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Research Article

KI -67 EXPRESSION IN TRIPLE NEGATIVE BREAST CANCER

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A R T I C L E I N F O

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A B S T R A C T

Background - Tumor proliferative activity, an important cellular function is closely related to tumor behavior in breast cancer. The objective of this study is to evaluate Ki 67 expression pattern in Triple negative breast cancer patients and correlate with clinicopathological prognostic parameters.

Method – This is a prospective study designed to quantitatively assess the Ki 67proliferative index in retrieved paraffin blocks of fifty triple negative breast cancer patients diagnosed at Department of Pathology, K S Hegde Medical Academy, Deralakatte, Mangalore Karnataka. The Ki 67 expression was correlated with their clinicopathological parameters.

Results - Ki 67 immunoreactivity was highly expressed (> 10% of the tumor cells were positve) in 29 patients. The Ki 67 proliferation index was significantly associated with high tumor grade (0.000). However, the association with age, tumor size, ductal carcinoma in situ, necrosis, lymphovascular invasion and lymph node metastasis were not statistically significant.

Conclusion- Ki 67 proliferation index is higher in triple negative breast cancer which significantly correlates with tumor grade. Ki 67 proliferation index may be useful in predicting prognosis and management of triple negative breast cancer.

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INTRODUCTION

Triple negative breast cancer (TNBC) is subgroup of breast cancer lacking estrogen receptor and progesterone receptor expression as well as HER- 2amplification. Triple negativity is common immunohistochemistry status for number of tumors with heterogeneous clinical presentation and display unique molecular profiles. [1] It is essential to identify subtypes with a better prognosis. Proliferation and autonomous growth are hallmarks of any malignancy. Ki 67 has emerged as rapid inexpensive method to detect proliferation in breast tumors. There is robust data to show that Ki 67 is an excellent prognostic and predictive marker. [2] Prognostic value of Ki 67 in triple negative breast cancer is yet unclear. The aim of this study was to evaluate expression of Ki 67 in TNBC and to explore its association with clinicopathological prognostic parameters.

MATERIAL AND METHODS

A total of fifty patients with invasive breast cancer diagnosed at Department of Pathology, K S Hegde Medical Academy, Deralakatte, Mangalore were included based on histopathology, after taking informed consent. Each case was reviewed with regard to clinicopathological parameters including age at diagnosis, tumor type, tumor grade, necrosis, lymphovascular invasion and lymph node metastasis. Histologic grade was assessed by Modified Bloom Richardson scoring system. Histologically confirmed invasive breast cancer cases were included. TNBC was defined based on immunohistochemistry proved ER, PR and HER-2 negativity. Only Modified radical mastectomy specimens were included. Estrogen and progesterone receptor were scored negative when proportion of positively stained cells was < 1% (Allred score). Negative HER-2 expression was determined based on ASCO/CAP guidelines. Cells stained for Ki 67 were counted and expressed as percentage. The percentage was determined by the number of Ki 67 positive cells among the total number of counted tumor cells. High expression of Ki 67 was defined as ≥ 10%. [3]

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Statistical analysis

Data were analysed using SPSS version 20.0. The Chi- square test was conducted to analyze the clinicopathological data. P< 0.05 was considered statistically significant.

Immunohistochemistry –
Estrogen receptor- Rabbit monoclonal, clone EP1,
progesterone receptor – rabbit monoclonal, clone EP2
HER2 – rabbit monoclonal, clone EP3
Ki67- mouse monoclonal, clone GM001
Regulatory status – IVD

Pathnsitu immunohistochemistry kits were used to detect expression of estrogen receptor, progesterone receptor, HER2 and Ki 67.

RESULTS

The clinicopathological characteristics of 50 female TNBC patients are shown in Table 1. The mean age was 46.8years (range 37-60years). The pathological examination showed invasive ductal carcinoma, not otherwise specified in 45 and invasive ductal carcinoma with medullary features in 5 cases. Tumor size distribution was T2, 2-5cm (78%), T3 >5cm (22%). Total 38 (76%) cases were grade 3, 28(56%) had necrosis and 21(42%) showed ductal carcinoma in situ (DCIS). Thirty seven cases (74%) had positive lymph nodes and 20(40%) cases had lymphovascular invasion.

Table 1 Clinicopathological characteristics and Ki 67 expression of 50 TNBC cases

Characteristics	Numbers (%)
Age (years)	
≤50	37(74%)
>50	13 (26%)
Tumor size	
T2: 2-5cm	39 (78%)
T3: >5cm	11 (22%)
Tumor type	
Invasive ductal carcinoma	45 ((90%)
Invasive ductal carcinoma with medullary features	5 (10%)
Tumor grade	
Grade 2	12 (24%)
Grade 3	38 (76%)
DCIS	
Positive	21
Negative	29
Necrosis	
Positive	22(44%)
Negative	28 (56%)
Lymph node metastasis	
Negative	13 (26%)
Positive	
1-3 lymph nodes	20 (40%)
>3 lymph nodes	17(34%)
Lymphovascular invasion	
Positive	20 (40%)
Negative	30 (60%)
Ki 67	
< 10%	21 (42%)
≥ 10%	29 (58%)

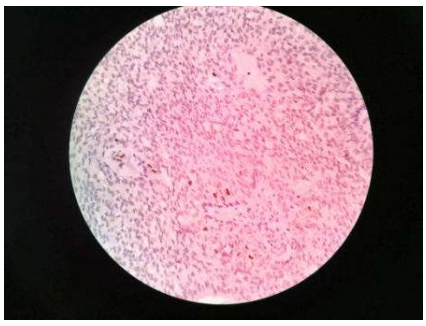

Figure 1a

Figure 1 a – Weak expression of Ki 67 (<10%) in Triple negative breast cancer tissue stained with Ki 67 antibody [x 40]

