

**Original article:**

## **Rare Breast Cancer Subtypes- Clinical and Immuno-Histopathological Study with Special Reference to Metaplastic and Medullary Carcinoma of the Breast**

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### **Abstract**

**Background:** Breast cancer (BC) heterogeneity is observed at different levels, from the classical histopathological characterization to the more modern molecular classification. Histopathological type is one of the crucial characteristic of a cancer which is associated with varying clinical course and prognosis. We have studied these rare types of BC cases which were reported during a period of five years. Metaplastic breast carcinomas (MpBC) and medullary carcinomas were studied in detail with clinical, histopathological and immunohistochemical (IHC) studies.

**Materials and methods:** This is a retrospective study of 19 cases of rare BC subtypes. Routinely processed histopathological slides were studied. IHC was carried out on a representative section with the following antibodies viz. ER, PR, HER-2, Ki67 in all cases and EGFR and CK5/6 in MpBC and CK5/6 in medullary carcinomas.

**Results:** One case each of tubular carcinoma, pure mucinous carcinoma, invasive cribriform carcinoma, secretory breast carcinoma and apocrine carcinoma were studied. There were 4 medullary carcinomas which were triple negative and 3 cases were CK5/6 immunoreactive suggesting basal like phenotype. 10 cases of MpBC were received. Six cases were of pure epithelial type of which five were mixed infiltrating duct carcinoma (IDC NOS) and squamous cell carcinoma. 4 cases showed mixed epithelial and sarcomatoid areas. Epithelial component was IDC (NOS) in all the cases. Seven cases showed triple negativity. Three cases showed HER2 overexpression. 9/10 cases showed immunoreactivity for EGFR suggesting basal like phenotype. Mean Ki67 proliferation index was high (60%) suggesting aggressive nature.

**Conclusion:** Thus it is crucial to be aware of various rare types of BC and study their immunohistopathological features to determine the prognosis and guide the clinicians to formulate the treatment options for better patient care.

**Key words:** Rare breast carcinoma, metaplastic carcinoma, medullary carcinoma, EGFR, CK5/6

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### **Introduction**

Breast cancer (BC) heterogeneity is observed at different levels, from the classical histopathological characterization to the more modern molecular classification.<sup>[1]</sup> Histopathological type is one of the crucial characteristic of a cancer which is associated with varying clinical course, and prognosis.<sup>[2]</sup> The World Health Organization (WHO) has presented a

detailed classification of BC.<sup>[3]</sup> Invasive epithelial tumors are divided into 19 different types. Most tumors are derived from the terminal ductolobular unit, and up to 75% of the diagnosed cases of infiltrating ductal carcinoma (IDC) are defined as invasive ductal carcinoma, not otherwise specified (IDC-NOS). The second most common epithelial tumor type is invasive lobular carcinoma, which

comprises 5–15% of the group. There are other variants which are less common, but well defined by the WHO classification, referred to as “rare types of breast cancer”.

We have studied these rare types of breast carcinoma cases which were reported in our institute during a period of five years. Metaplastic breast carcinomas (MpBC) and medullary carcinomas are studied in detail with clinical, histopathological and immunohistochemical (IHC) studies.

### **Materials and Method**

This is a retrospective study of 19 cases of rare BC subtypes. Formalin fixed and routinely processed histopathological slides were studied and reviewed by two pathologists and the diagnosis was confirmed. All the MpBCs were divided into three groups: 1. Epithelial, with the tumor expressing both adenocarcinoma and squamous cell carcinoma (SCC), or SCC alone, 2. Biphasic, with the tumor expressing the carcinoma component (either adenocarcinoma or SCC) and sarcomatoid or spindle cell component and 3. Monophasic, with the tumour being formed exclusively by the sarcomatoid or spindle cell component.

