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Tumor Infiltrating Lymphocytes (TILs) and Tumor Budding in Invasive Breast Carcinoma: Correlation with Known Prognostic Parameters

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ABSTRACT

Background: Invasive breast cancer (IBC) has long been thought as non-immunogenic, but in recent decades it has been reported that tumor micro-environment (TME) in breast cancer encompasses tumor-infiltrating lymphocytes (TILs), which help in creating anti-tumor immune response. On the other hand, tumor buddings (TB) from the invasive front of the tumor contribute to invasion and metastasis. We aim to evaluate TILs and TB in IBC and to correlate them with known prognostic parameters.

Methods: In this retrospective study, 50 cases of IBC were included. TILs and TB were observed and graded in H&E Stained slides following standard guidelines. Associations of TILs and TB with known clinicopathological parameters were established by statistical methods.

Results: The majority of cases were invasive breast carcinoma (IBC)-NST (78%). The cases with low TILs (involving <50% of stroma) had a significant correlation with positive lymph node metastasis (P = 0.017) and high-grade TB (P = 0.038). TB was associated with other adverse prognostic parameters such as tumor necrosis (P=0.043) and lympho-vascular invasion (LVI) (P=0.033) and large tumor size.

Conclusion: As tumor budding is associated with known poor prognostic factors such as necrosis, LVI and large tumor size, it can be regarded as a potential biomarker in predicting the aggressiveness of breast cancer. Low TILs are positively associated with invasion and lymph node metastasis of IBC. Thus, assessment of these protumor (TB) and antitumor (TILs) factors could be a promising approach for future research on breast cancer.

INTRODUCTION

Breast cancer (BC) is considered as the most common malignancy in women and is one of the most common causes of cancer related deaths in women.[1,2]

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BC has long been considered as non-immunogenic, but evidence-based research in recent decades consistently indicates that the TME in the BC consists of an extensive population of cells belonging to adaptive and innate immune systems. These cells have been thought to be biologically or clinically pertinent to varying degrees.[3] The TME comprises immune cells which are in direct contact with tumor cells. These are mononuclear TILs cells and are known as intra-tumoral lymphocytes (iTILs) and the mononuclear cells present in the stromal background

are known as stromal lymphocytes (sTILs) and both of these cell types are said to have prognostic significance.[4-7]

Immune targeted therapies for highly immunogenic tumors such as melanoma, prostate cancer, non-small cell lung cancers have emerged which are very effective.[8-10] Evaluation of TILs on H&E stained sections in HER positive and TNBC show good prognostic and predictive values. Based on these findings, many recent studies have reported that TILs can serve as a potential biomarker for antitumor immune response in BC.[11-13]

The first step of invasion and metastasis in any solid tumor is tumor budding (TB).[14] TB is defined as the presence of single cells or small groups of cells not more than 5 in number at the invasive margin of the tumor. It has been considered as a poor prognostic marker in oesophageal, colorectal carcinomas.[15-16] However, evidence of TB and its role as a prognostic marker in breast cancer is limited.

This study was designed to evaluate sTILs and TB in breast cancer. This study was done to find the statistical significance of various clinicopathological factors (age, size of tumor, histological grade, LN status, LVI and necrosis, focality) based on sTILs and TB. The study also focused on detecting the relation between antitumor and protumor factors (TILs and TB respectively) in invasive breast cancer.

METHODS

This retrospective observational study on BC was conducted in the Department of Pathology, Burdwan Medical College and Hospital, over a period of 1.5 years, after being approved the Institutional Ethics Committee. The patients who had received chemotherapy were also excluded. The histopathology slides (H&E stained) which were diagnosed as invasive breast carcinoma (IBC) were collected and their histopathological features were reviewed by an experienced pathologist. In total, 50 cases were analysed for this study. Thorough clinical histories, gross and histopathological findings of mastectomy specimens were retrieved. Immunohistochemical findings were not included in this study.

