

Clinicopathological Study of Medullary Breast Carcinoma: An Institutional Study

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ABSTRACT

Background: Medullary breast carcinoma (MBC) is a rare distinct type of invasive breast carcinoma with incidence being less than 5%. It usually occurs under the age of 50 years, often mistaken clinically for fibroadenoma. They are divided into typical, and atypical MBC with a prerequisite of syncytial growth pattern in more than 75% of the tumor cells. MBCs are often hormone (ER, PR, Her2/neu) negative with grade 3 Nottingham's criteria but have better prognosis.

Methods: Retrospective study of invasive carcinoma of the breast was undertaken in Pathology department from 2009-2016. Total numbers of invasive breast carcinomas were 388, of which MBC were 12 cases histologically. Clinical details and gross features were noted. Histopathology and Immunohistochemistry (ER, PR, Her2/neu) slides were reviewed.

Result: Age range was 35 to 64 years, with (mean 49.08). All presented clinically as solitary lump in breast. No side predilection. Most common site affected was upper inner quadrant constituting around 50% (6 out of 12) of cases. Overall tumour size ranged from 2.5 to 6 cms with a mean of 3.6 cms in typical and 4.25 cms in atypical MBC. Grossly majority of the tumors were soft to firm in consistency. Histologically 10 out of 12 cases (83.3%) were typical MBC and 2 cases were atypical MBC (16.7%). IHC showed triple negativity in 75% of MBC with majority in typical MBC (80 %)

Conclusion: MBC is unique type of breast carcinoma with good prognosis. Histopathology plays important role in diagnosing variants of MBC since the treatment differs.

Keywords: Medullary, Breast Carcinoma, Typical, Atypical, Histopathology, Immunohistochemistry

Introduction

Medullary breast carcinoma (MBC) is a rare, distinct type of invasive breast carcinoma¹ with incidence of less than 5% of invasive breast carcinoma.^{1,2} It usually occurs under age of 50 years, often mistaken clinically for fibroadenoma.³ MBC are divided into typical and atypical medullary carcinomas, with a prerequisite of syncytial growth pattern in >75% of the tumor cells in both. Syncytial growth pattern is characterized by tumor cells arranged in sheets, usually more than four or five cells thick, separated by small amounts of loose connective tissue.⁴ Typical MBC is characterised by a constellation of five histological features, as defined first by Ridolfi et al in 1977.² These carcinomas are often hormone (ER, PR, Her2/neu) negative with grade 3 Nottingham's criteria, basal phenotype; but have a better prognosis.² Strong association of marked inflammation with better prognosis is seen in triple negative carcinomas.⁵ Presence of lymphocytes and plasma cells keeps check on MBC and prevents its growth and spread.¹ Overall five year survival rate is 95% in typical, 80% in atypical medullary carcinoma and 70% in invasive breast carcinoma⁶.

With this background, the current study was undertaken to evaluate the prevalence of MBC and to study the clinicopathological and immunohistochemical profile in typical and atypical MBC.

Materials and Methods

Retrospective study of invasive carcinoma of the breast was undertaken in the department of Pathology from 2009-2016. Total number of invasive breast carcinomas were 388, of which 12 cases were MBC on histomorphology. All the 12 cases of MBCs were taken up for the study. The clinical data such as age of patient and type of surgery were collected from the medical records. Gross features of specimen and appearance on cut surface were noted. Histopathology and IHC (ER, PR, Her2/neu) slides were retrieved. Blocks were collected when slides were not available, subsequently sections were made and histopathology slides evaluated. Primary histologic feature defining both typical and atypical MBC, was presence of more than 75% syncytial tumour growth pattern and lymphoplasmacytic infiltrate in varying proportions.

Histological features characterising typical medullary carcinoma was the constellation of five histological features such as more than 75% syncytial growth pattern, complete lesional circumscription, moderate to marked diffuse lymphoplasmacytic infiltrate, moderate to severe nuclear pleomorphism, and lack of intraductal component and tubular differentiation.⁴

Atypical medullary carcinoma was defined histologically by not more than two of the following four atypical features such as margins with focal or prominent infiltrative pattern, mononuclear infiltrate mild or at the tumor margins only, benign appearing nuclei and presence of microglandular features.⁴

Immunohistochemical stained slides of ER, PR, Her2/neu were reviewed and analysed. Interpretation of ER, PR was done depending on the extent and intensity of nuclear staining as per Allred score. Interpretation of Her2/neu was done based on intensity of membrane staining pattern.