IHC was carried out on a representative section in all cases with the following antibodies viz. ER (clone 6F11, Novacastra), PR(clone PGR312, Novacastra), HER-2(clone CB11, Novacastra), and proliferation marker such as Ki-67 (MIB1; Dako; 1:100). EGFR (clone EGFR.25, Leica) was done in all cases of MpBC and CK5/6 (clone D5/16B4, Dako) was done in medullary carcinomas and MpBC. For ER and PR, moderate to strong nuclear staining of 1% or more of the tumor cells was considered to be positive and for HER2, moderate to strong complete membrane staining of 10% or more of the tumor cells was considered to be positive. Ki-67 staining was expressed as a percentage of cells showing moderate to strong nuclear staining, and was considered to be positive if the expression was >10%. For EGFR reporting, moderate incomplete (+2) to strong complete membrane (+3) staining was considered positive according to DAKO criteria. Weak and incomplete membrane (+1) staining was considered negative. The medical records of the patients were reviewed, with emphasis on lymph node status at the time of surgery, if performed.

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**Results**

Clinicopathological and IHC findings of five rare breast subtypes of BC are summarized in Table 1.

**Table 1 : Clinicopathological and IHC findings of rare breast subtypes**

Type of breast cancer	Age	Tumor size	Stage	Modified Bloom Richardson Grading	ER	PR	HER2	Ki67 index
Tubular carcinoma	50F	3x3x3cm	T2N0M0	Grade 1	Positive	Positive	N	2%
Colloid carcinoma	70F	7x6x5cm and 4x3x3cm	T3N0M0 T2N0M0	Grade 1	Positive	Positive	N	1%
Invasive cribriform cancer	65M	3.5x3x2cm	T2N1M0	Grade 2	90% tumor nuclei strong positive	50% tumor nuclei strong positive	Negative	2%
Secretory carcinoma	75F	5x5x5cm	T4N1M0	Grade 1	N	N	N	5%
Apocrine carcinoma	70F	4x3.5x3.8cm	T2N0M0	Grade 2	Strongly positive	N	Strongly positive	30%

Clinicopathological and IHC findings of four medullary carcinoma of the breast are summarized in Table 2.

**Table 2: Clinicopathological and IHC studies of medullary carcinoma breast.**

	Age	Tumor size	TNM stage	Immunoreactivity	CK5/6	Ki67 index
1	65F	3x2x1cm	T2N1M0	TN	+2	90%
2	49F	8x8x6cm	T3N2aM0	TN	+2	90%
3	48F	4x4x3cm	T2N0Mx	TN	+2	80%
4	38F	5x5x3cm	T3N2Mx	TN	N	90%

TN- triple negative

Clinicopathological and immunohistochemical features of ten cases of MpBC are summarized in Table 3 and 4 respectively.

**Table 3 :Clinicopathological features of MpBC**

	Age(y)/Sex	Tumor size (cm)	Gross	Histopathology	Staging	Grading
Case1	40F	5x4x4	lobulated, greyish white tumor	Biphasic IDC+ sarcomatoid	T3N0Mx – Stage II B	Grade III
Case2	47F	5x4x2.5	greyish white Nipple retracted, satellite nodule	Biphasic IDC+spindleNeuroglial tissue foci	T4N1Mx – Stage IIB Skin involvement 1 out of 9 LN	GradeII
Case3	50F	9x6.5x6	WC fluid oozed out on cutting	Biphasic IDC + sarcomatoidchondroidmyxoid differentiation	T3N1aMx – Stage IIIA 1out of 19 LN	GradeIII
Case4	66F	4x4x3	WC tumor Solid greyish white	SCC +IDC	T2N0Mx – Stage IIB	GradeIII
Case5	40F	5x4.5x3	WC tumor solid whitish	Biphasic IDC + sarcomatoid	T4N2Mx – Stage IIIb Skin involvement	GradeIII
Case 6	50F	5x4x3	WC tumor solid whitish	IDC+SCC	T2N0Mx Stage IIB	GradeIII
Case7	41F	6x5x4	Ill circumscribed greyish white	SCC	T3N1Mx 1 out of 27 LN	GradeIII
Case8	69F	4x3x2.5	Whitish with cystic degeneration	IDC+SCC	Lumpectomy	GradeIII
Case9	50F	4.5x2.5x2.5	Greyish white with cystic degeneration	IDC+SCC	T32N1Mx 3 out of 24 LN	GradeIII
Case 10	65F	3x2.5x2.5	Greyish white	IDC+SCC(focal)	T2N1aMx 5 out of 11 LN	Grade II

