



# Primary Breast Tumors with Mesenchymal Morphology

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## Abstract

**Overview** Mesenchymal tumors of the breast are rare. Few epithelial tumors also have mesenchymal components. It is crucial to identify these as per histogenesis. This can be facilitated by markers of epithelial–mesenchymal transition (EMT).

**Objectives** The aim of this study was to categorize the breast lesions with mesenchymal morphology and to study EMT on immunohistochemistry (IHC).

**Materials and Methods** This is a retrospective study of 5-year duration from January 2015 to December 2019. Inclusion criteria: all breast lesions showing mesenchymal/nonepithelial morphology, complete or partial, on histology. Exclusion criteria: Mammary carcinomas without any mesenchymal/nonepithelial morphology, fibroadenomas, and lymphomas. Demographics, clinical, gross examination, histology, and IHC findings of selected cases were reviewed and recorded. Three additional markers p53, E-cadherin, and  $\beta$ -catenin were performed.

**Statistical Analysis Used** Frequency calculation for each variable (IHC).

**Results** Thirteen (2.5%) out of total 510 breast specimens showed mesenchymal histology. Of these, five (38.5%) were metaplastic breast carcinomas (MBC), four (31%) were phyllodes tumor (PT), and one (7.7%) case each of malignant peripheral nerve sheath tumor, primary stromal sarcoma of breast, pseudoangiomatous stromal hyperplasia, and myofibroblastoma. Loss of E-cadherin was seen in 4/5 (80%) MBCs and was retained in ductal component of PTs. p53 was not expressed in any of the tumors except 3/5 (60%) MBCs.  $\beta$ -Catenin was aberrant in all MBCs.

**Conclusions** Primary breast tumors with mesenchymal morphology present a spectrum ranging from benign mesenchymal, fibroepithelial neoplasms to malignant tumors of mesenchymal and epithelial origin. Loss of E-cadherin, expression of p53, and aberrant expression of  $\beta$ -catenin are suggestive of EMT and molecular heterogeneity of MBCs.

## Keywords

- ▶ metaplastic
- ▶ mesenchymal
- ▶ sarcoma
- ▶ epithelial–mesenchymal transition

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## Introduction

Mesenchymal neoplasms comprise 0.5 to 1% of all breast tumors.<sup>1,2</sup> Malignant mesenchymal breast tumors are aggressive, have propensity to recur, and bear a poor prognosis. Although the World Health Organization classification of breast neoplasms<sup>3</sup> iterates different histological subtypes depending on cell morphology, it is challenging to differentiate between epithelial and mesenchymal tumors of breast owing to the rarity of the latter and presence of entities like metaplastic carcinomas that exhibit heterogenous morphology.

The clinical and pathological attributes of these rare neoplasms have been sparsely studied, especially in resource-limited countries like ours. With the rapid advent of molecular and genetic diagnostic tools, our knowledge of the pathogenetic underpinnings of breast neoplasms is expanding every day. TP53 and CTNNB1 mutations among others (like EGFR, PIK3CA, PTEN) have been hypothesized to play a significant role in epithelial–mesenchymal transition (EMT) in metaplastic breast carcinomas (MBCs).<sup>4–6</sup>

This study is an attempt to categorize the breast lesions that share mesenchymal morphology emphasizing on the diagnostic characteristics on histology and to study EMT with immunohistochemistry (IHC) markers such as p53,  $\beta$ -catenin, and E-cadherin.

## Materials and Methods

### Samples

This is a retrospective study of 5-year duration from January 2015 to December 2019. We included all reported mastectomies, lumpectomies, excision biopsies as well as core needle biopsies of breast lesions that exhibited mesenchymal/non-epithelial morphology, completely or partially. Mammary carcinomas without any mesenchymal/non-epithelial morphology, fibroadenomas, and lymphomas were not included.

The age, clinical details, radiology, gross examination findings, histomorphology, and IHC were reviewed, analyzed, and recorded.

