

MEDULLARY CARCINOMA OF BREAST: CLINICOPATHOLOGICAL STUDY

Sunil Vitthalrao Jagtap¹, Atul Abhimanyu Beniwal², Heena Pradeep Shah³, Suresh Jaywantrao Bhosale⁴, Pandurang G. Chougule⁵, Swati Sunil Jagtap⁶

¹Professor, Department of Pathology, Krishna Institute of Medical Sciences University, Karad, Maharashtra, India.

²Assistant Lecturer, Department of Pathology, Krishna Institute of Medical Sciences University, Karad, Maharashtra, India.

³Assistant Lecturer, Department of Pathology, Krishna Institute of Medical Sciences University, Karad, Maharashtra, India.

⁴Professor, Department of Surgery, Krishna Institute of Medical Sciences University, Karad, Maharashtra, India.

⁵Professor, Department of Surgery, Krishna Institute of Medical Sciences University, Karad, Maharashtra, India.

⁶Associate Professor, Department of Physiology, Krishna Institute of Medical Sciences University, Karad, Maharashtra, India.

ABSTRACT

AIM AND OBJECTIVES

To study the clinical and histopathological features of medullary breast carcinoma (MBC) in rural population in Western Maharashtra.

MATERIALS AND METHODS

This is a retrospective, analytic study which is done at a tertiary care hospital from March 2010 to April 2016 for a period of 6 years.

RESULTS

Total of 241 consecutive cases of breast malignancy surgically operated for mastectomy or modified radical mastectomy were studied. From these 241 cases, 11 were reported as medullary carcinoma (constitute 4.56%). From these 11 cases, 10 cases were of typical medullary breast while 1 case was of atypical medullary breast carcinoma was noted. Each case was studied for clinical, morphological, radiological and immunohistochemistry (IHC) findings. For typical medullary carcinoma, the age range in present study was 33 to 55 years with a mean age of 46.3 years. The common clinical presentation was painless lump in the breast with common location being upper outer quadrant. The size of the tumour ranged from 2.5 to 9 cm with a mean size of 5.6 cm. The axillary lymph nodes were involved in 4 (40%) cases. The ER, PR and HER-2 were found to be positive in 10%, 10% and 20% respectively. Triple negative cases were 70%.

CONCLUSION

The clinicopathological features of medullary breast carcinoma showed early disease stage, having high-grade histological features of tumour, more triple negativity for ER/PR/HER2 and low rate of nodal metastasis.

KEYWORDS

Breast Cancer, Histopathological Features, Medullary Subtype.

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INTRODUCTION: Moore and Foote (in 1949) described their experience with a well-circumscribed form of breast carcinoma with lymphoid stroma which was called as medullary carcinoma and was recognised to have favourable prognosis.¹ The histological definition of medullary carcinoma has varied with time (WHO 1968, WHO 1982). The histological diagnostic criteria for typical medullary carcinoma and atypical medullary carcinoma of the breast were proposed by Fisher et al (1975)² and Ridolfi et al (1977).³ Later on two significant studies by Rapin et al (1988)⁴ and by Wargotz and Silverberg (1988)⁵ showed the excellent prognosis of typical medullary carcinoma.

Medullary breast carcinoma is a rare distinct type of the invasive breast carcinoma. This subtype has relatively better prognosis as compared to invasive breast carcinoma no special type. So it is important to recognise this specific entity. The better prognosis is probably related to good immune host response. The reported incidence of medullary carcinoma is < 5%.^{6,7,8} The typical medullary breast carcinoma requires five criteria for diagnosis, these are: predominantly (>75%) syncytial growth pattern of tumour, moderate to marked diffuse mononuclear stromal infiltrate, absence of microglandular features and intraductal component, grade II-III nuclear pleomorphism and microscopically completely circumscribed tumour growth.^{3,5,9} In the present study, we found both typical and atypical type of medullary breast carcinoma.

MATERIALS AND METHODS: Study design: This is a retrospective, analytical study carried out at a tertiary care hospital from March 2010 to April 2016.

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Corresponding Author:

Dr. Sunil V. Jagtap,
Department of Pathology,
Krishna Institute of Medical Sciences, Karad.

E-mail: drsvjagtap@gmail.com

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The clinical data for these cases were collected from the medical records of hospital. The haematoxylin and eosin slides of the modified radical mastectomy specimens were retrieved from the archives and reviewed by the pathologist to confirm the diagnosis. Also immunohistochemical slides of ER, PR, HER2 were reviewed. The Ridolfi RL et al³ criteria for histopathologic diagnosis of medullary carcinoma was used.