**Table 4: Immunohistochemical profile of MpBC**

IHC marker	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case7	Case8	Case9	Case10
ER	N	N	N	N	N	N	N	N	N	N
PR	N	N	N	N	N	N	N	N	N	N
HER2 Neu	P	N	N	N	N	N	N	N	P	P
Ki 67	50%	80%	70%	70%	10%	20%	30%	50%	60%	20%
Vimentin	P	P	P	P	P	N	N	N	N	N
EGFR	N	P	P	P	P	P	P	P	P	P

10 cases of MpBC were received over a period of five years. Mean age of presentation was 44.9y. Mean tumor size was 5 cm. 7/10 (70%) cases showed lymph node metastasis though the number of lymph nodes involved ranged from one to five. Skin involvement was present in two cases. One case where only lumpectomy was done, the patient was lost for follow up.

Six cases were of pure epithelial type of which five were mixed IDC and squamous cell carcinoma (Fig 1a) and one case was of pure squamous cell carcinoma. (Fig 1a inset) Histomorphological study of 4 cases showed mixed epithelial and sarcomatoid areas. (Fig 1b) Epithelial component was IDC (NOS) in all the cases. Chondromyxoid area was seen in one case (Fig 1c). One case showed neuroglial differentiation (Fig 1d).

One case showed distant metastasis. Nine cases showed grade 3 nuclear features. Only one case showed grade 2 nuclear features. Seven cases showed ER, PR, HER-2 NEU negativity. Three cases were HER2 overexpression type. 9/10 cases showed Immunoreactivity for EGFR (Fig 1e). Mean Ki67 proliferation index was high (60%) suggesting highly

aggressive nature (Fig 1f). Most cases presented with stage II or higher.

**Discussion**

Tubular carcinoma accounts for less than 2% of invasive breast cancers.<sup>[4]</sup> Pure tubular carcinoma consist of at least 90% tubular architecture, composed of small round or oval tubules of single layer of epithelial cells with adjacent desmoplastic stroma as seen in present case. (Fig 2 a) On radiological examination it presents as a small spiculated lesion that mimics infiltrating ductal carcinoma or radial scars.<sup>[5]</sup> Tubular carcinomas are usually hormone receptor positive and of low grade. When compared with invasive carcinoma of no special type, tubular carcinoma is more likely to be diagnosed at older age and be smaller in size. Nodal involvement is reported in the range of 4%–17%. The prognosis of patients with tubular carcinoma is very good. Our case was of 50 years female with no lymph node involvement.

Pure mucinous carcinoma is characterized by the production of abundant extracellular and/or intracellular mucin. Pure mucinous carcinomas are generally defined as containing more than 90% of mucin, (Fig 2b) and mixed mucinous carcinomas are

those containing 50%–90% of mucin.<sup>[6]</sup> The presence of less than 50% of mucin identifies ductal carcinoma with a mucinous component. Pure mucinous carcinoma accounts for 1%–4% of all breast cancers, and it is generally diagnosed at older ages.<sup>[1]</sup> The axillary lymph nodes are rarely involved accounting to favorable prognosis of this BC subtype. Our patient was 70 year female with bilateral pure mucinous carcinoma showing strong ER (Fig 2b inset) and PR positivity. Lymph nodes were free of tumor.

Invasive cribriform carcinomas (ICCs) account for 0.1%–0.6% of breast cancers and are characterized by an invasive component showing a predominantly cribriform pattern.<sup>[7]</sup> These tumors are subdivided into pure and mixed. In our study 1 case of ICC of pure type was reported. The growth pattern was cribriform in 95% of the tumor area. (Fig 2c) Mixed type of ICC contain areas of less-well differentiated invasive carcinoma.<sup>[8]</sup> ICCs are generally ER positive, are of low grade and show low proliferative index. Our case showed strong ER ( Fig 2c inset) and PR immunoreactivity and was negative for HER2neu. Ki 67 labelling index was 2%. Axillary lymph-nodal metastases are reported in approximately 10% of the cases.<sup>[1]</sup> Eight out of 14 lymph nodes were involved by tumor in our case. ICC is known to have excellent prognosis in its pure form, whereas more caution is needed for the mixed variants.

