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Clinicopathologic study of triple-negative breast cancer with special reference to basal-like breast cancer phenotype in a tertiary care hospital of Eastern India

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ABSTRACT

Background: Triple-negative breast cancer (TNBC) is defined as absent expression of estrogen receptor (ER) and progesterone receptors and human epidermal growth factor receptors (HER2neu). These cancers are associated with poor prognosis. **Aims and Objectives:** We aimed at to study the clinicopathological profile and survival among women with TNBC. **Materials and Methods:** The study was conducted over a period of 4 years. Surgical specimens of patients with breast cancer were analyzed histopathologically as well as immunohistochemical analysis for estrogen, progesterone, HER2neu, and Ki-67 index was also done. Statistical analysis was done using software version 20.0. Results were expressed in number and percentage. Comparison was done by x^2 test. $P = 0.05$ was considered statistically significant. **Results:** In our study, 26.92% cases were of TNBC. Predominant age group affected was between 50 and 70 years. Most common histologic type was invasive carcinoma of no special type with higher grade (Grades 2 and 3) mostly with frequent nodal metastasis. Higher percentage of Ki-67 proliferation index and basal cytokeratin expression were associated with higher tumor grade and stage along with reduced short-term disease-free survival on follow-up. **Conclusion:** TNBCs are usually of higher grade with frequent recurrences and distant metastasis. There are no widely accepted prognostic markers available. Panel of immunohistochemical markers should be used specially to categorize the basal-like breast cancer subtype among TNBCs for better clinical outcome.

Key words: Basal-like breast cancer; Cytokeratin 5/6; Ki-67 proliferation index; Triple negative

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INTRODUCTION

Breast cancer is a heterogeneous group of disease. According to GLOBOCAN 2020, female breast cancer is the most common cancer (11.7%) surpassing the lung cancer.[1] Based on the clinical, morphological, and biological characteristics, it is divided into various groups. Among these groups, triple-negative breast cancer (TNBC) is a group in which there is tremendous increase in the research in recent times.

Triple-negative breast cancer is defined by low or absent expression of receptors for estrogen receptor (ER) and progesterone receptor, without overexpression of the human epidermal growth factor (EGF) receptor-2 (HER-2).[2] There is higher prevalence of TNBC reported among South Asian women (18.6–46%).[3,4] TNBC has more aggressive clinical behavior,[5,6] distinctive metastatic patterns,[7] and poor prognosis.[8] Different studies have shown that TNBC has worse short-term survival and associated with distinct clinicopathological features

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including younger age, post-menopausal status, larger tumor size, aggressive morphological features, necrosis, and lymph node metastasis.[9,10] Among the different subtypes of breast cancer, basal-like breast carcinoma (BLBC) is a subtype of breast carcinoma which expresses genes usually found in basal/myoepithelial cells of the normal breast.[11]

Although there is a distinct relationship between TNBC and BLBC, both are not synonymous; because not all BLBCs are triple negative and not all TNBCs show a basal phenotype.[11]

However, in comparison to non-basal subtypes, the TNBCs who express basal markers form clinically distinct subtype that has a poorer prognosis and different chemotherapeutic response.[12] With the advent of tissue microarray, gene expression profiling remains the gold standard for identification of the basal subtype. Still then, IHC is a more feasible method and convenient technique in the clinical setting in the view of cost and equipment availability issues of gene profiling in routine service laboratories.

Our objective was to study the clinicopathological characteristics of TNBC with special reference to basal-like sub type. Along with this, we have discussed novel prognostic markers in TNBC in brief.

Aims and objectives

We aimed at to study the clinicopathological profile and survival among women with Triple-negative breast cancer (TNBC).

MATERIALS AND METHODS

Duration and place of study

The study was conducted over a period of 4 years (including the follow-up period) in a tertiary care of eastern India, from December 2018 to December 2022.

Patient selection

Patients after provisional clinical diagnosis of breast cancer underwent trucut biopsy followed by modified radical mastectomy or breast conservative surgeries (as applicable for the case).

Inclusion criteria

All patients having a histopathological diagnosis of invasive epithelial tumors were included in the study.

Exclusion criteria

i. Cases who had the diagnosis of non-epithelial tumors, only ductal carcinoma *in situ* component or only microinvasive carcinoma were excluded from the study
ii. Poorly preserved specimens (for any reason) that might hamper the subsequent immunohistochemical analysis were also excluded.