Evaluation of sTILs

To evaluate sTILs, the percentage of stromal TILs was calculated according to the proposed guidelines set by international TILs working group 2014 (ITILWG).[4]

1. Stromal TILs (sTILs) were assessed using light microscope under low power (x10 objective) and were examined and confirmed under high power (x40 objective) on a single field.
2. All the mononuclear cells (lymphocytes and plasma cells) within the borders of invasive tumor were scored.
3. Intra-tumoral TILs (iTILs) were excluded in this study.
4. TILs which were present outside the tumor border and which were surrounding DCIS and normal lobules were excluded. Even TILs surrounding the crush artefact and necrosis were excluded.
5. sTILs were assessed as a continuous parameter as per recommendations and even dissociated growth patterns of lymphocytes were taken into account.
6. The cases were categorised into 3 groups according to the percentage of sTILs obtained, <10% sTILs, 10 -50%,>50% LPBC.

Evaluation of tumor budding[17]

1. Firstly, the invasive front of the tumor was identified under scanner power (x4 objective) of light microscope.
2. Tumor buds (≤5 cells) were assessed in low power (x10 objective).
3. Tumor buds were confirmed using high power (x40 objective) of light microscope and details of tumor buds were examined. It was made sure that the mimickers of tumor buds such as macrophages, multinucleate giant cells, artefacts, fibroblasts, endothelial cells, and smooth muscle cells were excluded from scoring.
4. The cytoplasmic and nuclear features of tumor cells proper were compared with tumor buds at the invasive front and the ones which exhibited similar morphology to that of tumor cells proper were counted (except polarity, because it can vary in tumor buds).
5. Tumor buds were counted in 10 high power fields and classified into high tumor budding (>20/10hpf) and low tumor budding (≤20/10hpf) as per the study done by BN Kumarguru *et al.*[17]

Data about sTILs, tumor budding was tabulated in Microsoft excel and analysed using SPSS V.24 software. The Chi square test was used for comparisons between the groups and clinicopathological correlations between the variables. The P value < 0.05 was considered to be statistically significant.

RESULTS

A total of 50 cases diagnosed as invasive carcinoma of breast were included in this study. Of these 50 cases, 46 were IBC-NST (92%), and 4 cases

were invasive lobular carcinoma (ILC) (8%) (Table 1).

The lesions were seen in females in the age range of 20 to 70 years. Most cases were seen in the age range between 41 and 50 years (30%) (Table 1).

Table 1. Age distribution with the type of breast carcinoma

Age range (years)	IBC-NST n(%)	ILC n(%)	P value
20-30	3(6.52%)	0(0.00%)	0.938
31-40	10(21.74%)	1(25%)	
41-50	17(36.96)	2(50%)	
51-60	8(17.39)	0(0.00%)	
>61	8(17.39)	1(25%)	
Total	46(100)	4(100%)	

Twenty five cases in our study had a tumor size ≤5 cm (50%) and the remaining 25 had a tumor size ≥5cm (50%). Lymph node metastasis was observed in the majority of cases (56%). Most of the cases had grades 2 and 3 (40% and 58%, respectively). Necrosis was found in 64% of the cases. The cases positive for LVI were 44% and negative cases were 56%. Perineural invasion (PNI) was found positive in 50% of the cases (Table 2).

Table 2. Distribution of the Clinicopathological parameters of breast cancer

Clinicopathological parameters		N (%)
Size	≤5	25 (50%)
	>5	25 (50%)
Lymph-node metastasis	Present	28 (56%)
	absent	22 (44%)
Histological type	IBC-NST	46 (92%)
	ILC	4 (8%)
Grade	1	1 (2%)
	2	20 (40%)
	3	29 (58%)
Necrosis	Positive	32 (64%)
	Negative	18 (36%)
LVI	Positive	22 (44%)
	Negative	28 (56%)
PNI	Positive	25 (50%)
	Negative	25 (50%)

Table 3. Correlation of sTIL (divided in three groups) with clinicopathological parameters

Clinicopathological parameters		sTIL			P value
		<10%	10-50%	>50%	
Size	≤5	14 (28%)	7 (14%)	4 (8%)	0.030*
	>5	5 (10%)	14 (28%)	6 (12%)	
Lymph node metastasis	present	10 (20%)	11 (22%)	7 (14%)	0.608
	Absent	9 (18%)	10 (20%)	3 (6%)	
Histological type	IBC-NST	18 (36%)	19 (38%)	9 (18%)	0.854
	ILC	1 (2%)	2 (4%)	1 (2%)	
Grade	1	0 (0%)	1 (2%)	0 (0%)	0.309
	2	5 (10%)	9 (18%)	6 (12%)	
	3	14 (28%)	11 (22%)	4 (8%)	
Necrosis	Positive	13 (26%)	12 (24%)	7 (14%)	0.86
	Negative	6 (12%)	8 (16%)	4 (8%)	
LVI	Positive	10 (20%)	9 (18%)	3 (6%)	0.501
	Negative	9 (18%)	12 (24%)	7 (14%)	0.951
PNI	Positive	9(18%)	11(22%)	5(10%)	
	Negative	10(20%)	10(20%)	5(10%)	