Medullary carcinoma represents less than 2% of breast carcinoma and occurs more frequently in younger women.<sup>[1]</sup> They show a circumscribed tumor with pushing margins and are composed of poorly differentiated cells, with large vesicular nuclei, prominent nucleoli, arranged in syncytial pattern with prominent lymphocytic infiltrate.<sup>[9,10]</sup> These features are essential in the entire tumor for the diagnosis of

classical medullary carcinoma. (Fig 2d) Most medullary carcinomas are triple-negative with cytokeratin 5/6 positivity.<sup>[11,12]</sup> Most medullary carcinomas are aneuploid and are highly proliferative. Despite these unfavorable histologic features, the prognosis of patients with medullary carcinoma is generally good. The medullary histotype is more common in the case of BRCA1 mutations. The incidence of nodal involvement is lower than other carcinomas of the breast.<sup>[11]</sup> In our study, there were four cases of medullary carcinoma. The mean age was 50 years. All cases were triple negative and 3 cases showed immunoreactivity for CK5/6 suggesting basal like type (Table/Fig 6d inset).

Secretory breast carcinomas (SBC) are considered one of the rarest types of breast carcinomas (BC) accounting for 0.15% of all breast cancers.<sup>[1]</sup> It accounts for most of the breast cancers diagnosed in childhood. SBC is considered a form of duct carcinoma. Tumor cells, glands and microcystic spaces contain abundant secretions, which is usually pale pink or amphophilic (Fig 2e). The ultrasonography (US) appearance generally resembles a benign lesion.<sup>[13]</sup> SBC are ER(-), PR(-), Her2/neu(-), and are called triple negative and have low Ki67 expression as seen in our case.<sup>[14]</sup> The tumor cells are known to be immunoreactive for S100, Ecadherin and focally for CK5/6.<sup>[3]</sup> Local excision is the preferred initial treatment in children. The characteristic ETV6-NTRK3 molecular alteration, leading to a stable chimeric tyrosine kinase fusion product, may be the target of promising new treatment for this unique BC. Children and adolescents with SBC have a favorable prognosis, but disease seems slightly more aggressive in adults. In our case, the patient was postmenopausal female. She had a large tumor with extensive cystic degeneration.

The cystic change has not been described in literature so far. Two lymph nodes showed tumor deposits. Overlying skin, nipple and areola were involved by tumor representing adverse prognosis. New definition for basal like carcinoma requires study of 5 markers and is defined as those lacking ER, PR, HER2 expression, and expressing CK 5/6 and/or EGFR.<sup>[15]</sup> Our case was triple negative with CK 5/6 immunoreactivity (Fig 2e inset) fulfilling the definition of basal-like BC. Tumors with basal-like immunophenotype constitute a heterogeneous group of tumors and SBC is one of the basal-like tumors that is documented to have good prognosis.<sup>[16]</sup> The patient was not given adjuvant chemotherapy due to old age. Though SBC has good prognosis, in an adult patient it can show high risk behavior, especially if the size is more than 2 cm.

The incidence of apocrine carcinoma is reported in the range of 0.3%–4% of all cases, mostly because of the lack of uniform criteria for its diagnosis. The apocrine epithelium is a normal constituent of apocrine glands.<sup>[17]</sup> Apocrine phenotype is observed in a spectrum of breast epithelial lesions, ranging from benign metaplasia to apocrine carcinoma. The more stringent definition considers only those neoplasms composed entirely or predominantly of apocrine-type epithelium as apocrine carcinoma as seen in our case. (Fig 2f) <sup>[18]</sup> Pure apocrine carcinomas are GCDFP-15 positive and are generally ER, PR and androgen receptor (AR) positive <sup>[19]</sup>. HER2 is overexpressed in up to 54% of the cases <sup>[20]</sup> In our case ER was positive and PR was negative. HER 2 was overexpressed. P53 and Ki 67 labeling index were 25 and 30% respectively. Most studies have shown no clear differences in behavior of apocrine carcinoma from invasive ductal carcinoma not otherwise specified. Some studies have shown

significantly better prognosis for apocrine carcinoma with overall six year survival of 72% as against 52% for IDC NOS. In our case, in spite of having tumor of large size, we did not observe lymphovascular invasion and lymph node metastasis indicating better prognosis. This observation needs to be substantiated by cumulative data in future.

