

Histopathological Spectrum and Immunohistochemistry Profile of Rare Breast Cancers - A Quick Review

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Abstract

Breast Cancer is the most frequent malignancy in women worldwide. These malignancies display an array of various clinical features affecting treatment regimen and prognosis. The current study enlightens the rare subtypes of breast cancer with distinct pathological attributes; thereby providing insight for the need of new treatment strategies and patient stratification for better management. Herein, each example taken in the study is quintessential to the categorised subtype.

A 15-months retrospective review of all breast resected specimen was done which summed up to 323 cases. However, cases with benign breast disease, cases who received prior neoadjuvant chemotherapy and those who did not undergo mastectomy/lumpectomy/wide local excision in our hospital, post tru-cut biopsy were excluded. Out of these 323 cases, only 63 cases were diagnosed to have breast cancer. In the absence of adequate histological follow-up data, 14 cases were further excluded. Thus, a total of 45 cases were included in the study. 39 cases (86.6%) belonged to the heterogeneous group of Invasive Breast Carcinoma of No Special Type (IBC-NST), and 6 cases (13.3%) were diagnosed as special and differentiated variants of breast carcinoma. These special variants included 3 cases (6.6%) of metaplastic carcinoma, 2 cases (4.4%) of lobular carcinoma, and one case (2.2%) of mucinous carcinoma.

Due to rarity of these subtypes of cancers, there is an extreme paucity of literature in this dimension, hence clear guidelines for management are not available thereby affecting the therapeutic regimen of such patients. Thus, an adequate histological diagnosis along with molecular subtyping of these rare subtypes will contribute to conceptualization of their treatment protocols.

Key words: Breast Cancer, Rare, Morphology, Molecular Subtyping

Introduction

Breast cancer is the most commonly diagnosed cancer, accounting for one-quarter of all female cancers and a leading cause of death worldwide.¹ It has been predicted that breast cancer-related deaths will increase by 61.7% by 2040 in the South-East Asia region.² In India, it is also the most common cancer, accounting for 28.2% of all female cancers.³ Aetiology and pathogenesis have been extensively studied, revealing it as a heterogeneous disease with variable presentation, clinical course, and classification, including both pathological and

molecular aspects. In general, invasive breast cancer arises from the lining epithelium of the ducts (85%) or lobules (15%), primarily from the terminal duct lobular unit.

According to the latest WHO classification of Breast Tumours, morphological nomenclature has undergone slight changes, with infiltrating duct carcinoma now falling under the umbrella of invasive breast carcinoma of no special type (IBC-NST). Similarly, cancers historically described as medullary carcinoma are now considered special morphological patterns of IBC-NST and labelled as IBC-NST with medullary pattern. The majority

of breast cancers (75% to 80%) fall under the IBC-NST group, followed by invasive lobular carcinoma, representing about 5% to 15%.⁴ Other histological types are rare and are infrequently studied. Breast cancer subtypes also exhibit different frequencies of clinical, morphological, and biomarker subtypes according to geographical and population characteristics. Thus, a retrospective study was conducted to understand the morphological and molecular characteristics of rare breast cancers in the northern region of India.

Methods

Study design: Retrospective Observational Study.

Study population: All surgically resected breast specimens (Tru-cut biopsy, lumpectomy, local wide excision, and mastectomy with or without axillary lymph node dissection) operated on in a tertiary care hospital (Lucknow, India) from January 1, 2023, to March 31, 2024.

Exclusion criteria: Cases with benign diagnoses, cases operated on after neo-adjuvant chemotherapy, breast carcinoma diagnosed on Tru-cut biopsy specimens where follow up mastectomy/ wide excision not available.

Data collection: All demographic, clinical, and disease outcome data were obtained from patients' hospital records (files), and laboratory data were retrieved from the hospital information system (HIS).

