoma of the breast. *Surg Gynecol Obstet*;

Wargotz, ES. and Silverberg, SG. 1988. Medullary carcinoma of the breast. A clinicopathologic study with appraisal of current diagnostic criteria. *Hum Pathol*.

Lespagnard, L., Cochaux, P., Larsimont, D. *et al*. 1995. Absence of Epstein-Barr virus in medullary carcinoma of the breast as demonstrated by immunophenotyping, in situ hybridization and polymerase chain reaction. *Am J Clin Pathol*.

Jensen, ML., Kiaer, H., Andersen, J., Jensen, V. and Melsen, F. ?. Prognostic comparison of three classifications for medullary carcinomas of the breast.

Ellis, IO., Galea, M., Broughton, N., Locker, A., Blamey, RW. and Elston, CW. 1992. Pathological prognostic factors in breast cancer. II. Histological type. Relationship with survival in a large study with long- term follow-up. *Histopathology* 20: 479-489.

Katrina, R., Bauer, MS. CTR, Monica Brown, PhD, Rosemary, D., Cress DrPH, Carol, A., Parise, PhD[4] and Vincent Caggiano, MD. ?. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype[†] A population-based study from the California cancer Registry.

Vinayak W Patil, Rajeev Singhai, Amit V Patil and Prakash D Gurav 2011. Triple-negative (ER, PgR, HER-2/neu) breast cancer in Indian women, Breast Cancer (Dove Med Press); 3: 9–19.

François Bertucci, Pascal Finetti, Nathalie Cervera, Emmanuelle Charafe-Jauffret, Emilie Mamessier, José Adélaïde, Stéphane Debono, Gilles Houvenaeghel, Dominique Maraninchi, Patrice Viens, Colette Charpin, Jocelyne Jacquemier, and Daniel Birnbaum, 2006. Gene Expression Profiling Shows Medullary Breast Cancer Is a Subgroup of Basal Breast Cancers, *Cancer Research*, AACR

p53 Mutation as a Genetic Trait of Typical Medullary Breast Carcinoma JNCI J Natl Cancer Inst (1999) 91 (7): 641-643.doi: 10.1093/jnci/91.7.641

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