Original Article

DOI: 10.7860/NJLM/2017/24782:2246

Pathology Section

# Immunophenotypic and Morphological Profile of Basal like and non Basal like Invasive Breast Carcinoma

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## ABSTRACT

**Introduction:** Breast carcinomas are heterogeneous disease with different prognosis and therapy responses despite similarities in histological types, grade and stage. Recently, gene expression profiling, a method using cDNA microarray to explore gene expression patterns, has classified breast cancer into 5 distinct subtypes based on variations in gene expression patterns. These 5 subtypes are luminal A and luminal B, normal breast like, Human Epidermal Growth Factor Receptor 2 (HER2) over expressing, and basal-like subtypes. A panel with four antibodies including ER, c-ERB-B2, EGFR and CK5/6 can be used to define Basal-like Breast Carcinoma (BLBC) with 55-76% sensitivity and 100% specificity. BLBCs have been defined as ER-ve, PR-ve, and c-ERB2-ve, CK5/6 and / or EGFR +ve tumours.

**Aim:** To evaluate the expression of cytokeratin 5/6, EGFR, vimentin, ER, PR and Her2/neu in all invasive breast carcinomas. To classify invasive breast carcinomas into basal like and non basal like breast carcinomas according to immunophenotypic pattern and to correlate the immunophenotypic profile of basal like and non basal like with morphological pattern.

**Materials And Methods:** Total 80 cases of invasive breast carcinoma were categorised into basal like and non basal like breast cancer by immunohistochemistry. BLBC was defined as a triple negative tumour with cytokeratin 5/6 and/or EGFR positivity. Morphological patterns of two groups were compared. Statistical analysis was performed using Student's 't'-test for the comparison of mean value by SPSS 20 software.

**Results:** The prevalence of BLBC was 26.3%. Patients with BLBC were younger (p=0.009) and had higher tumour grades (p=0.001). Morphologic features of BLBC include increased mitosis, nuclear pleomorphism, high tubular grade and stromal lymphocytic response. Univariate analysis showed significant association of BLBC with mitosis, tubular grade, nuclear grade, stromal lymphocytic response and histological grade (p=0.001). On multivariate analysis, BLBC were associated with high mitotic number (p=0.003), high tubular grade (p=0.01) and nuclear grade (p=0.01). Vimentin was positive in 76.2% of BLBCs, while cytokeratin was less frequently expressed (38.1%).

**Conclusion:** BLBCs have distinctive morphological features however not pathognomic. Knowing these features and addition of immunohistochemical markers can help to reach the definitive diagnosis of BLBCs.

**Keywords:** Antibody, Histological grade, Invasive ductal carcinoma

## INTRODUCTION

Breast carcinomas are heterogeneous disease having different prognosis and treatment responses despite the similarities in histological types, grade and stage [1]. Recently, gene expression profiling, a method using cDNA microarray to explore gene expression patterns, has classified breast cancer into 5 distinct subtypes based on variations in gene expression patterns. These 5 subtypes are luminal A and luminal B, normal breast like, HER2 over expressing, and basal-like subtypes [2]. These new classifications have provided valuable information on tumour biology which led to a better understanding of signalling pathways governing the process of formation, maintenance and expansion of the tumours.

Over the years, BLBC has become more commonly known as triple-negative (TN) breast cancer because the majority of this molecular subtypes lack expression of Hormone Receptors (HR) and overexpression and/or amplification of HER2. However, not all TN tumours are identified as basal-like by gene expression, and not all basal-like tumours are TN [3]. ER-negative tumours are sub-divided into tumours with gene characteristics of HER2-positive tumours, normal breast tissue and basal epithelial/myoepithelial cells [4]. The gold standard of defining the BLBC is by using Gene Expression Profile (GEP) however due to financial constraints; its use during routine practice is limited. Therefore, Immunohistochemical (IHC)

markers have been used instead of the gene analyses [5-7]. Four antibodies including ER, c-ERB-B2, EGFR and CK5/6 can be used to define BLBC with 55-76% sensitivity and 100% specificity [6,7]. BLBCs have been defined as ER-ve, PR-ve, and c-ERB2-ve, CK5/6 and /or EGFR +ve tumours [5].