Laboratory assay and interpretation

All operated breast specimens were retrospectively analysed, and malignant breast lesions diagnosed on local wide excision/ lumpectomy/mastectomy were included. All excised specimens (less than total mastectomy) and total mastectomy specimens

were fixed in 10% buffered formalin, grossed, and stained with haematoxylin and eosin stain, and reported according to the protocol of the College of American Pathologists. All cases underwent immunohistochemistry (oestrogen receptor, progesterone receptor, HER2, and MIB1/Ki-67 labelling index). Various other markers were used for further differentiation (E-cadherin, CK5/6, AE1/AE3, EGFR (HER1), SMA, P63).

ASCO/CAP Guidelines were used for reporting and scoring of ER, PR, and HER2.⁵

Breast carcinomas were further divided into biomarker-defined subtypes and groups based on ER and ERBB2 (HER2): ER-positive, HER2-negative; ER-positive, HER2-positive; ER-negative, HER2-positive; ER-negative, HER2-negative.

Results

Out of 323 breast specimens received during the study period, carcinoma was diagnosed in 63 cases (19.5%). Patients' ages ranged from 20 to 78 years, with a mean age of 51.59 years. The most common age of presentation was the 5th to 6th decade. All patients were females. In 14 cases, the diagnosis was made through Tru-cut biopsy, and follow-up local wide excision/ mastectomy specimens were not available, thus they were excluded from the study. Similarly, 4 mastectomy specimens received after neo-adjuvant chemotherapy were also excluded. Thus, a total of 45 cases were included in the study; in 41 cases (91.1%), modified radical mastectomy (MRM) was performed, and in 4 cases (8.88%), wide local excision was performed. 39 cases (86.6%) belonged to the heterogeneous group of Invasive Breast Carcinoma of No Special Type (IBC-NST), and 6 cases (13.3%) were diagnosed as special and differentiated variants of breast carcinoma. These special variants included 3 cases (6.6%) of metaplastic carcinoma, 2 cases (4.4%) of lobular carcinoma, and one case (2.2%) of mucinous carcinoma [Table 1].

S.No	Age (Year)	Laterality	Site	Histological diagnosis	ER	PR	HER2	Ki-67	Molecular subtype
1	48	Right	Lower outer quadrant	Metaplastic carcinoma with heterologous mesenchymal differentiation	-	-	-	30-40%	Basal -like
2	20	Left	All quadrant	Metaplastic spindle cell carcinoma	-	-	-	50%	Basal -like
3	65	Left	Lower outer quadrant	Metaplastic Low-grade Adenosquamous carcinoma	+	+	-	3-5%	Luminal A
4	30	Left	Upper outer quadrant	Invasive lobular carcinoma	+	+	-	20%	Luminal B
5	75	Left	Upper outer quadrant	Invasive lobular carcinoma	+	+	-	3-4%	Luminal A
6	60	Left	Lower outer quadrant	Mucinous carcinoma	+	+	-	5%	Luminal A

Table 1

Metaplastic carcinoma

Case 1: A 48-year-old female presented with a lump in the right breast (Figure 1A). There was no skin or muscle involvement and nipple was retracted towards the lump. Mammography revealed a large hypodense mass involving the outer part of the right breast with indistinct inferior margins and multiple coarse calcifications (Figure 1B). Radical right mastectomy revealed a bosselated firm lump measuring 5 x 4 cm in the lower outer quadrant (Figure 1C) with fleshy cut surface along with areas of haemorrhage and necrosis (Figure 1D). Microscopy revealed carcinomatous areas along with mesenchymal differentiation, chondroid, and osseous areas (Figure 1E and F). Tumour cells were negative for ER, PR, HER2, while positive for EGFR (HER1). Finally diagnosed as triple-negative metaplastic carcinoma with heterologous mesenchymal differentiation pT3 pN0.