Data was analysed and evaluated using descriptive statistics such as median, range standard deviation.

Result

During the study period a total of 388 cases of invasive breast carcinoma were diagnosed out of which 12 (3.1%) were MBC. Age range was 35-64 years (mean 49.08). All cases clinically presented as solitary lump in breast. There was no side predilection however the most common quadrant affected was upper inner quadrant constituting around 50% (6 of 12) of cases. Modified radical mastectomy

(MRM) was performed in all cases since FNA was reported as carcinoma breast.

Clinical features of typical and atypical medullary carcinomas are summarized in table 1. Overall tumour size ranged from 2.5 to 6 cm (mean 3.70 cm). Average size in typical MBC was 3.6 cms (range 2.5 to 6 cms) and atypical MBC was 4.25 cms (range 3.5-5.0 cms). One of the twelve cases clinically presented with involvement of nipple areola region.

Grossly majority of the tumors were soft to firm in consistency. Fine needle aspiration cytology showed large, pleomorphic, singly scattered and disintegrated tumor cells with dense lymphoplasmacytic infiltrate in the background.

Histologically 10 out of 12 cases (83.3%) were diagnosed as typical MBC and 2 cases were atypical MBC (16.7%). Histological features of typical and atypical MBCs are summarised in **table 2 and 3**. Axillary lymph node dissection was done and lymph nodes were isolated. Overall 40% of typical MBC and 50% of atypical MBC showed metastatic deposits. (Table 2 & 3)

IHC showed triple negativity in 75% cases of MBC comprising of 80 % in typical and 50% in atypical MBC

Discussion

MBC was first described by Moore and Foote in 1949.⁷ These are well circumscribed lesions, often soft, fleshy and tend to bulge above the surrounding parenchyma, hence the term encephaloid.⁸ Medullary carcinoma is

Table1: Clinical and Gross Features of Typical and Atypical medullary Carcinoma

	Age	Type of Surgery	Side Quad	Size (cm)	Nipple/Areola
Case 1 Typical MBC	35	MRM	Right UOQ	3X2.4X2	No
Case 2 Typical MBC	58	MRM	Right UIQ	3X2X2	No
Case-3 Typical MBC	64	MRM	Right central Q	4x3x2	ulceration noted
Case 4 Typical MBC	47	MRM	Left LOQ	3X2.5x2	No
Case 5 Typical MBC	40	MRM	Left LOQ	6x5x3	No
Case 6 Typical MBC	45	MRM	Right UIQ	4x3x3	No
Case 7 Typical MBC	42	MRM	Left UIQ	4X3x2.5	No
Case 8 Typical MBC	45	Biopsy	Left UIQ	3x2x2.6	No
Case 9 Typical MBC	45	MRM	Right UOQ	3.5X2.5X2	No
Case 10 Typical MBC	50	MRM	Right UIQ	2.5X2.1X2	No
Case 11 Atypical MBC	60	MRM	Left UIQ	5X4x3	No
Case 12 Atypical MBC	58	MRM	Left UOQ	3.5X3X3	No

UIQ-Upper inner quadrant, LOQ-Lower outer quadrant, UOQ-Upper outer quadrant, RCQ-Right central quadrant

Table2: Histopathological Features of Typical Medullary Carcinoma

	Case 1	Case 2	Case3	Case4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
>75% Syncytial group	+	+	+	+	+	+	+	+	+	+
Lp infiltrate	marked	marked	Marked	mod	mod	marked	mod	marked	marked	mod
pleomorphism	mod	mod	Marked	mod	marked	marked	marked	marked	marked	mod
IDC features	-	-	-	-	-	-	-	-	-	-
Necrosis % 1-10% >10%	nil	nil	1-10%	nil	nil	nil	nil	nil	nil	nil
Tumor border	wc	wc	wc	Push	push	wc	wc	wc	wc	push
Lymph node	0	1/6	0/16	0	0/7	0/3	1/6	1/4	0/6	2/8
SBR Grade	II	II	III	II	III	III	III	III	III	II
Stage	Ila	Ilb	IIIb	Ila	Ilb	Ila	Ilb	Ilb	Ila	Ilb
ER/PR/HER 2 neu	-/-/-	+/+/-	+/+/+	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-

Table 3 : Histopathological Features of Atypical Medullary Carcinoma

	Case11	Case 12
>75% syncytial group	+	+
Lp infiltrate	mild	mild
pleomorphism	marked	mod
DCIS/IDC	DCIS	DCIS LVI
Necrosis % 1-10% >10%	>10%	nil
Tumor border	infiltr	infiltr
Lymph node	3/8	12/26
SBR Grade	II	II
Stage	Ila	IIIc
ER/PR/HER 2 neu	-/-/-	+/+/-