The sTILs<10% were found in 19 cases (38%), 10-50% sTILs were found in 21 cases (42%) and >50% of sTILs were found in 10 cases (20%).

When these sTILs were correlated with clinicopathological variables, it was found that the majority of cases with a tumor size of >5cm had 10-50% of sTILs (28%) and the majority of cases with a tumor size of ≤5cm had <10% of sTILs (28%) as shown in Table 3. This correlation of the percentage of sTILs with tumor size was significant (with P value of 0.030). The correlation of other variables with sTILs showed no statistical significance in our study but 22% of the cases with positive lymph node metastasis showed the presence of 10-50% of sTILs and 28% of the cases with a high tumor grade had a low percentage of sTILs (<10%) and 26% of the cases who were positive for necrosis had a low percentage of sTILs (<10%) as shown in Table 3. When sTILs

were classified into 2 groups, one group with <50% of sTILs infiltration and the other with >50% sTILs infiltration, it was found that the cases with positive lymph node metastasis had <50% sTILs (P value = 0.017) (Table 4). The majority of tumors with a small size (<5cm) also showed the presence of <50% sTILs (P value = 0.042). The correlation with other variables showed no statistical significance even in these 2 groups (Table 4).

Table 4. Correlation of sTIL (divided in two groups) with clinicopathological parameters

Clinicopathological parameters		TIL		P value
		Group 1 (<50%)	Group 2 (>50%)	
Size	≤5	21 (42%)	4 (8%)	0.042*
	>5	19 (38%)	6 (12%)	
Lymph node status	Positive	21 (42%)	7 (14%)	0.017*
	Negative	19 (38%)	3 (6%)	
Histological type	IBC-NST	37 (74%)	9 (18%)	0.794
	ILC	3 (6%)	1 (2%)	
Grade	1	1 (2%)	0 (0%)	0.333
	2	14 (28%)	6 (12%)	
	3	25 (50%)	4 (8%)	
Necrosis	Positive	25 (50%)	7 (14%)	0.145
	Negative	14 (28%)	4 (8%)	
LVI	Positive	19 (38%)	3 (6%)	0.318
	Negative	21 (42%)	7 (14%)	
PNI	Positive	20 (40%)	5 (10%)	0.988
	Negative	20 (40%)	5 (10%)	

Among the 50 cases, high TB was seen in 37 cases (74%) and low TB was found in 13 cases (26%). The majority of cases with high grade TB were observed in IBC-NST (70%). (Table 5) (Figure 1)

Table 5. Correlation of Tumor budding with clinicopathological parameters

Clinicopathological parameters		TB		P value
		Low	High	
Size	≤5	6 (12%)	18 (36%)	0.876
	>5	7 (14%)	19 (38%)	
Lymph node status	Positive	10 (20%)	18 (36%)	0.132
	Negative	3 (6%)	19 (38%)	
Histological type	IBC-NST	12 (24%)	35 (70%)	0.76
	ILC	1 (2%)	2 (4%)	
Grade	1	0 (0%)	1 (2%)	0.574
	2	4 (8%)	16 (32%)	
	3	9 (18%)	20 (40%)	
Necrosis	Positive	13 (26%)	20 (40%)	0.043*
	Negative	2 (4%)	15 (30%)	
LVI	Positive	2 (4%)	20 (40%)	0.033*
	Negative	11 (22%)	17 (34%)	
PNI	Positive	5 (10%)	19 (38%)	0.423
	Negative	8 (16%)	18 (36%)	