## MATERIALS AND METHODS

The present cross-sectional descriptive study was conducted in Department of Pathology and Surgery, PGIMER Dr. RML Hospital, New Delhi, India, for the period of 18 months, starting from November 2013 till May 2015. Study included all trucut biopsies and mastectomy specimens of histologically proven invasive breast carcinomas, received during the study priod. However, benign lesions, non-invasive breast carcinomas and patients who have received pre-operative chemo/radiotherapy were excluded from the study.

The study was conducted after taking patient's consent and ethical approval. Total 58 trucut biopsies and 22 mastectomy specimens of histologically proven invasive breast carcinomas were graded according to the Scarff-Bloom-Richardson system [8]. Immunohistochemistry was performed on all the 80 cases with streptavidin-biotin complex using a panel of antibodies viz. Estrogen Recepor (ER SP1), Progesterone Receptor (PR SP2), human epidermal growth factor receptor 2 (HER2/neu c-erb-2 SP3), epidermal growth factor receptor (EGFR EP3), cytokeratin 5/6 (monoclonal mouse anti-human CK 5/6 clone D5/6 B4) and vimentin. BLBC are grouped according to the criteria by Carey LA et al., [5], and defined as ER, PR, HER2/ neu negative and EGFR and/or CK 5/6 positive tumours. Tumours that did not fulfil the criteria are categorised into non basal like breast carcinoma (NBBC) [5].

After applying IHC with respective antibodies, the intensity and percentage of staining were evaluated. Membranous staining for EGFR and cytoplasmic staining for CK5/6 and vimentin were noted. Tumour cells with no staining were considered as negative.

## STATISTICAL ANALYSIS

Results of statistical analysis was obtained using the SPSS 20 software program. Morphological features, which appear to be predictive for BLBCs, were evaluated by univariate logistic regression analyses followed by multivariate logistic regression analysis to determine the most significant morphological features distinguishing BLBC from NBBC. Statistical significance was defined as a p-value less than 0.05.

## RESULTS

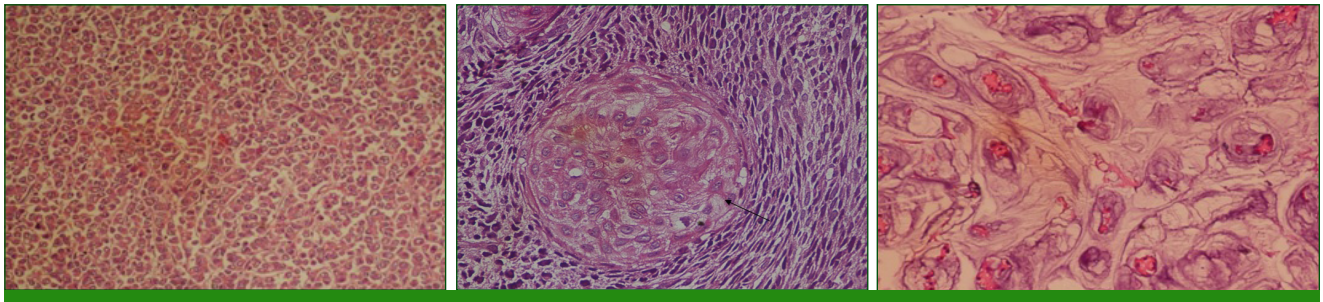
Eighty cases of histologically proven invasive breast carcinoma were included in the study. These included trucut biopsies (n=58) as well as mastectomy specimens (n=22). Histological grade and immunohistochemical correlation of basal like and non basal like invasive breast carcinoma was done. These parameters were also correlated with patient's age and morphological subtypes.

**Age distribution:** Out of 80 cases studied, 5% (4/80) were in the age range of 0 to 30 years, 26.2% (21/80) in the age range of 31 to 40 years, 27.5% (22/80) in the age range of 41 to 50 years, 26.2%(21/80) in the age range of 51 to 60 years and 15%(12/80) in the age range of >60 years [Table/Fig-1].