Cases were divided into 2 categories, typical medullary carcinoma and atypical medullary carcinoma. All these two categories were analysed according to clinicopathological features separately.

The detail of analysis included: patient's age, sex, clinical history, side, site of tumour in breast, duration of lump, size of tumour, gross and microscopic features, secondary changes, axillary nodal status, radiological features and immunohistochemical study. Sonomammography of the breast and fine needle aspiration cytology were done and findings were evaluated.

RESULTS: During study period from March 2010 to April 2016, total of 241 malignant breast specimens were received in the Department of Pathology. Out of 241 cases, 10 cases were diagnosed to have typical medullary carcinoma breast, 1 was diagnosed with atypical medullary carcinoma.

All patients in present study group were female. The median age was 46.3 years with minimum age of 33 years and maximum age of 55 years. All patients presented with history of lump in the breast. Average duration of symptom was of 5.4 months. All patients had single lump and on one side of breast. No multifocal or bilateral lumps were noted in present study. None of the patients were pregnant or lactating or were on hormonal therapy during the time of diagnosis. None had family history of breast cancer. The detailed clinicopathological features of typical medullary carcinoma, and atypical medullary carcinoma are summarised in table-1 and 2 respectively.



Fig. 1: MRM specimen showing, round, circumscribed grey-white tumor with pushing borders on cut section.

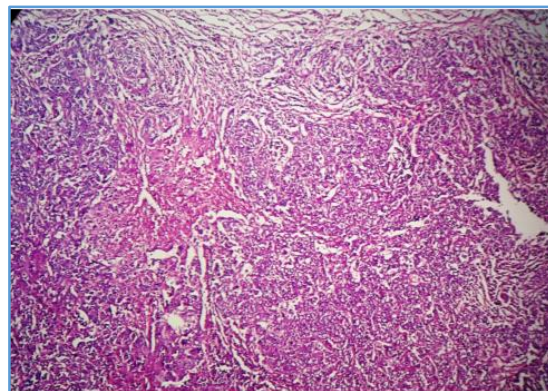


Fig. 2: Photomicrograph showing large syncytial growth pattern with circumscribed borders (H and E 100x)

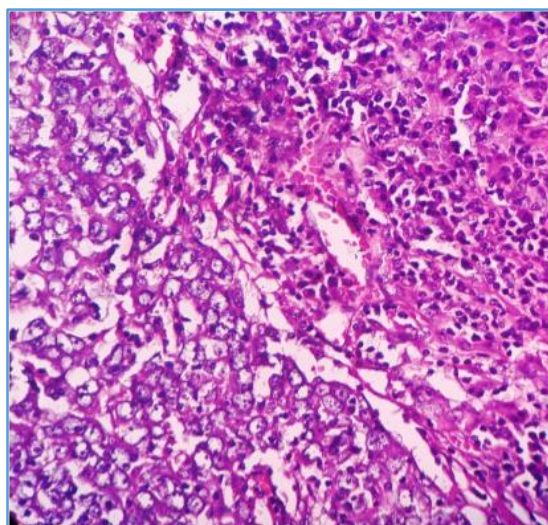


Fig. 3: Photomicrograph showing typical medullary carcinoma breast with high grade nuclear features and rim of heavy lymphoplasmacytic infiltration (H and E, 400x)

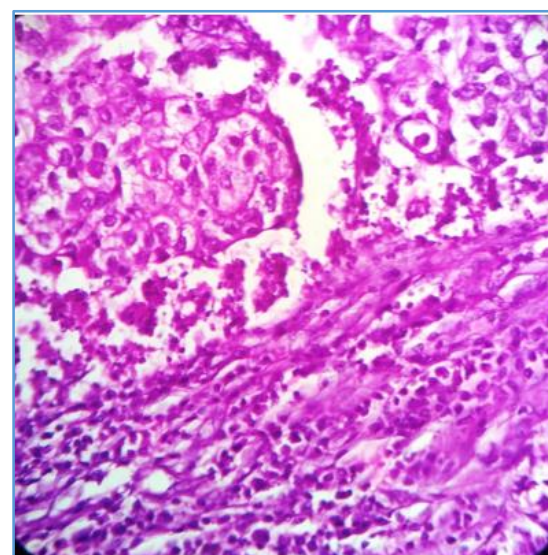


Fig. 4: Photomicrograph showing high power view of typical medullary carcinoma breast having high grade nuclear features and rim of heavy lymphoplasmacytic infiltration. (H and E stain)

