

Invasive lobular triple negative carcinoma of breast: A clinico-pathological study done in south eastern part of India

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Abstract

Background: Triple Negative Breast Carcinomas (TNBC) are breast carcinomas which are negative for Estrogen receptor (ER) Progesterone receptor (PR) and no overexpression of Human Epidermal Growth Factor receptor-2 (HER-2). The five-year survival rate for breast carcinomas in general is good but the same is bad for TNBC. TNBC has got worse prognosis compared to hormone positive breast carcinomas.

Aim: The aim of present study is to compare invasive lobular TNBC with invasive ductal TNBC with morphologic, immunohistochemical and prognostic parameters.

Materials and Methods: One-year study was done at Tertiary Care Centre. Patients of all ages were included. Most of them were in 4th and 5th decade. Mammography, FNAC and Biopsy was done. Formalin-fixed mastectomy specimens received at MGM hospital are screened, diagnosed histopathologically for carcinoma of breast over a period of one year. Immunohistochemistry (IHC) was performed to diagnose TNBC.

Results: Total no of cases – 72. No of Cases with positive ER, PR and or Her 2/neu are – 61. No of Cases with ER, PR and Her 2/neu negative (Triple negative) – 11 Percentage of Triple negative cases – 15 %. Most of the TNBCs show high grade and high mitotic count 74% and 82% respectively. Other hand, some cases 60% showed only ER and PR positivity without Her-2 and 25% showed only Her-2 positivity without ER and PR. Invasive lobular TNBC subtype is reported in 18%.

Conclusion: Overall TNBCs are high grade aggressive tumors and are more common in younger age groups. Whereas TNBCs associated with invasive lobular carcinoma are more common in 5th decade and were more aggressive compared to other subtypes.

Keywords: Invasive lobular carcinoma; Triple Negative Breast Carcinoma (TNBC); ER; PR; Her 2/ neu

1. Introduction

Breast cancers are the second leading cause of death. Invasive ductal carcinoma is the most common type followed by invasive lobular carcinoma which represents 5–15% of all breast cancers. ^[1]

Invasive lobular carcinoma (ILC) which represents 5–15% of all breast cancers is the second most common type of carcinoma of breast. ^[1] Microscopic examination of invasive lobular carcinoma shows cellular pleomorphic tumor with proliferation of non-cohesive small cells individually dispersed in fibrous connective tissue or organized in single-file

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(Indian file arrangement) linear cords invading the stroma. Its pleomorphic counterpart is a rare aggressive variant with more nuclear atypia and pleomorphism. [4] Most of the ILC express receptors for estrogen and progesterone (hormone receptor-positive tumors, HR+), while HER2 amplification/overexpression is rare. [1,5].

Triple Negative Breast carcinomas(TNBC) are breast carcinomas which are negative for Estrogen receptor (ER) Progesterone receptor (PR) and no overexpression of Human Epidermal Growth Factor receptor -2 (HER-2). These account for 10 -17% of all breast cancers. [6] They are frequently seen in younger patients and in tumors which show BRCA mutations. TNBC has got worse prognosis compared to hormone positive breast carcinomas. Aggressive behavior and Lack of effective targeted therapies are mainly responsible for this bad prognosis. Recurrence and mortality within 3 to 5 years after diagnosis is very common in TNBC patients. [7] TNBCs are seen in Invasive ductal carcinoma, Lobular carcinoma and medullary carcinomas.

There are lot of studies on TNBCs and most of them focused on invasive ductal carcinoma. Only little study is done for triple negative invasive lobular carcinoma (TN-ILC) which is rare and much ignored. Although some studies have reported the existence of rare TN-ILCs expressing basal cytokeratin. [8,9] but still data is insufficient for TN-ILC. [10-13]

The TNM staging system is an important prognostic indicator which is determined by three parameters viz tumor size, lymph node metastasis, and distant metastasis. In addition, other features such as necrosis and Ki-67 index are also associated with high mortality. [14] The association between tumor stage and the prognosis in different subtypes of TNBC is still yet not explored clearly. To bridge this knowledge gap, the present study was aimed to compare invasive lobular TNBC with invasive ductal carcinoma using morphologic, immunohistochemical and prognostic parameters.

2. Material and methods

2.1. Patients

One-year study was done at MGM hospital/Kakatiya Medical College, Warangal, Telangana, India. Patients of all ages were included in the study. After taking consent, each patient was examined clinically and patients with breast lump were investigated further.