Clinical data

All the clinical data such as age, parity, history of breast feeding, menopausal status, family history of breast carcinoma, and follow-up details were collected from the clinical records.

Specimen handling

a. After receiving the specimens, fixation followed by grossing of the specimen done using standard protocol,[13] tumor size and lymph node status noted, and TNM staging done according to AJCC 8th edition[14]
b. Tissue processing done and hematoxylin and eosin-stained slides were prepared for routine microscopic examination.

Histopathological parameters

Studied as follows:

i. Tumor typing done according to the WHO classification 4th series (2012).[15]

Epithelial tumors

- Microinvasive carcinoma
- Invasive breast carcinoma of no special type (NST)
  - Pleomorphic carcinoma
  - Carcinoma with osteoclast-like giant cell
  - Carcinoma with choriocarcinomatous features
  - Carcinoma with melanotic features
- Invasive lobular carcinoma
- Tubular carcinoma
- Cribriform carcinoma
- Mucinous carcinoma
- Carcinoma with medullary features
- Carcinoma with apocrine differentiation
- Invasive micropapillary carcinoma
- Metaplastic carcinoma of NST

Rare types

- Carcinoma with neuroendocrine features
- Secretory carcinoma
- Invasive papillary carcinoma

ii. Tumor grade determined by Modified Bloom-Richardson grading system basing on Nottingham's scores.[16] Tubule formation is given score 1 if it is more than 75% and it is 3 if tubule formation is <10%. Score 2 awarded if it is 10–75%. Nuclear pleomorphism is scored 1, 2, and 3 for mild, moderate, and severe variation, respectively. Mitotic count (per 10 high power field) is scored 1, 2, and 3 if it is 0–9, 10–19, and more or equal to 20. Total score for three above-

mentioned features is added and if score is 3–5, it is Grade 1. If score is 6–7, it is Grade 2, and Grade 3 if score is 8–9.

iii. Presence of necrosis, *in situ* component, calcification, lymphovascular invasion, and tumor-infiltrating lymphocytes were also noted. The presence of necrosis was categorized as focal, <50% (moderate), or >50% (extensive). TILs were categorized as absent, mild, moderate, and severe.

IHC analysis

In each case, one representative section from the tumor was taken for the immunohistochemical staining for ER, PR, HER2neu, Ki-67, and CK 5/6. The IHC testing was done by Dako EnVision method.

The results for ER and PR interpretated and scored in a semiquantitative fashion basing on the intensity (0–3) and percentages (0–5) of the cells stained.

Intensity scoring:

0 - negative, 1 - weak, 2 - intense, 3 - strong

Percentage scoring:

0 - no cells show nuclear positivity

1 - (<1%), 2 - (1–10%), 3 - (11–33%), 4 - (34–66%), 5 - (67–100%) cells show nuclear positivity.

Allred score interpretated as 0–1 - no effect, 2–3 - small (20%) effect, 4–6 - moderate (50%), and 7–8 - good (75%) effect.

The Allred scoring system was used where the expression limit is 10% of weakly or 1% of medium-stained cancer cell nuclei.[17]

HER2neu was scored based on the intensity and percentage of positive cells from a score of 0 to 3+, 0 (negative) - no staining or membrane staining in <10% of the tumor cells. 1+ - (negative) - faint/barely perceptive membrane staining in >10% of tumor cells. 2+ - (weak positive or equivocal) - weak to moderate complete nuclear stain of >10% cells, and 3+ - (positive) - strong complete nuclear stain >30% of cells.

In cases of equivocal or weak-positive cases, FISH was done to know HER2neu receptor status.

For Ki-67 immunostaining, the interpretation was done basing on the proportion of positive tumor cells (0–100%) and reported as high Ki-67 (immunostaining ≥g 30%), low (immunostaining <15%), and intermediate (between 16 and 30%) according to St Gallen International Expert Consensus.[18,19]

Ethical clearance

The study was approved by the Institutional Ethics committee.

Statistical analysis

Statistical analysis was done using software version 20.0. Results were expressed in number and percentage. Comparison was done by x^2 test. P=0.05 was considered as statistically significant.