### Immunohistochemistry

Three additional immunohistochemical markers namely, p53 (clone BP-53–12, PathnSitu, Cat #CM101), E-cadherin (clone EP6, PathnSitu, Cat#CR039) and  $\beta$ -catenin (clone EP35, PathnSitu, Cat#CR005) were performed on representative formalin fixed paraffin blocks. Sections of 3  $\mu$ m were applied on poly-L-lysine coated slides and incubated for 24 hours. Deparaffinization was facilitated with 3 changes of xylene and hydration in graded series of alcohol. Antigen retrieval was achieved in Decloaker at medium pressure for 7 minutes in citrate buffer (pH- 6.0). After washing in distilled water (DW), tissue was incubated with H<sub>2</sub>O<sub>2</sub> for 10 minutes to block endogenous peroxidase activity and rinsed with tris-buffered saline (TBS). Primary antibody was applied and incubated in moist chamber for 1 hour at room temperature. Slides were washed with TBS, treated with PolyExcel Target binder (PathnSitu, Hyderabad, Telangana, India) for 10 minutes and washed again to be incubated with PolyExcel Horse radish peroxidase (PathnSitu, Hyderabad, Telangana, India) for 15 minutes. Subsequently, tissue was treated with 3,3'-diaminobenzidine substrate chromogen for 5 minutes and washed in DW. These slides were then counterstained with hematoxylin, dehydrated, cleared, and mounted. Known controls were used for p53, while  $\beta$ -catenin and E-cadherin were assessed with internal controls (endothelial cells and duct epithelium, respectively). Frequency of positive cases was calculated for each of the above IHC markers.

### Interpretation of IHC

p53 was considered positive if strong nuclear positivity was noted in more than 10% tumor cells after examining at least five high power fields or 1,000 tumor cells.<sup>7,8</sup> Membranous staining of cells was considered positive for E-cadherin. The

**Table 1** Details of metaplastic breast carcinomas

Case	Specimen received	Radiology findings	Gross examination	Metaplastic component	IHC
1	Lumpectomy	Well circumscribed solid cystic lesion with foci of calcification-BI-RADS IV	3×2×1.5 cm solid cystic tumor with hard consistency	Osteosarcoma and angiosarcoma	ER(-), PR(-), Her2 neu(-), p63(-), CK (+), FLI(-), CD10(-), S100(-), CD34(-), Mib 1–25%
2	Lumpectomy	NA	14×8×7 cm fungating growth with solid areas and cystic change	Spindle cell	ER(-), PR(-), Her2 neu(-), Mib1- 18–20%
3	Trucut biopsy	NA	NA	Spindle cell	ER(-), PR(-), Her 2 neu(-), CK(+), Vimentin(+)
4	Paraffin blocks for review	NA	NA	Spindle cell, squamous	ER(-), PR(-), Her 2 neu(-), HMWCK(+), p63(+)
5	Paraffin blocks for review	NA	NA	Spindle cell	ER(-), PR(-), Her2neu(-), CK(+), Vimentin(+), EMA(+), SMA(), K <sub>i</sub> 67–70%

Abbreviations: BIRADS IV, Breast Imaging Reporting and Data System IV; IHC, immunohistochemistry; NA, not available.

expression of  $\beta$ -catenin was noted as normal or aberrant. Strong membranous staining was considered normal, while aberrant expression was classified as:

- Complete loss of membranous (LOM) without cytoplasmic/nuclear staining.
- Partial LOM without cytoplasmic/nuclear staining.