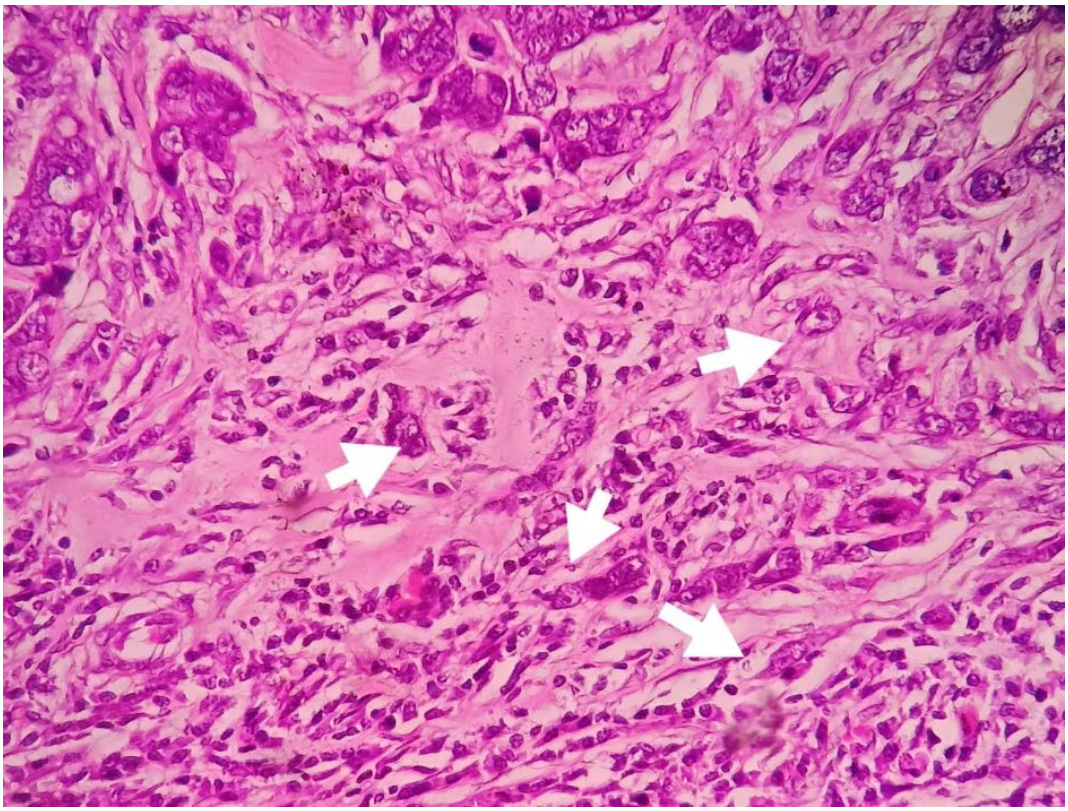

Figure 1. Histopathology picture of invasive breast carcinoma: showing many tumor buds (white arrows) and high tumor infiltrating lymphocytes. (H & E Stain, 40x)

In this study, when the correlation between TB and clinicopathological variables was examined, it was found that the cases which were positive for necrosis and LVI had a high-grade TB (P-value=0.043, P-value=0.033, respectively) which was statistically significant. Other variables like the size of tumor, PNI, status of lymph node metastasis, histological type, and the grade of the tumor had no significant correlation with the grade of TB. But the majority of cases with 2 and 3 grades showed high grade tumor buds (32%, 40%, respectively) and 38% of the cases with a large tumor size had a high-grade TB (Table 5).

The correlation between sTILs and TB was also determined in our study. To do so, sTILs were divided into 2 groups, group 1 (<50% sTILs), and group 2 (>50% sTILs) and these two groups were compared with the low-grade and high-grade TB. The Chi-square test showed that the cases with <50% of sTILs had a high-grade TB (60%) with the P value of 0.038, which was statistically significant (Table 6), whereas cases with >50% of sTILs did not show any significant correlation with the low-grade TB in our study.