RESULTS

In our study, of the total 234 of breast cancers, 63 cases were triple negative. (ER, PR, and HER2neu negative) (Figure 1). Among these, 63 cases of TNBC most commonly affected age group were 51–70 years (31/63) (Table 1). The most common histologic type detected was invasive carcinoma of NST (56, 88.88%) (Table 2 and Figure 2) with higher histological grade (Grade 3) in 39 cases (61.90%). Histological Grade 2 was found in 7 cases (11.11%) and Grade 2 was found in 17 cases (26.98%) (Figure 3). Necrosis is seen in 47 cases (74.6%). Tumor-infiltrating lymphocytes are seen in 27 cases (42.85%) (Figure 2). Out of 63 cases, high Ki 67 proliferation index is seen in 36 cases, intermediate in 18 cases, and low in 9 cases (Figure 4). Basal cytokeratin CK 5/6 expressed in 13 cases. Clinicopathological parameters were correlated with Ki 67 index and basal cytokeratin expression (Table 3).

DISCUSSION

Breast cancer encompasses numerous distinct histologic and molecular subtypes among which TNBC is an aggressive subtype. One distinctive feature of TNBC is that it has overlapping features with that of basal-like breast

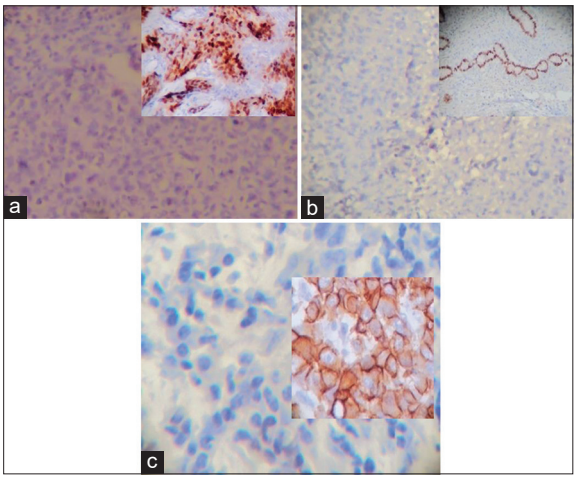

Figure 1: (a) ER-negative breast cancer and control (inset), ×100, (b) PR-negative breast cancer and control (inset), ×100 and (c) HER 2 neu-negative breast cancer, control (inset), ×400

Table 1: Clinical presentation of patients diagnosed with triple-negative breast cancer (n=63)

Parameters	Number	Percentage
1. Mean (±SD) age at diagnosis=45.3±13.2		
2. Age-specific groups		
<30 years	3	4.76
31–40 years	9	14.28
41–50 years	13	20.63
51–60 years	14	22.22
61–70 years	17	26.98
>70 years	7	11.11
3. Tumor size		
≤2 cm (pT1)	07	11.11
2–5 cm (pT2)	20	31.74
>5 cm (pT3)	31	49.20
pT4	05	7.93
4. Tumor presentation		
Unifocal	46	73.01
Multifocal	17	26.98
Presence of satellite nodule	9	14.28
Skin ulcerations, peau d'orange	11	17.46

Table 2: Histopathological features of triple-negative breast cancer (n=63)

Parameters	Number	Percentage
a) Histologic type		
IC-NST	56	88.88
ILC	1	1.58
Mixed ducal and lobular carcinoma	3	4.76
Metaplastic carcinoma	2	3.17
Invasive papillary carcinoma	1	1.58
b) Histological grade (basing on Nottingham's score)		
i) Grade 1	7	11.11
ii) Grade 2	17	26.98
iii) Grade 3	39	61.90
c) Tumor-infiltrating lymphocytes		
i) Present	36	57.14
ii) Absent	27	42.85
d) LVI		
i) Present	25	39.68
ii) Not seen	38	60.31
e) Necrosis		
i) Present	47	74.6
ii) Not seen	16	25.39
f) Lymph node status		
Negative LN	7	11.11
1–3+ve LN	17	26.98
4–9+ve LN	36	57.14
≥10+ve LN	3	4.76

cancers due to the manifestation of basal-like markers such as basal cytokeratin (CK 5/6, CK14, CK17, 34ßE12) and EGFR. According to the study by Foulkes et al., TNBC s have ~80% concordance with basal-like breast cancer.[20] According to the TNBC type 4 classification, it has 4 distinct subtypes, i.e., basal like-1, basal-2, mesenchymal, and luminal androgen receptor like.[21] TNBC has distinct pathological features along with various risk factors associated with it. Most of the population studies have shown the incidence of TNBC between 10 and 16%.[3,22] In