## Results

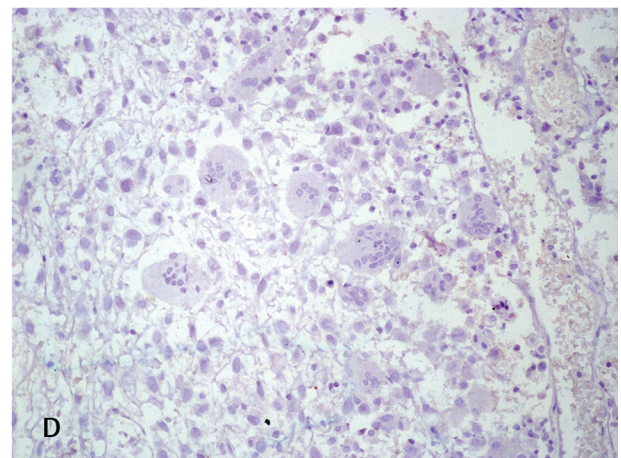
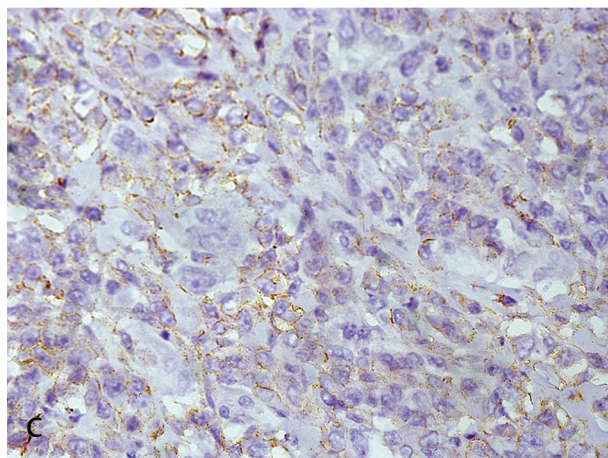
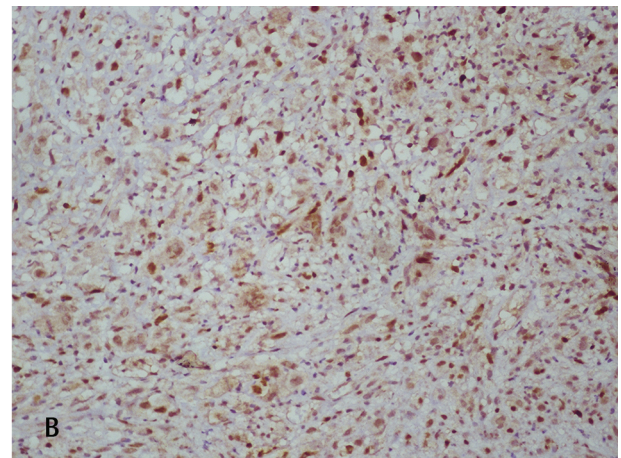
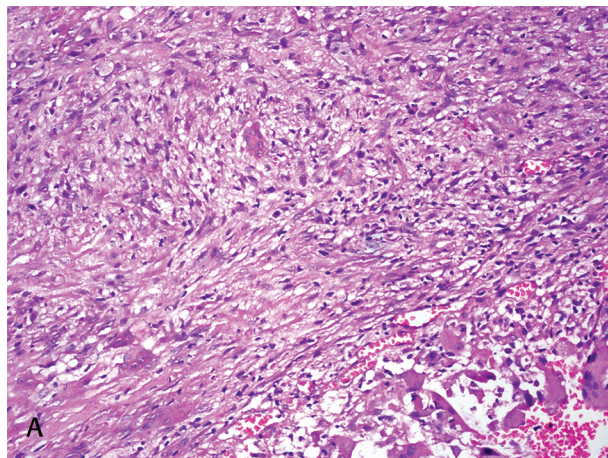
A total of 510 breast specimens were received for histopathological examination from January 2015 to December 2019. Of these, thirteen (2.5%) cases were found to have the histology showing mesenchymal morphology partially or completely. As proven by gross, histomorphology, and IHC examination, these included five cases of MBCs, four cases of phyllodes tumors (PTs), one case each of malignant peripheral nerve sheath tumor (MPNST), primary spindle cell sarcoma of breast, myofibroblastoma, and pseudoangiomatous stromal hyperplasia. Age of the 12 female patients ranged from 23 to 52 years while that of one included male patient was 85 years. The mean age of the participants was 44 years with a standard deviation (SD) of 14.89.