Table 6. Correlation between TIL and TB

Clinicopathological correlation		TB		Total	P value
		Low (%)	High (%)		
TIL	Group-1 (<50 %)	10 (20%)	30 (60%)	40 (80%)	0.038*
	Group-2 (>50%)	3 (6%)	7 (14%)	10 (20%)	
	Total	13 (26%)	37 (74%)	50 (100%)	

DISCUSSION

The aim of this study was to evaluate sTILs and TB in invasive breast carcinoma. Previous studies have demonstrated that there is a significant association between the clinical response in patients with a variety of solid tumors and the presence of immune cells.[18] Numerous studies point out that the adaptive immunity mediated by B and T lymphocytes can lead to the formation of sustained and effective antitumor immune response.[4,13] On the other hand, tumor budding is considered as a strong adverse prognostic factor and its prognostic significance has been demonstrated in colorectal cancer.[19,20] TB is considered as the first step in invasion and metastasis.[14] It is associated with poor prognostic factors such as necrosis, lymph node metastasis, high

tumor grade and LVI.[21,22] It can be considered as a protumor factor, as it leads to the progression of tumor.

In our study, we attempted to find if there is any significant correlation between sTILs (antitumor factor) and TB (protumor factor) in breast carcinoma. We found that the cases with <50% sTILs infiltration had high-grade TB (P-value=0.038) but the cases with >50% sTILs infiltration did not show the presence the low-grade TB. Lugli *et al.*[23] did a study on CD8+ lymphocytes /tumor budding index in colorectal cancer and concluded that this index can be used as an independent prognostic factor in colorectal cancer. In their study, they confirmed that in patients with high tumor budding and low CD8+ lymphocytes index, this was associated with tumor progression and worse survival in colorectal cancer patients.

A study by Angelico *et al.*[13] showed that all patients with an advanced stage of the disease at the time of diagnosis showed low levels of TILs (<10%). Similarly, in our study we found that patients with grade 3 BC had low levels of TILs (<10%), indicating that the aggressive behaviour of BC is inversely proportional to the immune response. We cannot conclude in our study whether immune exhaustion led to aggressiveness in BC or vice versa.

According to DeNardo *et al.*[24], T lymphocytes play a role in regulating other immune cells such as macrophages (M1, M2), and they are important for cellular cross-talk in shaping the TME. We could infer from our study that TILs are required for modulating the TME so as to either inhibit or escalate tumor progression. To support this, we have found in our study that the cases in whom the lymph node metastasis was positive, there was <50% infiltration of sTILs (P-value=0.017), indicating that a decreased percentage of TILs can lead to metastasis of tumor cells in breast cancer.

When the grade of TB was correlated with clinic-pathological variables, it was found that high-grade TB was seen in cases, which were positive for necrosis and LVI with significant P values. The majority of cases with high grade TB presented with large tumor size (38%), but no significant correlation between TB and lymph node metastasis, size of the tumor, PNI, grade of tumor was found in our study. In contrast, studies by Lian F *et al.*[20], Gujam *et al.* [21] and Kumarguru *et al.*[17] reported a significant association between high TB and LN metastasis, high tumor grade, size of tumor, and tumor stage. The significant association of high TB with necrosis and LVI was also found in a study by Kumarguru *et al.*[17], which was not found in our study.

The method of assessing TB is different in various studies. The present study and the study done by Salhia *et al.*[22] used x40 (high power) objective to count the buds. Contrary to our study, studies done by Liang *et al.*[20] and Gujam *et al.*[21] used x20 objective. By using x20 objective, it would be difficult to differentiate tumor buds from other mimickers on H&E stained sections. Hence, using x40 objective is suggested for evaluating tumor buds on H&E stained sections.

CONCLUSION

In this study, it was shown that high grade TB was significantly associated with poor prognostic factors such as necrosis and LVI; hence, it can be considered as a poor prognostic factor because it has the potential to predict the aggressiveness of breast carcinoma. When the association between sTILs (antitumor factor) and TB (protumor factor) was studied, it was found that the cases with<50% infiltration of sTILs had high-grade TB and lymph node metastasis, indicating that reduced local immune response can significantly lead to tumor progression. On the contrary, the presence of high stromal lymphocytic infiltration did not show the suppression of tumor progression and lymph node metastasis in breast carcinoma in our study, indicating that there might be other factors responsible for tumor progression or suppression than TILs.

The present study shows that TILs can be considered as an antitumor factor and TB as a protumor factor. We recommend that further studies should be done to gain a more in-depth insight into this antitumor and protumor dynamics in invasive breast cancer along with their prognostic significance as these can be considered to be potential prognostic biomarkers.

CONFLICT OF INTEREST

None to declare.

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