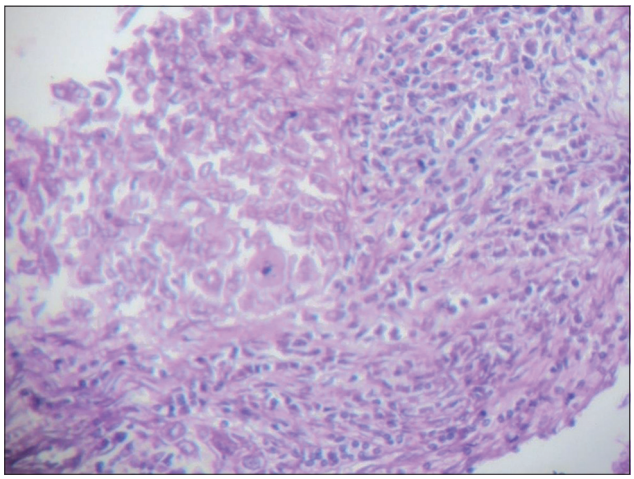

Figure 2: Invasive carcinoma breast no special type with pushing margins and tumor-infiltrating lymphocytes (H and E, ×100)

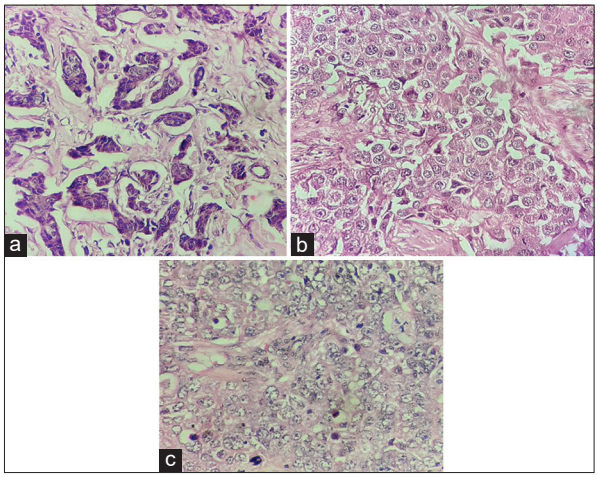

Figure 3: (a) Features of Grade 1 invasive breast carcinoma of no special type (NST) (H and E, ×400). (b) Features of Grade 2 invasive breast carcinoma of no special type (NST) (H and E, ×400). (c) Features of Grade 3 invasive breast carcinoma of no special type (NST) (H and E, ×400)

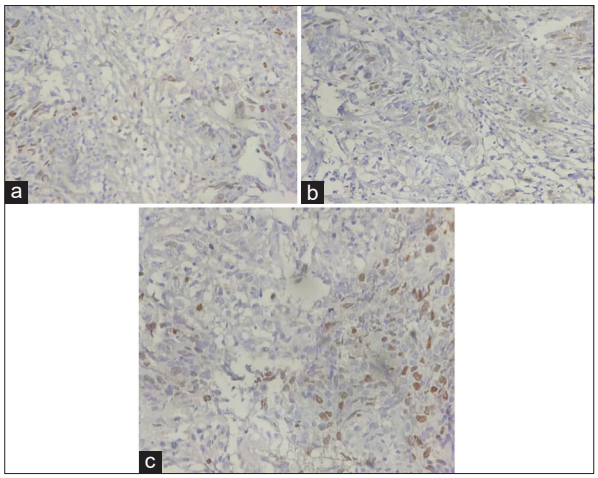

Figure 4: Ki 67 proliferation index in triple-negative breast cancer - low (a) (×100), intermediate (b) (×100), and high (c) (×100)

Table 3: Correlation of Ki-67 index, CK 5/6 expression with tumor size, tumor grade (n=63)

Parameters	Tumor size (number of cases)			P-value
Ki 67 index				
	T1	T2	T3	
Low	5	3	1	<0.001
Intermediate	1	9	8	<0.001
High	1	13	22	<0.001
CK 5/6				
Positive (n=13)	1	2	10	<0.001
Negative (n=50)	19	11	13	<0.001
Parameters	**Grade 1 tumor**	**Grade 2 tumor**	**Grade 3 tumor**	**P-value**
Ki 67 index				
Low	5	4	3	<0.001
Intermediate	1	9	7	<0.001
High	1	4	29	<0.001
CK5/6				
Positive	2	3	8	<0.001
Negative	29	12	9	<0.001