2.2. Histo-Pathological examination

After the clinical examination, the patients were sent for mammography, FNAC and biopsy was performed. Formalin-fixed modified radical mastectomy specimens obtained from MGM hospital and those cases which are positive for carcinoma breast are subjected to Immunohistochemistry for triple biomarkers (ER, PR, and Her-2). Each section was reviewed by two pathologists independently and Cancer staging, type, histological features, and nuclear degree were sorted according to the standard manuals in criteria of the Cancer diagnosis. [15]

2.3. Immunohistochemistry (IHC)

The expression of triple biomarkers ER, PR and HER2 were investigated with the previously described avidin-biotin complex immunohistochemical method. [16] After surgery specimens are submitted for IHC staining with 5 mm thickness tissue slices fixed in 10% formalin fixation followed by xylene-deparaffinization, paraffin-embedded tissue sections and rehydrated with ethanol followed by immersion in Tris-buffered saline. 4µm tissue sections were made. Primary antibodies for HER2 (clone 1D5, New Castle-Upon-Tyne, UK), ER and PR (PgR6361, clone CB11, Carpinteria, CA, USA) were used as mouse monoclonal antibodies. The dilution was done as per the product protocol such as 1:50 for ER, and PR and 1:200 for HER2. Biotinylated anti-mouse antibody as secondary antibody and a horseradish peroxidase conjugated with streptavidin (Zymed Laboratories, San Francisco, CA) were used in this study as per manufacturer instructions. Presence of 10% or more positively stained nuclei under the 10X microscopic power field was defined as ER and PR positive. Whereas, the 0, 1+, 2+ or 3+ tumor scores were defined as per the HER2 membrane stain intensity. If the tumor was score 3+, classified as HER Positive, score 0 or 1+ falls under HER2 negative and score 2+ was defined as an undetermined tumor. [16]

3. Results

During this one-year period, about 72 cases of breast carcinoma cases were enrolled in this study. Out of these 72cases, 61 cases (84.7%) were positive for triple markers i.e. ER, PR, and Her-2 whereas in 11 cases (15.27%) ER, PR, and Her-2 were negative. The percentage of Triple negative carcinoma of the breast (TNBC) was 15%. Our results showed TNBC was statistically significant ($p < 0.05$) in younger individuals with the mean age group of 31-40 years (63.56%) as

compared to Non-TNBC (Table I). Our results revealed Invasive ductal cell carcinoma was more prevalent (81.8%) as compared to other subtypes of TNBC tumor subtypes (Figure 1). Interestingly, the incidence of invasive lobular carcinoma in TNBC was also reported in this study (18.2 %) (Figure 1).

Table 1 Prevalence of TNBC and Non- TNBC among the study age groups

Age group (Years)	TNBC N (%)	Non-TNBC N (%)
20 – 30	01(9.1)	08 (6.54)
31 – 40	06(54.6)*	14(11.48)
41 – 50	04(36.4)	64(52.48)*
51 – 60	0(0)	24(19.68)
61 – 70	0(0)	12(9.82)

*p< 0.05 considered as statistically significant; TNBC: Triple-negative breast cancer

Table 2 Age wise distribution of patients with comparison between Invasive ductal and Invasive lobular carcinoma

Age group (Years)	TNBC (Invasive ductal) N (%)	TNBC (Invasive lobular) N (%)
20 – 30	01(9.1)	0(0)
31 – 40	06(54.6)*	0(0)
41 – 50	02(18.2)	02(18.2)*
51 – 60	0(0)	0(0)
61 – 70	0(0)	0(0)

Table 3 Prevalence of different TNM stages among the TNBC patients. Data are shown in mean ± SD and Percentages

Stage	Tumor size (cm)	Lymph node involvement		Metastasis	
		Present (%)	Absent (%)	Present (%)	Absent (%)
I	1.63±0.20	0	100	0	100
II	3.7±0.76	40	60	0	100
III	13.52±1.86	28.57	71.43	0	100
IV	0.00±0.00	0	0	0	0

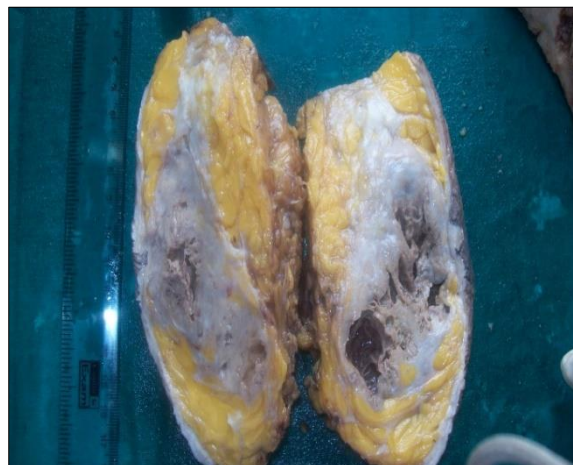


Figure 1 Gross appearance of the invasive lobular TNBC showing tumor necrosis and infiltrating margins



Figure 2 Gross appearance of the invasive lobular TNBC showing tumour tissue occupying all the four quadrants of the breast



Figure 3 Gross appearance of metastatic lymph nodes associated with invasive lobular TNBC