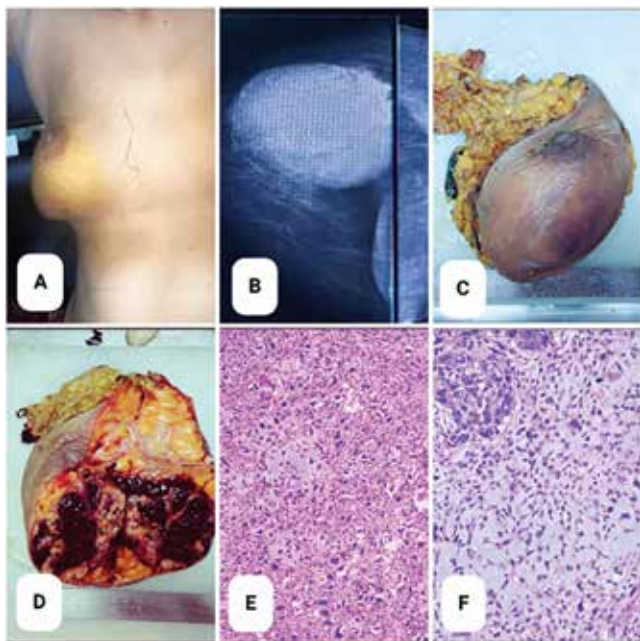


Figure 1: Metaplastic carcinoma with heterologous mesenchymal differentiation (a) Lump in the LOQ of the right breast. (b) Mammography -large hypodense mass with multiple coarse calcifications. (c) Resected mastectomy specimen. (d) Cut surface– Fleshy mass with haemorrhage. (e) Tissue section-both carcinomatous and sarcomatous foci (H and E $\times 20$). (f) Chondroid differentiation (H and E $\times 40$)

Case 2: A 20-year-old female presented with a fungating left breast tumour with a provisional diagnosis of malignant Phyllodes tumour and underwent left mastectomy. A large tumour occupying the whole breast protruded through the skin and exposed raw areas with spontaneous bleeding [Figure 2A]. Cut surface was fleshy, grey white [Figure 2A]. Microscopy revealed atypical spindle cell proliferation arranged in long fascicles [Figure 2C]. On extensive sampling, atypical epithelial cells were also identified. Tumour cells were positive for P63, CD10, and EGFR (HER1) and negative for ER, PR, and HER2. A diagnosis of triple-negative (basal-like) Spindle Cell Metaplastic Carcinoma pT4b pNX was given.

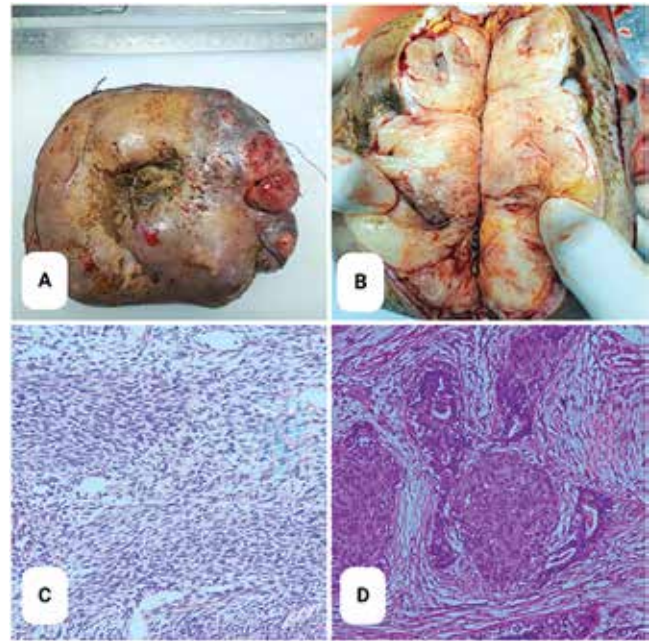


Figure 2: Spindle cell metaplastic carcinoma

- (a) Bulging, protruding and ulcerated left breast mass
- (b) Tan to pink fleshy cut surface
- (c) Tissue Section-Intersecting bundles of atypical cells (H and E $\times 20$)
- (d) Low grade Adeno squamous metaplastic carcinoma with glandular structures and squamous epithelial nests (H and E $\times 40$)

Case 3: A 65-year-old female presented with a left breast lump and underwent breast conservation surgery and axillary lymph node dissection. The cut surface revealed a greyish-white hard lump measuring 2.0x1.5x1.5 cm. Microscopy showed expansion of stroma into leaf-like structures (fronds) with well-developed tubular and glandular formation and solid nests of squamous cells [Figure 2D]. The tumour cells were ER-positive, PR-positive, and HER2-negative. Diagnosed as luminal A Low-grade adenosquamous carcinoma with co-existent Phyllodes tumour pT1c pN0.