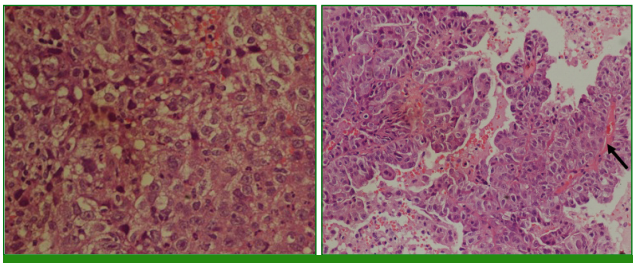
| Age group | | BLBC | Non BLBC | Total |
|---|---|---|---|---|
| <30 years | Case | 1 | 3 | 4 |
| | % | 4.7% | 5.08% | 5% |
| 31-40 years | Case | 7 | 14 | 21 |
| | % | 33.3% | 23.7% | 26.2% |
| 41-50 years | Case | 9 | 13 | 22 |
| | % | 42.8% | 22.03% | 27.5% |
| 51-60 years | Case | 4 | 17 | 21 |
| | % | 19% | 28.81% | 26.25% |
| >60 years | Case | 0 | 12 | 12 |
| | % | 0.0% | 20.3% | 15% |
| Total | Case | 21 | 59 | 80 |
| | % | 100.0% | 100.0% | 100.0% |

**[Table/Fig-1]:** Age group distribution in BLBC and NBBC.

**Percentage distribution based on morphological subtypes:** Out of eighty cases studied, invasive ductal carcinoma constituted 83.8% (67/80) of cases, metaplastic constituted 10% (8/80), mucinous constituted 3.8% (3/80), medullary and papillary breast carcinoma constituted 1.2% each (1/80 each) of cases [Table/Fig-2-6].



**[Table/Fig-2]:** (IDC) Sheets of tumour cells with minimal pleomorphism. **[Table/Fig-3]:** Metaplastic carcinoma: Cells with hyperchromatic oval nuclei and a malignant squamous island (arrow). **[Table/Fig-4]:** Mucinous carcinoma: Mucin filled tumour cells in pool of mucin.



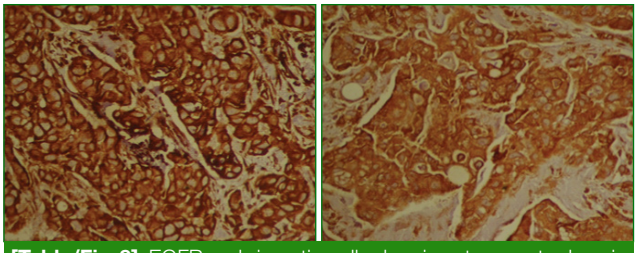
**[Table/Fig-5]:** Medullary carcinoma: Indistinct cell borders, prominent nucleoli with inflammatory infiltrate.
**[Table/Fig-6]:** Papillary carcinoma: papillary fronds with vascular core (arrow shows fibrovascular core)

**Percentage distribution on histological grade:** Of the 80 cases studied, 42.5% (34) cases are histological Grade 1, 45%(36) Grade 2 and 12.5% (10) Grade 3 [Table/Fig-7].

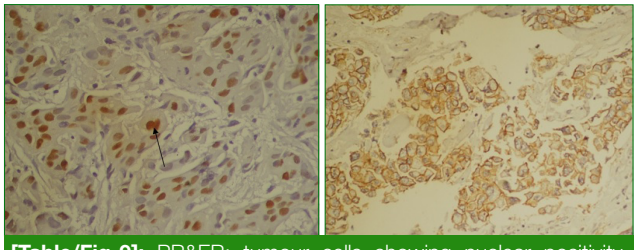
**Immunohistochemical parameters:** ER, PR and HER2/neu were negative and EGFR positive in all BLBC cases as per the definition. Vimentin was positive in 76.2% of BLBCs, while CK 5/6 was less frequently expressed (38.1%) [Table/Fig-8-11].