## Metaplastic Carcinomas

Of the five MBC cases reported, two were received as lumpectomies, two as paraffin blocks for review consultation, and one as trucut biopsy. The details are described in **Table 1**. The mean age was 43.20 years (SD = 7.02). All five cases showed presence of tumor necrosis, while osteoclast like multinucleated giant cells were seen in four out of five cases. Though the mesenchymal component (**Fig. 1A**) was initially not graded in the previous reports, on review by the authors, in all the cases it was found to be of high histological grade.

## Phyllodes Tumors

Four cases of PT of breast were reported, of which one was benign, one was borderline, and two were malignant. Age of the patients ranged from 34 to 48 years, mean age being 40 years (SD = 5.17). One case was received for review and the rest as wide local excision specimens in which the tumors ranged grossly from 4.5 to 12 cm in largest dimensions. One of the malignant tumors was accompanied with an axillary lump with similar histology measuring 2.5 cm. p53 was not expressed in any of the PTs. E-cadherin and  $\beta$ -catenin, though normally expressed in the ductal component, showed no expression in the stromal component.



**Fig. 1** (A) Metaplastic breast carcinoma (MBC) showing spindle cell morphology (Hematoxylin and Eosin, 200 $\times$ ). (B) Strong nuclear p53 positivity in MBC (200 $\times$ ). (C) Partial loss of membranous staining of  $\beta$ -catenin in MBC (200 $\times$ ). (D) Complete loss of E-cadherin in MBC (200 $\times$ ).

### Primary Sarcomas of the Breast

Two cases of sarcoma were reported. Trucut biopsy was reported initially, one was reported as fibrosarcoma breast and the other as metaplastic carcinoma. This was followed by modified Radical mastectomy with axillary dissection in both cases.

The former a 30-year-old female presented with recurrent left breast lump. There was history of previous lumpectomy diagnosed as malignant phyllodes elsewhere. Positron emission tomography scan showed fluorodeoxyglucose avid enhancing solid mass lesion in retroareolar region. Mastectomy specimen showed two tumor masses measuring 6 and 7 cm with white firm to hard cut surface both ulcerating the skin. Histology showed spindle cells arranged in short, intersecting fascicles with alternating hypocellular areas. On IHC, tumor cells were CK & EMA(-), Vimentin(+), CD10(+), S100(+), CD34(-), Desmin(-), SMA(focal), c-Kit(-), p63(-), CD99(-), CD31(-), ER(-), PR(-), and Her 2 neu(-). All 14 lymph nodes were free from tumor. The final diagnosis was revised as MPNST, high grade, in view of histomorphology and IHC findings.

The latter, a 23-year-old female, presented with a left breast lump. Grossly, a tumor measuring 12 cm with firm gray white cut surface was noted. Radiology findings were not available in this case. Histology showed spindle cells arranged in loose intersecting fascicles with abundant eosinophilic cytoplasm and pleomorphic nuclei with nucleoli. Few cells had epithelioid appearance. On IHC, tumor cells were CK & EMA(-), Vimentin(+), CD10(+), SMA(+), S100(-), Desmin(-), Myogenin(-), CD 31(-), CD34(-), HMB 45(-), HMWCK(-), LMWCK(-), p63(-), and c-Kit(-). All 23 lymph nodes were free from tumor. The diagnosis offered was primary spindle cell sarcoma of the breast.

Both the cases showed extensive areas of necrosis and presence of tumor giant cells. p53, E-cadherin, and  $\beta$ -catenin were not expressed in either of these cases.