Lobular carcinoma:

Case 1: A 30-year-old female presented with a left breast lump and underwent local wide excision and axillary lymph node dissection. The cut surface revealed a firm to hard infiltrative growth measuring 1.5x1.2x1.0 cm in the upper outer quadrant. Microscopy showed infiltrative tumour dispersed in single linear cords in fibrous connective tissue stroma. [Figure 3c]. Cells were ER-positive, PR-positive, and HER2-negative, diagnosed as Luminal B invasive lobular carcinoma pT1c pN1a.

Case 2: A 75-year-old female presented with a left breast lump and underwent local wide excision. The cut surface revealed a greyish white solid growth measuring 2.7x2.0x1.0 cm in the upper outer quadrant. Microscopy showed infiltrative tumour with pleomorphic cells without apocrine features dispersed in single linear cords in fibrous connective tissue stroma with surrounding lobular carcinoma in situ. Cells were ER-positive, PR-positive, and HER2-negative with lack of E-cadherin expression diagnosed as Luminal A invasive lobular carcinoma pT1c pNx.

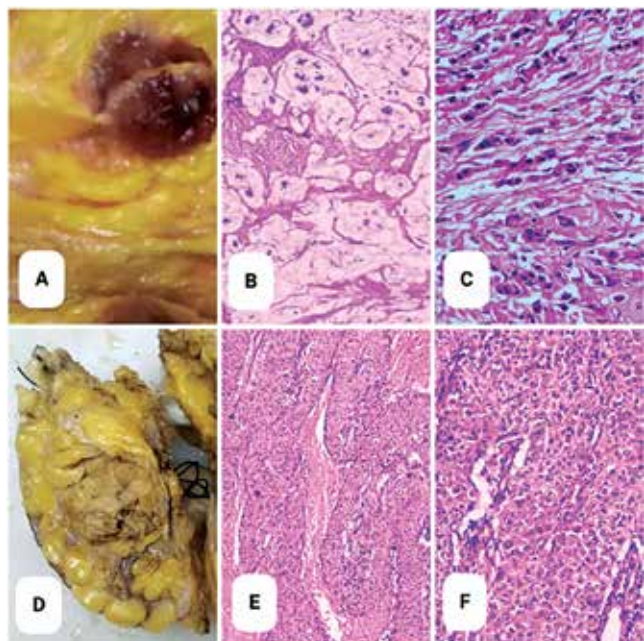


Figure 3: Mucinous carcinoma (a) Gelatinous cut surface with pushing margin. (b) Tissue Section-Sparse clusters of tumour cells in abundant extracellular mucin (H and E $\times 20$)

Invasive lobular carcinoma (c) Tissue section- discohesive cells in single-file linear cords carcinoma with desmoplastic stroma

Invasive breast carcinoma with medullary pattern (d) fleshy cut surface with pushing margins. (e) Tissue section- sheets of cells with areas of necrosis (H and E $\times 20$)

(f) syncytial architecture of high nuclear morphology (H and E $\times 40$)

Mucinous carcinoma

A 60-year-old female with a left breast lump underwent radical mastectomy and axillary lymph node dissection. The cut surface revealed a glistening gelatinous nodule with a pushing margin measuring 2.5x2.0x2.0 cm in the lower outer quadrant. [Figure 3a]. Microscopy showed clusters of neoplastic cells suspended in abundant extracellular mucin partitioned by delicate fibrous septa. [Figure 3b]. The cells were of low to intermediate grade and positive for ER and PR and negative for HER2, diagnosed as Luminal A Mucinous carcinoma; type B pT2 pN1a.

Mixed carcinoma

Two cases were diagnosed as mixed carcinoma containing an admixture of IBC-NST and a specialized subtype constituting 10-90% of cancer. They were mixed IBC-NST with lobular carcinoma (one case), mucinous carcinoma (one case). In two IBC-NST cases focus of squamous cell carcinoma ($<10\%$) was found.