| Grade | | BLBC | NBBC | Total |
|---|---|---|---|---|
| 1 | Case | 0 | 34 | 34 |
| | % | 0.0% | 57.6% | 42.5% |
| 2 | Case | 13 | 23 | 36 |
| | % | 61.9% | 39% | 45% |
| 3 | Case | 8 | 2 | 10 |
| | % | 38.1% | 3.4% | 12.5% |
| Total | Case | 21 | 59 | 80 |
| | % | 100.0% | 100.0% | 100.0% |

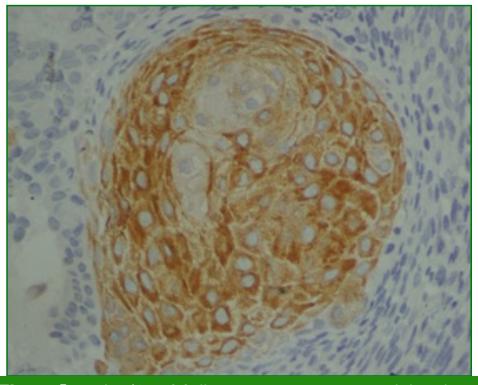
**[Table/Fig-7]:** Histological grades of BLBC and NBBC.



**[Table/Fig-8]:** EGFR and vimentin:cells showing strong cytoplasmic and membranous positivity.



**[Table/Fig-9]:** PR&ER: tumour cells showing nuclear positivity.
**[Table/Fig-10]:** HER2/neu: Cells with moderate membranous positivity.



**[Table/Fig-11]:** ck5/6: Malignant squamous island showing membranous and cytoplasmic positivity.

**Triple negative cases in all invasive breast carcinoma:** Out of 29 (36.2%) triple negative cases amongst the 80 total cases, 21 cases belong to basal subtype and 8 cases were NBBC.

**Mean age distribution among basal and non basal like invasive carcinoma:** Patients with BLBC were younger with mean age of 42.85 years than patients with non basal like invasive breast carcinoma with mean age of 50.62 years which was statistically significant (p=0.009).

**Percentage distribution of basal like and non basal like invasive carcinoma:** Out of eighty cases included basal like invasive breast carcinoma constituted 26.3% (21/80) of cases and non basal like invasive breast carcinoma constituted 73.6% (59/80) of cases.

**Histological grades of BLBC and NBBC:** Of the 21 BLBC cases, 61.9% (13) belong to Grade 2 and 38.1% (8) Grade 3.

| Parameters | Grades | BLBC | NBBC | p-value |
|---|---|---|---|---|
| Mitosis | 1 (0-7/10hpf) | 1 | 42 | <0.001 |
| | 2 (8-14/10hpf) | 15 | 17 | |
| | 3 (>15/10hpf) | 5 | 0 | |
| Tubule Formation | 1 (>75%) | 0 | 4 | 0.005 |
| | 2 (10-75%) | 8 | 41 | |
| | 3 (<10%) | 13 | 14 | |
| Nuclear Grading | 1 (mild) | 0 | 7 | <0.001 |
| | 2 (moderate) | 10 | 48 | |
| | 3 (marked) | 11 | 4 | |
| Stromal Lymphocytic Response | 1 (none) | 1 | 35 | <0.001 |
| | 2 (mild) | 8 | 19 | |
| | 3 (moderate) | 10 | 5 | |
| | 4 (marked) | 2 | 0 | |
| Geographic Necrosis | Absent | 1 | 17 | 0.019 |
| | Present | 2 | 2 | |
| Central Necrosis | Absent | 0 | 16 | 0.002 |
| | Present | 3 | 3 | |

**[Table/Fig-12]:** Distribution of grades in BLBC and NBBC.

And of the 59 NBBC cases, 57.6% (34) belong to Grade 1, 39% (23) Grade 2 and 3.4% (2) Grade [Table/Fig-7].

**Morphological parameters:** There is higher grade of mitosis (p<0.001), less tubule formation (p=0.005), high nuclear grade (p<0.001), increased stromal response (p<0.001), geographic necrosis (p=0.019) and central necrosis (p=0.002) in BLBC as compared to the NBBC [Table/Fig-12].

Factors significantly associated with BLBCs on univariate and multivariate analysis are shown in [Table/Fig-13,14].