Case Number	1	2	3	4	5	6	7	8	9	10
Age (years)	50	45	35	45	55	50	55	50	33	45
Breast Side	R	R	L	R	L	R	R	R	L	L
Location	UOQ	UOQ	UOQ	UIQ	UOQ	UOQ	Central	UOQ	UOQ	UOQ
Lump Duration (months)	1	6	3	3	6	18	4	6	3	4
Consistency	Firm	Soft-firm	Firm	Soft-firm	Firm	Firm	Firm	Soft-firm	Soft	Soft-firm
Tumour Fixed/mobile	Mobile	Mobile	Mobile	Mobile	Mobile	Mobile	Mobile	Mobile	Mobile	Mobile
Tumour border	Pushing	Pushing	Circumscribed	Pushing	Pushing	Pushing	Pushing	Pushing	Pushing	Pushing
Nipple/areola	N	N	N	N	N	N	Black	N	N	N
Skin changes	No	No	No	No	No	No	Black	No	No	No
Tumour size (cm)	5x3.5x2.5	4.1x3x2	2.5x1x0.8	7x4.5x3.5	9x6x4	7.5x7x3.5	5.8x3x2.5	7.5x7x5	4x3x1	4x3.5x2
Tumour emboli	No	Yes	No	Yes	Yes	No	No	Yes	No	Yes
Tumour necrosis	No	Yes	No	Yes	Yes	No	No	Yes	No	Yes
Axillary LN status (invo/total)	0/8	7/10	0/13	0/13	8/10	0/16	0/12	4/16	0/10	5/12
ER/PR/HER2	-/-/+	-/-/-	-/-/-	-/-/+	-/-/-	+/+/-	-/-/-	-/-/-	-/-/-	-/-/-

Table 1: Showing Clinical, Gross and Microscopic Features of Typical Medullary Carcinoma of Breast

R=right, L=left, UOQ=upper outer quadrant, UIQ=upper inner quadrant, N=Normal, LN=Lymph node, invo/total=involved lymph node/total lymph node.

Case number	1
Age (years)	55
Breast Side	Right
Location	Upper outer quadrant
Lump Duration (months)	2
Consistency	Soft-firm
Tumour Fixed/mobile	Mobile
Tumour border	Pushing
Nipple/areola	Normal
Skin changes	Induration/redness
Tumour size (cm)	5x4.5x4
Tumour emboli	No
Tumour necrosis	No
Axillary LN status (invo/total)	0/8
ER/PR/HER2	-/-/-

Table 2: Showing Clinical, Gross and Microscopic Features of Atypical Medullary Carcinoma of Breast

All cases undergone modified radical mastectomy, the median tumour size was 5.6 cm, ranging from 2.5 to 9 cm. On microscopic examination, tumours were arranged in large sheets, syncytial growth pattern. Individual neoplastic cells were large, round, having highly pleomorphic,

hyperchromatic or vesicular nuclei and 2-3 prominent nucleoli (Fig. 2, 3, 4) and moderate to ample amount of eosinophilic cytoplasm. Increased mitotic activity and bizarre cells were noted. Areas of haemorrhage and necrosis were seen. The tumour sheets and scant intervening stroma

showed prominent lymphocytic infiltration. Also at periphery of tumour rich lymphoplasmacytic infiltration was noted. Microscopically, all the cases showed complete circumscribed limited tumour growth. Axillary lymph node metastasis was confirmed in 4 (40%) cases. On immunohistochemistry, 70% cases were triple negative for ER/PR and HER2.

DISCUSSION: Invasive breast carcinoma is the most common histologic type comprising 72–80 % of all invasive breast cancers.¹⁰ Medullary breast carcinoma is a rare histological type of breast cancer having unique morphological, immunohistochemical and prognostic features. Present study revealed 10 cases of typical medullary breast carcinoma out of total 241 breast malignancies detected on histopathology on mastectomy/modified radical mastectomy specimens. The purpose of present study is to compare clinicopathological profile of medullary carcinoma with commonly encountered invasive breast carcinoma-NST.

Clinically, the patients of medullary carcinoma usually present at a relatively younger age than the patients with other breast carcinomas.^{11,12} The study Vu-Nishino H et al showed higher proportion patients in the typical medullary breast carcinoma group were younger than 35 years¹³. The average age of presentation of medullary breast carcinoma reported is between 47-52 years.³ In present study, the mean age was 46.3 years. Rarely medullary breast carcinoma is reported in males. The mean size of tumour was 5.6 cm in our study. Clinically, majority of patients with medullary breast carcinoma present with palpable lump, larger lump size and usually in the upper outer quadrant and usually do not show multicentricity. Some patients were interestingly presented with axillary lymphadenopathy which may be related to metastatic disease phase. On sonomammography, medullary breast carcinoma are generally well circumscribed, hypoechoic, frequently lobulated and show no evidence of calcification.