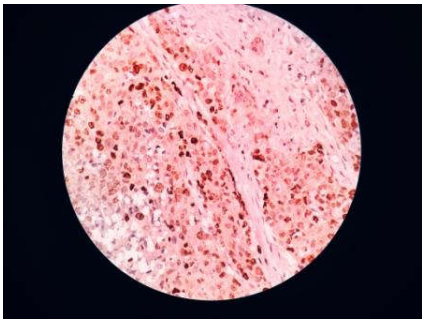

Figure 1b

Figure 1b – High expression of Ki 67 (≥10%) in Triple negative breast cancer tissue stained with Ki 67 antibody [x40]

Assessment of Ki 67 immunostaining

The expression of Ki 67 in breast cancer tissues is shown in figure 1a, 1b. The Ki 67 positive cells exhibited brown punctuate granules in the nucleus. The percentage of positive cells was calculated according the mean proportion of positive cells in high magnification visual fields and positive rate of Ki 67 expression was determined. Invasive edge of the tumor and data from hot spot included in the overall score. [4] (Figure 2) The Ki 67 staining was highly expressed in (≥10%) in 29(58%) cases. (Figure 3) Ki67 expression was significantly associated with tumor grade (p = 0.000). However, association with age, tumor size, DCIS, necrosis, lymph node metastasis and lymphovascular invasion were not significant. (Table 2)

Table 2 Ki 67 correlation with clinicopathological parameters

Parameters	Low Ki 67(<10%)	High Ki 67 (≥ 10%)	p value
Age (years)			
≤50	15	22	0.724
>50	6	7	
Tumor size			
<2cm	0	0	
2-5cm	17	22	0.668
>5cm	4	7	
DCIS			
Positive	10	11	0.493
Negative	11	18	
Necrosis			
Positive	7	15	0.196
Negative	14	14	
Grade			
I	0	0	
II	11	1	0.000
III	10	28	
Lympho vascular invasion			
Positive	13	7	0.390
Negative	18	22	
Lymph node metastasis			
Negative	4	9	
1-3	7	13	0.218
>3	10	7	

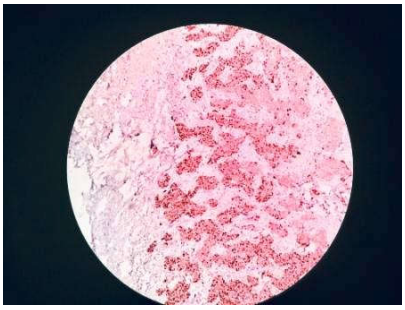

Figure 2 – Invasive edge of the tumor showing high Ki 67 expression in Triple negative breast cancer tissue stained with Ki 67 antibody [x10]

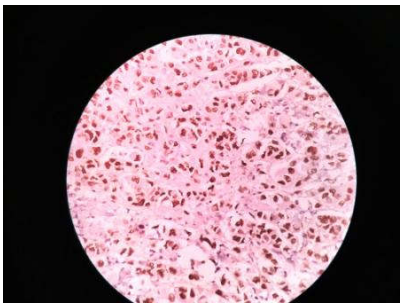

Figure 3 Strong positive Ki 67 expression (>80%) in Triple negative breast cancer tissue stained with Ki 67 antibody [x40]

DISCUSSION

Breast cancer is heterogeneous disease displaying high diversity in clinical manifestation, pathology, prognosis and molecular features. [5] TNBC is group of tumor having aggressive tumor biology with poor outcome and lack of targeted therapy. [1] To improve the outcome for TNBC patients it is essential to understand the biological behaviour of the tumor. Ki 67 has emerged as a rapid and inexpensive method to detect proliferation in breast tumors. Despite controversies related to tissue fixation, staining techniques, interpretation of the stain and standardized cut off values, there is good evidence in the literature regarding usefulness of Ki 67 as predictive and prognostic biomarker. [2, 4, 6] The use of Ki 67 as prognostic marker in breast cancer has been widely investigated but only few studies have investigated in TNBC. In this study Ki 67 expression was assessed in fifty TNBC patients using immunhistochemical staining. The standardised guidelines of breast cancer working group for assessment of Ki 67 were followed and cut off level used was 10% , according to the experience of different pathologists as well as national and international recommendations. [3, 7] Cutoff points of Ki 67 index employed in clinical trials and studies differed widely, ranged from 10 to 60%. Since baseline value for triple negative and HER2 positive tumors are much higher than luminal tumors. [8] Cut off selection of Ki 67 might be more apparent if it was considered with each subgroup respectively. The increased expression of Ki 67 may be an important factor for the poor prognosis of TNBC. [5] The use of Ki 67 as prognostic marker has been widely investigated.

Few researchers explored prognostic value of Ki67 in whole cohort of breast cancer. [8] A Korean group study showed that in preoperative setting a high Ki67 expression (≥10%) was significantly associated with poor relapse free survival and overall survival in TNBC in spite of higher pCR rate. [9] Muzonne *et al* reported that Ki 67 expression is associated with different prognosis subgroups in node negative TNBC with different with cut off value of 35%. [10] In line with these results, our study demonstrated high Ki 67 proliferation index in most specimens (58%), in addition Ki 67 expression correlated with tumor grade in TNBC. This indicates increased proliferation of tumor cells, enhanced invasive ness and faster growth.

In conclusion, these results suggested that increased expression of Ki 67 may be an indicator of poor prognosis in TNBC.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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