Of all the individual parameters included in this study nuclear grade, tubular grade and mitosis were able to predict BLBCs.

| Parameters | Odd's Ratio | Wald | p-value |
|---|---|---|---|
| Mitosis | 0.023 | 13.097 | <0.001 |
| Tubule Grade | 0.197 | 9.548 | 0.002 |
| Nuclear Grade | 0.071 | 15.926 | <0.001 |
| Histological Grade | 0.058 | 15.009 | <0.001 |
| Stromal Lymphocytic Response | 0.133 | 18.642 | <0.001 |

**[Table/Fig-13]:** Univariate analysis

| Parameters | Odd's Ratio | 95% CI | Wald | p-value |
|---|---|---|---|---|
| Nuclear Grade | 0.022 | 0.001-.482 | 5.876 | 0.015 |
| Tubule Grade | 0.018 | 0.001-.390 | 6.540 | 0.011 |
| Mitosis | 0.006 | 0.000-.166 | 8.988 | 0.003 |

**[Table/Fig-14]:** Multivariate analysis

## DISCUSSION

Breast carcinoma is the leading cause of carcinoma death among women worldwide [1]. Breast carcinomas are heterogeneous with variable prognosis and therapy responses despite similarities in histological types, grade and stage. Based on gene expression patterns they have been classified into 5 molecular subtypes; luminal A and luminal B, normal breast like, HER2 over expressing and basal-like subtypes [5]. These molecular classes correlate with prognosis and response to therapy and thus have taken on clinical importance.

The basal like subgroup constitute approximately 10-15% of invasive breast cancers [9]. This subgroup occurs frequently in younger patients and are associated with larger tumour size, high histological grade with high mitotic rate and nuclear/cytoplasmic ratio, presence of spindle or squamous metaplasia, pushing growth pattern, central acellular areas of hyalinization or necrosis and lymphocytic infiltrate and hence poorer prognosis in comparison with the other subtypes [4,5,10]. In this study, there was significant correlation between BLBC and NBBC under following parameters: morphological subtypes, histological grade like increased mitosis, less tubule formation, high nuclear grade, increased stromal response and age of the patient.

In the present study, the mean age at diagnosis of basal like invasive breast carcinoma was 42.85 years (age range,30-60 years) and that of non basal like invasive breast carcinoma 50.62 years (age range, 25-90 years) which is lower as compared to the study by Cakir A et al., [9] where the mean age of basal like invasive breast carcinoma was 49.3 years (age range,19-78 years) and that of non basal like invasive breast carcinoma was 53.3 years, (age range, 28-86 years). So basal like invasive breast carcinoma was observed in much younger age as compared to non basal like invasive breast carcinoma (p=0.02).

Prat A et al., [11] showed that mean age at diagnosis of BLBCs was significantly lower than the rest of subtypes (50.8 years vs. 55.0 years; p< .0001, normal-like tumours excluded).

Anders CK et al., [12] evaluated that tumours diagnosed at younger age to be more aggressive and/or less responsive to treatment.

**Basal-like invasive breast carcinoma versus triple negative breast carcinoma:** In this study, out of 29 (36.25%) triple negative cases amongst the 80 total cases, 21(72.41%) cases turned out to be basal like and 8(27.58%) non basal subtype. BLBC cases constituted 26.3% of the total 80 cases.

Cakir A et al., study showed 79.7% of triple negative carcinomas are basal like [9]. Studies in literature showed approximately 71-85% of TN to have basal like phenotype which is in concordance with the present study i.e., 77.3% [7,13-15].

Bertucci F et al., evaluated 172 cases of triple negative cancers, out of which 123 (71%) were basal and 49 (29%) were non basal [13].

The finding in our study that all triple negative breast cancers are not basal like breast cancers and vice versa is well supported by the literature [7,13,16]. However, not all basal-like cancers determined by gene expression profiling lack ER, PR and HER2 and conversely not all triple-negative cancers show a basal-like phenotype by gene expression array analysis [13,17].