our study, TNBC accounts for 26.92% of the total breast carcinomas. This was similar to the study by Wijesinghe et al.[23] According to the study by Japanese Breast cancer society,[24] TNBCs were diagnosed at more advanced stage with frequent nodal metastasis. In our study, majority of the cases were diagnosed between 50 and 70 years of age with clinical Stage III and multiple nodal metastases at the time of diagnosis. This was similar to the Japanese study but according to Korean study[25] and study by Reis-Filho and Tutt,[22] the majority of TNBCs were diagnosed at younger age (<50 years). TNBC subtypes (basal-like subtypes) are associated with distinctive risk factors such as age, race, ethnicity, reproductive and parity history, breast feeding, and obesity. According to Trivers et al.,[19] TNBCs were associated with black race, young age at first birth, history of recent birth, and obesity. According to Carcinoma Breast cancer study, increased parity, younger age at first term full-term pregnancy, longer duration of breast feeding, and increasing number of children breastfed are associated with an overall decrease in the risk of basal-like breast cancer. In our study, the exact clinical data regarding the duration of breast feeding were not available. According to various studies, it has been seen that TNBC is associated with poorly differentiated high-grade and high-stage tumors.[3,8] In our study, out of 63 cases of TNBC, 39 cases were of Grade 3 and 17 cases were of Grade 2 tumors. Cases were of higher TNM stage. In our study, most of the TNBC were associated with high Nottingham's score (high nuclear grade, increased mitotic count, and absence of tubule formation). There was presence of severe necrosis, pushing tumor margins, and dense lymphoid infiltration also seen (Figure 1). This was similar to the study by Wijesinghe et al.[23] and Schmadek et al. Some of the rare subtypes such as papillary carcinoma and metaplastic carcinomas also seen having ER, PR, and HER2neu-negative immunohistochemistry which imply that triple negativity can occur in all histological subtypes. In our study, majority of the cases of TNBC showed aggressive phenotype, i.e., larger tumor size >5 cm (PT3) with frequent nodal metastasis (Table 1). Histologically higher nuclear grade, necrosis, and tumor-infiltrating lymphocytes are also seen in majority of the cases. This was similar to the study by Thike et al.,[10] but in contrast to the study by Dent et al.,[26] who showed no relationship between tumor size of TNBC and nodal metastasis. Immunohistochemical analysis of the surrogate markers showed high Ki-67 proliferation index in 36 cases and basal cytokeratin (CK 5/6) expression is seen in 13 cases. According to some study, BLBC identified by immunohistochemical markers is associated with young age and higher grade tumors. In our study, both these markers, i.e., high Ki 67 proliferation index and basal cytokeratin expression were associated with higher tumor size and grade (Table 3). This was similar to the study by Chen et al. There is a long-debated discussion on the relationship between basal-like breast cancer and TNBC. To define basal-like cancer, Nielsen et al.[6] proposed using negative ER and cerbB2 with a positive expression of CK5/6 and EGFR with 100% specificity and 76% sensitivity. It has been found that 15–45% of basal-like cancer is triple negative and 56–84% of TNBC express basal cytokeratins.[22] According to Liu et al., patients with TNBC who express basal cytokeratin CK 5/6 or CK 17 had significantly shorter disease-free survival and overall survival than those devoid of basal cytokeratins. In our study, on follow-up, it has been seen that TNBC has worse short-term survival with increased rate of recurrence/metastasis in comparison to other subtypes. Although there is a continuous research and progress in the management of TNBC patients, it still poses a great challenge. Hence, understanding of their relationship with basal-like cancer might provide potential new therapeutic targets for better patient management.

Limitations of the study

In our study, there was limited sample size and shorter duration of follow-up.

CONCLUSION

In our study, the percentage of TNBC was higher (26.92%) than most of the other populational studies. Technical errors leading to false IHC negativity might be one reason for this higher percentage. Basal-like breast cancer (BLBC) subtype among TNBC accounts for 20.63% basing on the immunohistochemical analysis. TNBC typically presents with higher grade and higher stage and has a significant overlap in their histological and clinical characteristics among the molecular subtypes.

Despite of high histological grade, TNBC tumors have limited therapeutic options than the other breast cancer subtypes. They typically treated with chemotherapy with frequent relapses and distant metastasis. Hence, to the development of new prognostic indicators to complement the basal markers and to enhance the spectrum of therapeutic targets, more therapeutic options are extremely valuable for better patient management and clinical outcome.

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Authors Contribution:
RP- Concept, design, data collection, result analysis, and first draft of manuscript; **SM**- Design, result analysis and interpretation, and review of literature; **MS**- Concept, coordination, and review of literature; **SC**- Coordination, review of literature, preparation, and final revision of manuscript.

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