### Benign Tumors

A lumpectomy specimen of a 62-year-old female with radiology findings of ill-defined high-density lesion and Breast Imaging Reporting and Data System (BIRADS) score V was received. Gross examination showed a tumor measuring 4 cm with gray white firm to hard cut surface. Histology showed proliferation of fibroblastic stromal elements admixed with dilated breast ducts, stromal hyperplasia with dense keloid like quality, and anastomosing pattern of slit like clefts lined by single layer of spindle cells simulating blood vessels. The final diagnosis was pseudoangiomatous stromal hyperplasia. Due to nonavailability of paraffin blocks, additional IHC was not performed.

A trucut biopsy from left breast in an 85-year-old male was received. Ultrasonography showed a 4 cm nodule in left breast, but BIRADS score was not mentioned. The 04 linear tissue cores with largest measuring 1.2 cm showed a spindle cell tumor disposed in relatively hypercellular fascicles and whorls along with inflammatory cells like mast cells, eosinophils, plasma cells, and lymphocytes on histology. Tumor cells were Vimentin(+), SMA(+), CD34(+), Desmin(+), S100(-),

HMB45(-), and Mib 2%. It was diagnosed as myofibroblastoma. None of the additional IHC markers were expressed.

### Discussion

Breast parenchyma is composed of two major lobular components—ducts and the periductal stroma. Besides these, interlobular hormone responsive stroma, the supportive structure for the terminal duct lobular units is the third component. This physiology gives rise to biphasic pathologies and the problem arises when the stromal component is predominantly involved. This coupled with decreasing size of biopsies poses a challenge, one which can only be mitigated by collating the clinical, histological and IHC findings to determine the histogenesis of the mesenchymal component. Whereas epithelial tumors of the breast have multipronged treatment strategies, the management of phyllodes and sarcomas begins with surgical excision and negative margins. Moreover, sarcomas have a poorer prognosis than PT with an overall 5-year survival rate ranging from 50 to 90% depending on tumor size.<sup>9,10</sup>

Over 5-year duration, we found 2.5% tumors with mesenchymal morphology, a small but sizeable number. Primary sarcomas of breast are rare accounting for < 1% of all breast neoplasms. MPNSTs are extremely rare soft tissue sarcomas (10% of soft tissue tumors and incidence of 0.001% in general population), especially with primary in breast.<sup>11</sup> They are often associated with Von Recklinghausen neurofibromatosis. The mean age at diagnosis is 35 years.<sup>12,13</sup> In our case, the lady was young, 30 years of age, presented with a recurrent rapidly growing large tumor, previously diagnosed as malignant phyllodes. Another rare entity in our study, a case of primary stromal sarcoma of breast, was diagnosed in a 23-year-old female. Stromal sarcomas are malignant mesenchymal tumors arising from hormone-sensitive specialized stroma of mammary gland and tumor cells characteristically express CD10.<sup>14</sup>

It is essential to perform extensive sampling to ascertain or rule out presence of leaf like architecture, epithelial component in the form of clefts/hyperplasia (PTs), or islands of metaplasia/epithelioid cells (MBCs). IHC markers for neuron-specific enolase, Vimentin, and S-100 are instrumental in confirming the diagnosis in MPNST, while Ki 67 proliferation index helps to rule out benign neural tumors. Vimentin and CD10 positivity after excluding other cells of origin are diagnostic for stromal sarcomas.

PTs are derived from periductal stroma and account for approximately 0.3 to 1% of all breast tumors.<sup>15</sup> The diagnosis is based on the assessment of stromal cellularity, mitotic activity, and the microscopic character of the tumor border. Although some studies<sup>16</sup> have shown that p53 expression significantly separates benign from malignant PTs, none of the PTs in our study showed significant p53 expression. E-cadherin and  $\beta$ -catenin expression was comparable to control in all PTs.