IBC-NST with Medullary Pattern: Six cases were diagnosed as IBC-NST with a medullary pattern historically described as medullary carcinoma. The average age in these 6 cases was 38.8 years. Majority of tumours were having pushing margins (Figure 3D). Microscopy showed syncytial architecture with no glandular structures, areas of necrosis and prominent tumour infiltrating lymphocytes [Figure 3 E and F]. All of them were triple-negative breast carcinoma with no lymph node involvement.

Discussion

The broad spectrum of histological diversity in breast carcinomas holds significant prognostic implications. Four histological features characterize tumour biology, including:

1. Histological subtypes
2. Nottingham score
3. Presence or absence of angiolymphatic invasion
4. In situ component

Other important features include tumour size, distance to margin, stromal changes, and tumour-infiltrating lymphocytes. The majority of cases belong to invasive breast carcinoma of no special type (IBC-NST) and are well-studied, with clear recommendations for clinical management. Special histologies are rare, and treatment options and outcomes are often derived from small series and case reports. Therefore, in this review, we summarize the special histological variants diagnosed within a short duration at a single tertiary care hospital.

In our study, Metaplastic carcinomas (MpBCs) are the most commonly diagnosed special variant, constituting 6.6% of cases. However, in the literature, they have been reported to account for only 0.2-1% of all invasive breast carcinomas.⁶ MpBCs are divided into various subtypes, including low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, metaplastic carcinoma with mesenchymal differentiation, myoepithelial carcinoma, and mixed metaplastic carcinoma. Classifying these subtypes can be challenging, although several studies suggest that squamous cell carcinoma is the most commonly encountered subtype of MpBC.⁷ In our study, we identified three different subtypes of MpBCs, and in two cases, a squamous cell carcinoma component ($<10\%$) was present along with IBC-NST. Usually, MpBC does not express ER, PR, or HER2, often categorizing it as a subgroup of triple-negative breast cancer (TNBC), based on its immunohistochemical characteristics. All three cases in our study were TNBC.

Lobular carcinoma (ILC) is described as the most common pattern of special subtype, accounting for 5-15% of all IBC.⁸ The diagnosis of ILC is made through microscopic examination of tumour specimens, revealing distinct morphology. We diagnosed two cases of invasive lobular carcinoma (4.4%) of classical and pleomorphic patterns. Loss of E-cadherin expression was demonstrated in these cases, which is one of the most consistent molecular alterations of ILC contributing to the characteristic discohesive nature of lobular cells.⁹ Both cases were positive for ER and PR and negative for HER2, consistent with current practice indicating that ILCs are almost invariably ER-positive.

Mucinous carcinoma (MC) generally mimics a benign process both clinically and on mammography, accounting for 2% of IBC.¹⁰ We diagnosed one case of pure mucinous carcinoma, while another case presented as mixed carcinoma. Pure mucinous carcinoma requires a mucinous component $> 90\%$, while mixed carcinoma has 10-90%. Our case was ER and PR positive and HER2 negative, consistent with the luminal A molecular subtype.

In our study, six IBC-NST cases showed characteristic medullary features. These well-circumscribed tumour masses were of high histological grade, with pushing margins, syncytial architecture lacking glandular structures, and a very high proliferative index. They are triple-negative tumours typically seen in a relatively younger age group.¹¹

Credit authorship contribution statement

Dr Anju Shukla: Study concept and design, Definition of intellectual content, Literature search, manuscript editing and review

Dr Zoya Qamar: Data acquisition, Data analysis, Manuscript preparation

Conflicts of interest

None of the authors reported any conflict of interest

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Conclusion

Special subtypes of IBC can be morphologically differentiated and molecularly characterized. Metaplastic breast carcinoma, both in pure and mixed forms, along with lobular and mucinous carcinoma, are the subtypes observed during the limited time period of our study. Hence, proper histopathological evaluation and molecular subtyping is of utmost importance for formulation of treatment guidelines for these rare breast carcinomas.

Further research will involve prospective data collection and follow-up of cases to draw more meaningful conclusions.

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