Lp: Lymphoplasmacytic infiltrate; DCIS/IDC: Ductal carcinoma in situ/ Invasive ductal carcinoma; SBR : Modified scarff bloom richardson grading; mod: moderate; wc: well circumscribed; push: pushing borders; infiltr: infiltrating margins

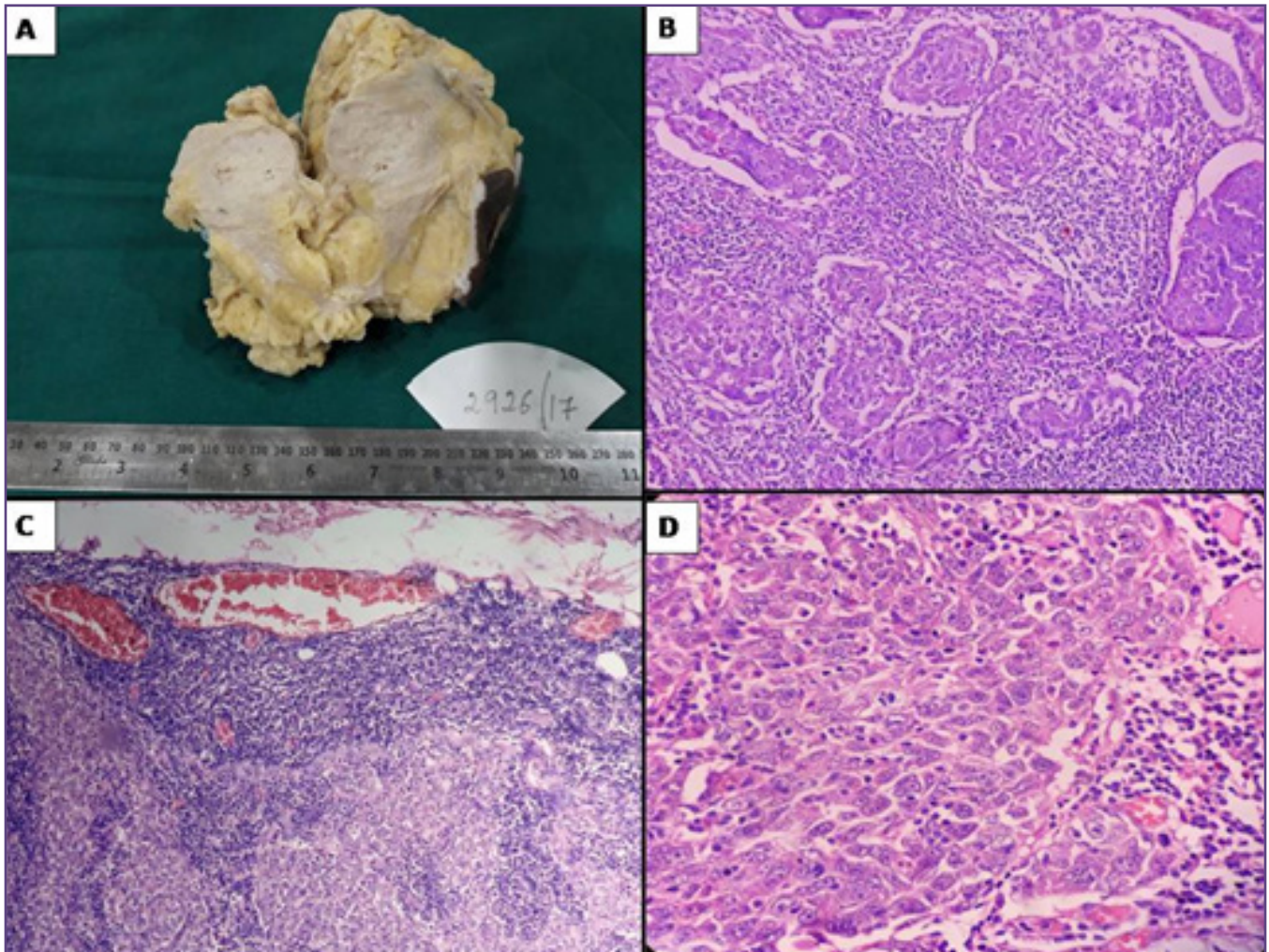


Fig. 1: Typical MBC: A - GROSS showing well circumscribed, nodular fleshy grayish pink lesion; B -Syncytial growth pattern of tumor cells (H&E 10x); C- Circumscribed tumor with moderate to marked lymphoplasmacytic infiltrate(H&E 4x); D -Cells exhibiting high grade nuclear features (H&E 40 x)