**Histological grade:** Of the total 80 cases, 21 cases were of BLBC subtype and 59 cases were of NBBC type. 8 of 21 BLBC cases showed histological Grade 3 and rest 13 cases showed histological grade 2 as compared to most NBBC cases showing Grade 1(34/59), Grade 2(23/59) and Grade 3(2/59). All of BLBC cases showed stromal lymphocytic response with majority showing moderate to marked stromal response (59.1%). However, all of the grading factors included in this study were statistically determinant for BLBC (p=0.001), thereby favouring that BLBCs are more solid, high grade tumours with higher mitotic count, pleomorphic atypical nuclei and marked stromal lymphocytic response. In the present study BLBCs had more mitotic figures (p=0.001), more solid architecture with less tubule formation (p=0.005), higher nuclear grade (p<0.001), more stromal lymphocytic response (p<0.001), than NBBCs. Geographic necrosis (p=0.019) and central necrosis (p=0.002) were performed on the 22 mastectomy specimens.

Amongst these features, on multivariate analyses the most important factors were mitosis (p=0.003), nuclear grade

(p=0.015) and tubular grade (p=0.011). However, correlation of pushing borders was not done due to presence of single medullary carcinoma case.

Fulford LG et al., also performed multivariate analyses and reported that presence of squamous metaplasia, central scar, tumour necrosis, high mitotic count and absence of prominent cytoplasm were strongly associated with BLBC [18].

**Morphological suptypes:** The present study showed 21 cases of BLBCs contributed mainly by the invasive ductal carcinoma NOS occupying major share of 57.1% (12/67 cases) and the others by metaplastic 33.3% (7/8), medullary 4.8% (1/1) and papillary 4.8% (1/1). The other morphological subtypes like mucinous and majority of invasive ductal carcinoma NOS constituted the NBBCs.

Invasive ductal carcinoma was the most frequent histological subtype identified for the BLBCs in this study (57.1%), which is in accordance with literature [5,19,20].

Kim MJ et al., demonstrated that 75.0% metaplastic carcinomas (6/8 cases) were the basal-like subtype [19].

**Immunohistochemical patterns:** As per definition criteria by Carey LA et al., [5], we defined BLBC as ER, PR, c-ERB-B2 negative and CK5/6 and/or EGFR positive tumours. So all basal like tumours were triple negative (ER, PR and HER2/neu) and all showed EGFR and/or CK5/6 positivity.

In this study, EGFR was positive in 95.2% of the BLBCs and 33.9% positivity in NBBC with significant correlation (p=0.001). Several studies showed association between EGFR expression and basal-like phenotype [6,7].

Livasy CA et al., study showed (13/18, 72%) significant EGFR expression in BLBC as compared to luminal tumours (0/23 0%), p<0.0001 and thus concluded that EGFR expression is seen exclusively in basal-like phenotype [6].

CK 5/6 was positive in 8 cases (38.1%) of the 21 BLBCs and significantly associated with BLBCs (p=0.001) in this study which is in accordance with study by Livasy CA et al., [6] and other studies in the literature [9,20,21]. They showed that CK 5/6 is not expressed in all basal-like tumours classified by gene microarray analysis.

In this study vimentin was positive in 76.2% (16/21) of BLBCs and 28.8% of NBBCs which showed significant association with BLBCs (p=0.001). In study by Laakso M et al., more than 90% of basal-like carcinomas were found to have strong and diffuse vimentin expression [22].

Domagala W et al., suggested that vimentin expression in breast carcinoma may have association with poor prognosis, hormone receptor negativity and co-expression of EGFR, which are consistent features for basal-like carcinomas [23].

## LIMITATION

Classification into luminal subtypes was due as a lack of gene expression profiling in our institute. Longer duration of studies would have included more cases and update the follow-up of patients.

## CONCLUSION

There is a statistically significant correlation between younger age group, higher histological grade and BLBCs. Significant correlation was also seen with morphological subtypes and BLBCs. Follow-up and further long term studies with larger sample size are required to establish the role of immunohistochemistry in the prognosis and overall survival of patients with BLBC.

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**FINANCIAL OR OTHER COMPETING INTERESTS:** None.

Date of Publishing: **Oct 01, 2017**