Metaplastic carcinomas are complex neoplasms showing variability in phenotype. MBCs are also notorious for high rate of metastasis and are triple negative tumors with poor

prognosis. Studies show that the different histologies, especially spindle cell transformation of the tumor, are the result of genetic alteration rather than shift in histogenesis.<sup>17</sup> EGFR gene amplification, TP53 mutations, and CTNNB1 mutations (through Wnt canonical pathway) have been implicated in EMT that, in turn, decreases cell to cell adhesion and increases propensity to metastasize. Loss of E-cadherin seen in 80% MBCs in our study is a marker of EMT.<sup>18</sup> We used p53 and  $\beta$ -catenin as surrogate markers to study the pathways (induced by TP53 and CTNNB1 mutations) involved in EMT. p53 was expressed in 60% cases, consistent with similar studies on TP53 mutational analysis.<sup>3</sup>

In colorectal or pancreaticobiliary carcinomas, nuclear localization of  $\beta$ -catenin is suggestive of  $\beta$ -catenin stabilization by activation of Wnt signaling pathway. In our study, none of the cases showed nuclear localization.  $\beta$ -Catenin expression was aberrant in all cases but with LOM staining without cytoplasmic/nuclear staining. This leads us to believe that activation of Wnt signaling pathway in breast carcinomas is induced by somatic mutations other than APC, CTNNB1, FAM123B, etc. seen in colorectal cancers.<sup>4,18,19</sup> Studies suggest that this type of aberration may implicate other molecular pathways and is associated with tumor invasiveness, lymph node metastasis, and poor prognosis.<sup>20</sup>

It is worthy of mentioning that 80% MBCs showed presence of osteoclast like multinucleated giant cells, although their significance is unknown. Although rarity of these cases remains an obstacle, further preferably multicentric studies are required to better elucidate the molecular and genetic characteristics of these tumors.

Myofibroblastomas, though rare, are the commonest benign mesenchymal neoplasm of breast after haemangiomas.<sup>3</sup> They are known to affect elderly males and postmenopausal women. It is challenging to diagnose on core biopsy since they can mimic both ductal and mesenchymal malignancies. But, lack of necrosis, nuclear atypia, and mitoses compounded with characteristic nuclear and stromal features should nudge one into excluding myofibroblastic origin.

## Conclusion

Primary breast tumors with mesenchymal morphology are rare and present a wide spectrum of neoplasms ranging from benign mesenchymal, biphasic fibroepithelial neoplasms to malignant tumors of mesenchymal as well as epithelial origin. Malignant mesenchymal tumors are much rarer and require a high index of suspicion for their diagnosis after diligently excluding commoner entities. Loss of E-cadherin in triple negative breast carcinomas should prompt a search for mesenchymal component (MBCs) indicative of EMT. Expression of p53 and aberrant (LOM) expression of  $\beta$ -catenin are exclusive to MBCs among other mesenchymal tumors and are indicative of the molecular heterogeneity in MBCs through involvement of various pathways, waiting to be explored through further molecular analysis.

## Statement of Conforming to the Declaration of Helsinki

This is a retrospective study and does not involve any intervention or human participants. For this type of study, formal consent is not required as all personal identification data are anonymized. We, the authors, have performed the research in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

## Authors' Contribution

Manvir S Tevatia was involved in concept, design, definition of intellectual content, data analysis, statistical analysis, manuscript editing, and manuscript review. Prabhaskar Mishra was involved in concept, design, definition of intellectual content, data analysis, statistical analysis, manuscript preparation, and manuscript review. Ajay K Baranwal was involved in concept, design, definition of intellectual content, data analysis, manuscript preparation, and manuscript review. Prachi B Nichat was involved in concept, design, definition of intellectual content, literature research, data acquisition, statistical analysis, manuscript preparation, and manuscript review. Divya Shelly was involved in concept, design, definition of intellectual content, data analysis, statistical analysis, manuscript editing and review. Shivali Awasthi was involved in concept, design, definition of intellectual content, literature research, data acquisition, and manuscript review. Prashant Sengupta was involved in concept, design, definition of intellectual content, data analysis, statistical analysis, and manuscript editing and review. Prachi B Nichat is guarantor for this manuscript.

## Conflicts of Interest

Nil.

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