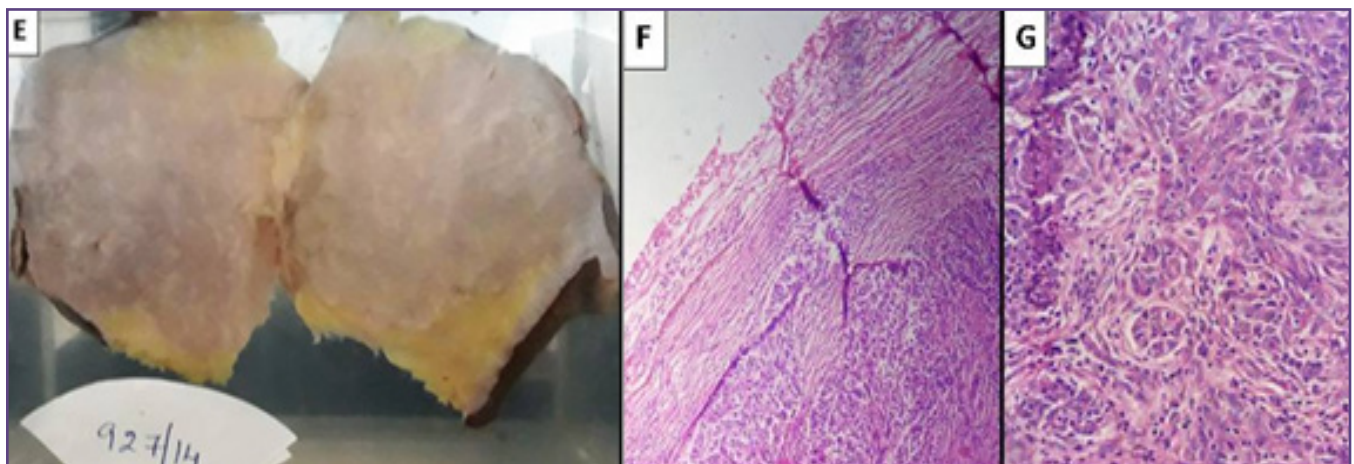


Fig. 2: ATYPICAL MBC: E- Gross showing Large fleshy grey pink with infiltrative margins.; F - Tumor exhibiting infiltrative margins (H&E 10x); G - High power showing glandular pattern (H&E 40x)