MpBC is a rare and histologically diverse subtype of breast carcinoma. It accounts for less than 1% of all breast cancers. <sup>[21]</sup> This term is used by many to denote tumors with mixed epithelial and sarcomatoid components, as well as primary squamous or mixed adenocarcinoma and squamous cell carcinoma. In those cases with sarcomatoid component the tumor cells can be classified into monophasic, composed of spindle cells only or biphasic, being admixed with a carcinomatous ( ductal carcinoma or SCC) component.<sup>[22]</sup> MPC tend to be relatively large tumors and incidence of axillary lymph node involvement is less compared to invasive carcinoma, IDC NOS of similar size and grade. <sup>[23]</sup>

MpBC cells have a lower degree of estrogen and progesterone receptor expression, and HER2 expression, and higher Ki-67 and p-53 scores compared to ductal cancers.<sup>[24,25]</sup> Microarray based gene expression profiling suggest basal like subtype. Distant metastasis can be found in absence of lymph node metastasis. MpBCs have lower response rates to conventional adjuvant chemotherapy and a worst clinical outcome than those of other forms of triple negative breast cancer. The aim of this study was to evaluate MBC patients to find out their clinical and immunohistopathological characteristics and their grading and staging. It has been found in the medical literature that studies on MpBCs rarely include more than 20 cases because of their rarity. <sup>[26]</sup>

A number of studies have consistently reported that MpBC is usually larger than typical breast cancer at presentation.<sup>[21]</sup> The mean tumor size in our study was 5 cm. All the tumors were >2 cm, which were comparable to previous reports showing larger tumor size in MpBC than in other types. Though axillary LN involvement was seen in 3 out of 6 cases, the numbers of involved nodes were only one or two in spite of large tumor size. Two cases showed locally advanced cancer with skin involvement.

In imaging tests MpBC do not exhibit any characteristic features aside from greater propensity for the formation of cystic lesions observed in carcinomas with the squamous epithelial component.<sup>[27]</sup> In our study, 2 out of six cases with squamous differentiation showed cystic degeneration. MpBC rarely cause the expression of steroid or HER2 receptors (detected in only up to 25% of cases). In the present study HER2 overexpression was identified in three cases. No ER expression was present in any of the patients, which corroborates the findings of other authors. In our study mean Ki67 proliferation index was high (60%) suggesting aggressive nature. In a study of 11 cases of MpBC it was found that these tumors were of larger size, high grade lesions with prominent nuclear pleomorphism. They rarely expressed hormone receptors and HER2 and had basal like immunophenotype. In their study CK5/6 was positive in all cases and EGFR was positive in half cases. Six out of 7 TN cases were positive for CK5/6 and or EGFR and were found to be consistent with basal like immunophenotype.<sup>[28]</sup>

Bae et al reported that MpBC exhibited higher expression of EGFR compared to TN IDC.<sup>[29]</sup> Reis-Filbo et al observed that 19 out of 25 MpBC cases exhibited EGFR expression.<sup>[30]</sup> In another study EGFR overexpression was identified in 71.9% of TN MPBC.<sup>[31]</sup>

In our study EGFR was positive in all 9 cases of TN MpBC suggesting the basal like phenotype. It was particularly of strong intensity in the areas of squamous differentiation. CK5/6 was positive in 4 out of 9 cases of TN MpBC.