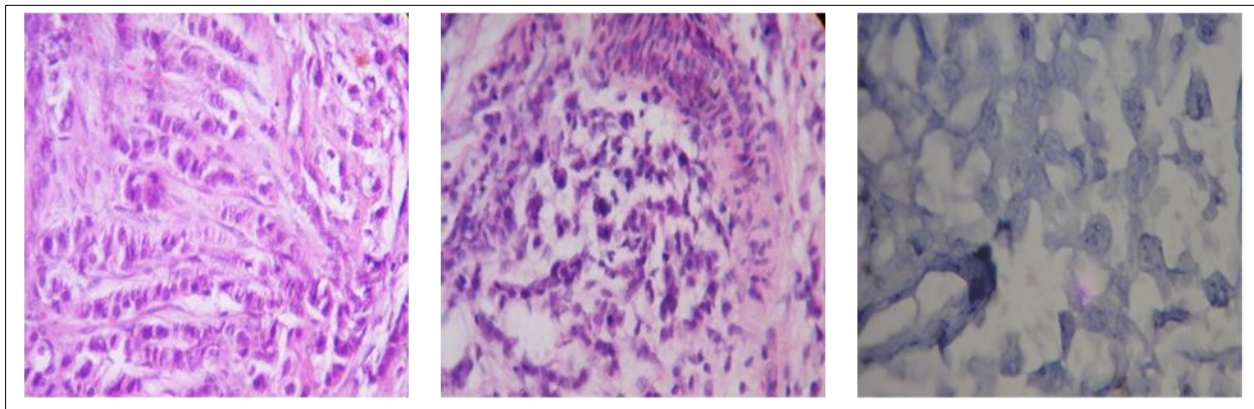


Figure 4 Invasive lobular TNBC: H&E and Immunohistochemistry of TNBC in invasive Lobular carcinoma subtype (10x and 40x)

4. Discussion

Triple negative breast cancer are categorized as heterogeneous subgroups of breast cancer as per its prognosis and response to medical therapy. Main focusing current health issues related to TNBC is its absence of specific systemic treatment, poor clinical symptoms and limited clinical data available for Asians. [17]

TNBCs account for 10-20% of total breast carcinomas based on threshold defined for ER, PR positivity and methods for HER2 assessment. [18] In the present study, 15.3% (11/72) of the individual patients diagnosed as TNBC with the mean age group between 31 - 40 years whereas the high prevalence of average age group for Non-TNBC observed in this study was about 40-50 years. These results are supported by the earlier studies on Asian women stated that the prevalence of 17% breast cancer among the study population was TN subtype. [19] Whereas, few studies reported the less prevalence of TNBC in an Indian population with breast cancer, which may be because of small sample size or invalid IHC procedures or error in the sample collection procedure. [20]

TNBCs are seen frequently in invasive duct cell carcinoma. However, invasive lobular carcinoma and medullary carcinomas, also show triple negativity. Present study showed 81.8% of Invasive ductal cell carcinoma followed by 18.2 % of invasive lobular carcinoma. These results were supported by Magdalena et al (2016) study stated that the high prevalence of (85%) invasive duct cell carcinoma followed by the various subtypes of breast carcinoma such as medullary, adenoid cystic, metaplastic, adenocarcinoma, mucinous etc. [23]

In our study patients had undergone radical mastectomy and most of the patients had undergone surgical treatment as compared to chemotherapy. Mastectomy is done because it defines tumor margins. The main issue with chemotherapy is patients are older succumb to complications of chemotherapeutic agents. [27]

Sharma B et al. (2013) observed 66% of tumors occurs between 21-40 years with of TNBC which concurrence with our study results of 63.56% of TNBC among 31-40 years' age group. [21] Liedtke et al. [2008] revealed that age is indirectly proportional to the tumor grade in TNBC. [22] Our study results also correlated with these findings that, a majority of the TNBC in our study belong to the tumor stage III statistically significant ($P < 0.05$) in younger age patients [Table:1]

There is lot of uncertainty in clinical relationship between tumor stage and prognosis. There are some studies which reported that there is no correlation between grade and survival outcome. [14,22,23] Present study showed direct correlation between TNM stage III and positive lymph nodes and it implies that the grading is a significant prognostic factor [Figure 3] [Table 2]. Necrosis plays a potential role in the prognosis of TNBC, however, very few scientific literature data is available in this regard. [25] Accordance with this hypothesis, 63% of TNBC tumors in our study showed necrosis [Figure 1]

Aggressiveness of Triple negative invasive lobular carcinoma is reflected by infiltrating margins seen in these tumors, high grade and high mitotic count also shows aggressiveness. [26] Present study showed significant aggressiveness of invasive lobular TNBC with the features of infiltrating margins, high grade, and a high mitotic count was observed among age between 20-40 years as compared to above 40 years' age group [Figure 2 and 4]. This observation is supported by the previous studies that states aggressiveness of TNBC decreases drastically with advancing age. [7]

5. Conclusion

In present study we have analyzed clinical, morphologic and immunohistochemical features of 11 invasive lobular TNBC tumors. Invasive lobular TNBCs usually involve all the four quadrants of the breast with infiltrating margins, and central necrosis. This shows their aggressive behavior. This clinical subset represents one of the most important treatment challenges. These rare tumors are associated with bad prognosis compared to invasive ductal TNBC. Though sample size is less but it gives a gateway to newer modalities of investigations required to go into more insight of this devastating subtype of tumors.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There is no conflict of interest between the authors in this study.

Statement of ethical approval

Ethical approval was taken from the ethics committee of Kakatiya Medical College/ Mahatma Gandhi Memorial Hospital, Warangal, Telangana, India.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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Author's short Biography



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