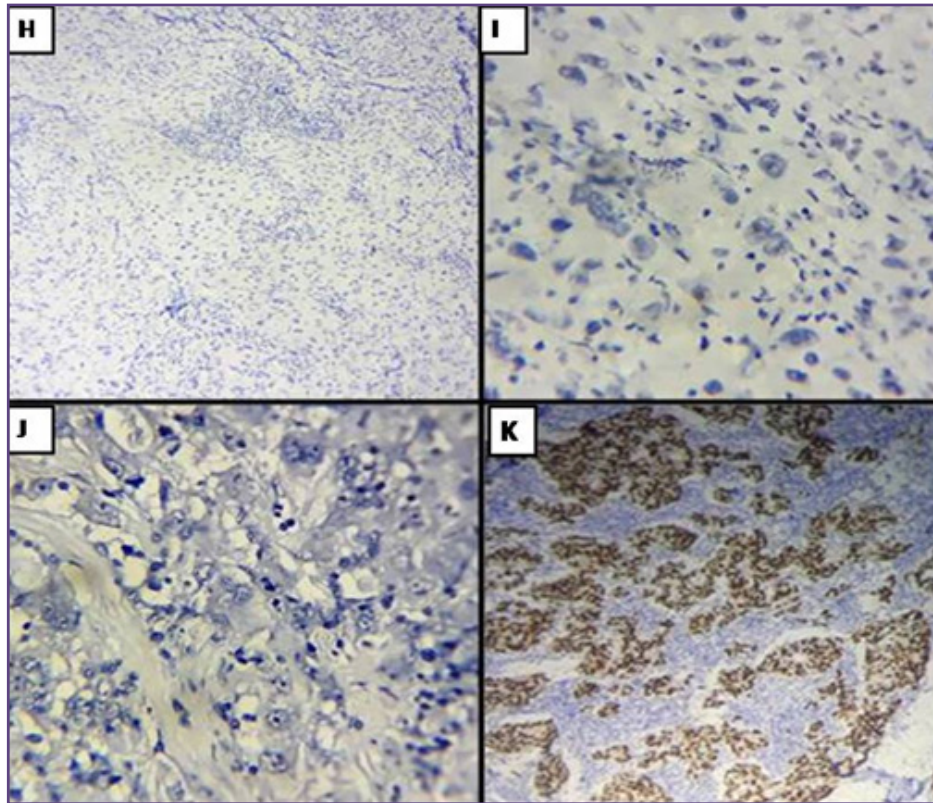


Fig. 3: Immunohistochemistry showing triple negativity (ER, PR, Her2neu negative) in fig H,I,J respectively and fig K showing ER positivity in one of the typical MBC.

an uncommon tumor accounting for less than 5% of all invasive breast carcinomas. Prevalence of MBC in our study was 3.1% which is in concordance with various studies available in literature.^{1,2} Radiologically and clinically MBC mimics fibroadenoma due to its smaller size. Median size of the tumor ranged from 2-3 cms.³ Clinically they present as circumscribed tumor with tendency for cystic degeneration and ulceration of the skin in few. In present study 1 out of 12 cases showed ulceration of the skin involving the nipple areola region. According to the study conducted by Ridolfi et al⁹, age of presentation ranged from 47-52 years. Our study showed similar age range. 60% of typical MBC occurred in age group of 40-49 years, while 50 % of atypical MBC occurred in age group of 50-59 and 60-69 years (Table 1).

Grossly, medullary carcinomas are circumscribed, nodular, fleshy with grey pink appearance on cut surface (Fig 1A). Cystic degeneration, hemorrhage and necrosis are seen. Histologically, MBC is characterized by syncytial growth pattern (Fig 1B), complete circumscription (Fig1C), moderate to marked diffuse lymphoplasmacytic infiltrate (Fig 1C), moderate to severe nuclear pleomorphism (Fig 1D)

and absence of glandular pattern. Presence of microglandular pattern, infiltrative margins, mild mononuclear infiltrate and benign appearing nuclei characterizes atypical MBC⁴. Atypical MBC is synonymously named by some authors as invasive carcinoma with medullary like features.¹⁰

Wargotz et al reported 5 year survival rate of 95%, 80% and 70% in typical MBC, atypical MBC and invasive breast carcinomas respectively. In our study atypical MBC distinctly had IDC like areas with glandular formation of tumour cells and infiltrative tumour margins (Figure 2 F, G). The incidence of atypical MBC was 16.7%, similar to study conducted by Jagtap et al.¹ Histopathological categorization of atypical MBC is necessary since adjuvant chemotherapy is given along with MRM, unlike in typical medullary carcinoma where MRM is the mainstay of treatment¹⁰. The average number of lymph nodes found grossly in axillary dissection specimen from a patient with MBC is greater than for the other types of carcinoma. This difference is due to the greater ease of finding enlarged hyperplastic reactive lymph nodes in MBC.¹¹ Most studies indicate that the incidence of axillary lymph node metastases is lower in patients with medullary carcinomas (19%-

46%) than in those with atypical medullary carcinomas (30%-52%) or invasive ductal carcinomas (29%-65%).¹² In our study, the number of positive metastatic lymph node involvement were more in atypical MBC (50%) compared to typical MBC. Typically MBCs are almost invariably triple hormone receptor negative, although some typical and atypical MBCs are ER, PR and/or HER-2 positive, indicating the heterogeneity of this type of breast carcinomas.¹³ In our study IHC showed triple negativity in 75% cases of MBC (Fig 3) with majority of in typical MBC (80%) similar to study conducted by Jagtap et al¹. Of the two cases of atypical MBC, one case was ER, PR positive, while Her 2/neu negativity was noted in both.

Typical MBC and atypical MBC are similar in presentation, treatment and prognosis.^{14,15} Few cases of atypical MBCs were treated with adjuvant chemotherapy based on Her2 status and lymph node status along with Modified radical mastectomy in studies conducted by Jagtap and Kleer et al.^{1,10}. However the division into typical and atypical MBC has prognostic significance^{1,16}

Conclusion

MBC is a unique type of breast carcinoma with good prognosis. Larger studies are essential to understand the tumour biology in MBC. Atypical MBC have histological features of IDC as well. Histopathology plays an important role in diagnosing variants of MBC since the prognosis varies.

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Financial or other Competing Interests: None.

Date of Submission : 03.08.2017
Date of Acceptance : 27.10.2017
Date of Publication : 28.01.2018