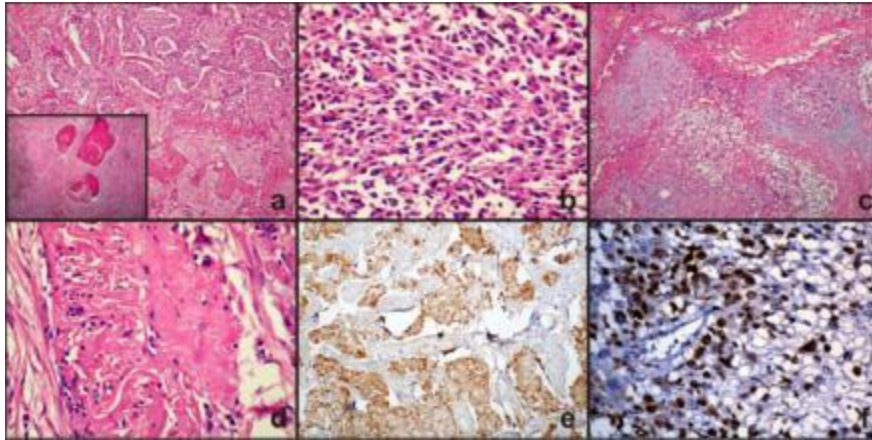
Genetic profiling shows deregulation of BRCA1, PTEN and TOP2A pathways (molecular targets of doxorubicin), which may account for the lower proclivity of MpBC for forming metastases in the lymph nodes, resistance to chemotherapy and, possibly, sensitivity to radiotherapy.<sup>[24]</sup>

There are reports of good therapeutic responses, including nearly complete pathological responses, to cisplatin-containing chemotherapy in MpBC with a squamous epithelial component.<sup>[32]</sup> Low incidence of MBC in combination with scarce literature data, however, make it impossible to draw any definite conclusions about the optimum treatment regimen. New therapy targeting EGFR in tumors with overexpression of EGFR should be further explored.

#### **Conclusion:**

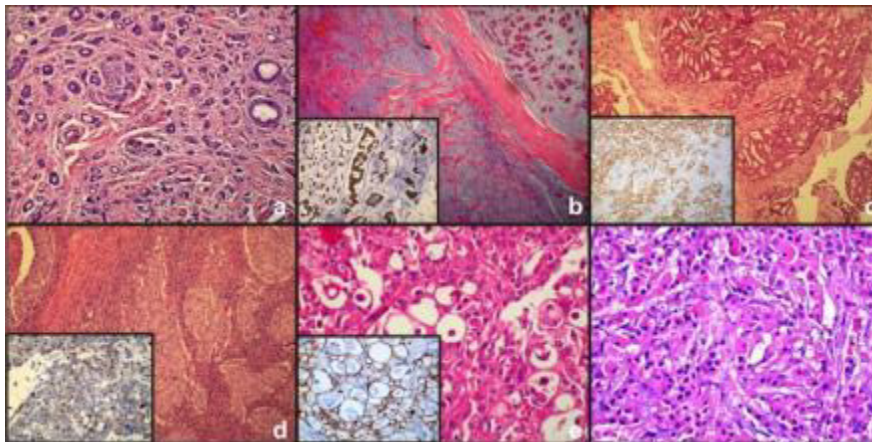
Thus it is crucial to be aware of various rare types of BC and study their immunohistopathological features to determine the prognosis and guide the clinicians to formulate the treatment options for better patient care.





**Fig 1:** Metaplastic carcinoma

- a. Infiltrating duct carcinoma (IDC) (NOS) with squamous cell carcinoma (SCC), (H&E, X100), Inset-SCC (X100)
- b. Sarcomatoid areas (H&E, X400)
- c. Chondromyxoid areas (H&E, X100)
- d. Neuroglial areas (H&E, X400)
- e. EGFR positivity (X100)
- f. Ki67 positivity (X400)



**Fig 2**

- a- Tubular carcinoma (H&E, X100)
- b- Pure mucinous carcinoma (H&E, X100), Inset-ER immunoreactivity (X100)
- c- Invasive cribriform carcinoma (H&E, X100), Inset-ER immunoreactivity (X100)
- d- Medullary carcinoma (H&E, X100), Inset-CK5/6 immunoreactivity (X400)
- e- Secretory carcinoma (H&E, X400), Inset-CK5/6 immunoreactivity (X400)
- f- Apocrine carcinoma (H&E, X400)

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