Though radiological features for medullary breast carcinoma are described, histopathological diagnosis plays important role for confirmatory diagnosis. On gross examination, lesions are rounded, well-circumscribed, soft, tan brown to grey. Tumour may bulge above the cut surface of the specimen, appears fleshy or brain like. In present study, cases showed round circumscribed soft to firm tumour with pushing margins (Fig. 1).

For the histological diagnosis of medullary carcinomas, three distinct classification systems are proposed with strict criteria by Ridolfi et al³ Wargotz and Silverberg⁵ and Pedersen et al.⁹ In spite of rigid histological criteria, the diagnosis of medullary breast carcinoma is difficult and controversial among pathologists.

In addition to these histological criteria, medullary breast carcinoma may be associated with ductal carcinoma in-situ component. Other changes like haemorrhage, cystic degeneration, metaplastic change, tumour necrosis, etc., are noted. Many of our cases also showed these secondary changes. The histological grading of Bloom-Scarff-

Richardson does not apply to medullary breast carcinomas, as by definition these are high grade tumours.

In present study, 4 cases (40%) showed nodal metastasis. This was in concordance with study done by Rapin et al.⁴ in which they found less than 10% of nodal metastasis. Most studies indicate that the axillary nodal metastasis incidence is lower in medullary carcinomas as compared to invasive breast carcinoma-NST which is 19-46% and 29-56% respectively.^{11,12} Comparatively more nodal metastases in present study may be related to delayed presentation of patient due to low socio-economic status, and therefore seek treatment at a later stage. Atypical medullary breast carcinoma differs from typical MBC in terms of pathologic features with an infiltrative margin, mild mononuclear infiltration, a low nuclear grade, and presence of an intraductal component.¹¹ Present study has one case of atypical medullary carcinoma.

The differential diagnoses for medullary breast carcinoma are large cell lymphoma and high-grade invasive breast carcinoma; however, if strict histological criteria are applied then these differential diagnoses can be excluded.

Despite the presence of poor prognostic factors such as large tumour size, high nuclear grade, hormone receptor negativity, the medullary breast carcinomas are associated with favourable prognosis as noted in many previous studies.^{13,14,15} The study by Wargotz ES et al⁵ observed that medullary breast carcinoma, atypical medullary breast carcinoma, and invasive breast carcinoma (NST) had 5-year survival rates were 95%, 80%, and 70% respectively. These findings confirmed those of other investigators that when specific criteria are applied, medullary carcinoma proves to be a form of mammary carcinoma with a favourable prognosis. The prognosis of medullary carcinoma, whether typical or atypical, is better than that of high grade infiltrating breast carcinoma.¹⁶ It has been proposed that extensive presence of plasma cells and lymphocytes helps to keep the medullary carcinoma in check, preventing it from growing and spreading quickly.¹⁷ The overall 10-year survival rate is 74% and more than 90% in patients with negative lymph nodes.⁶ It is interesting to note that atypical medullary carcinoma has better prognosis as compared to the one with atypical features. Hence, strict adherence to diagnostic criteria is critical to provide a more accurate prognosis.

The treatment modality for medullary carcinoma, whether typical or atypical, is similar to invasive breast carcinoma.¹⁸ In present study, patients were treated with surgical resection (MRM) and chemotherapy. Patients were kept on regular follow-up and were doing well.

Overall, medullary breast carcinoma is treated by local therapy which includes surgical resection (mastectomy, modified radical mastectomy). However, few cases require additional chemotherapy and/or radiotherapy depending on HER2 status, lymph node status and evidence of local recurrence.

CONCLUSION: Medullary breast carcinoma is a rare breast cancer subtype associated with unique clinicopathological features. In present study, patient with typical medullary breast carcinoma presented in early disease stage, having high grade histological features of tumour, more triple negativity for ER/PR/HER2 and low lymph nodal metastasis.

For diagnosis of medullary breast carcinoma, the histological criteria are very strict and utmost care should be taken on histopathology. If medullary like features are seen it should be mentioned in the report. As treatment modality is different, the histopathology plays an important role in the diagnosis of such rare subtypes.

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