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Original Article

Pathology Section

Peritumoural Mast Cell Density in Invasive Breast Carcinoma: Possible Antitumourigenic Effect with Potential Role for Immunotherapy

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ABSTRACT

Introduction: The interaction of cancer cells and the host within the tumour microenvironment plays a major role in determining the outcome of cancers. Mast cells are part of the innate immune system that interact with tumour cells and known to have pro-tumourigenic and antitumourigenic action through their mediators. Their role in the outcome of invasive breast cancer is still not clear with studies showing both a beneficial role as well as a role in tumour progression.

Aim: To assess Mast Cell Density (MCD) in tissues of invasive carcinoma of breast and compare with clinicopathological parameters to infer their biological significance.

Materials and Methods: The study was a retrospective cross-sectional study carried out in the Department of Pathology at SRM Medical College Hospital and Research Centre, Kattankulathur, Chennai, India on 51 cases of invasive carcinoma of breast received between January 2011 to July 2013 and the study conducted between August 2013 to November 2013. Clinical parameters and histopathological findings were recorded. Mast cells were clearly demonstrated in tissue using Toluidine Blue stain at pH 2.3. The MCD within primary malignant breast tumour tissue (mastectomy specimens, n=51) was assessed using an eyepiece grid and expressed as number of cells/per sq. mm. Statistical analysis of all parameters was performed using Statistical Package for the Social Science (SPSS) software (version 17.0) to analyse association of MCD with clinicopathological parameters.

Results: The MCD was significantly higher in malignant breast tissue compared to non neoplastic breast tissue (p-value <0.0001). No significant difference in MCD was observed between tumour size groups (T1, T2, and T3) (p-value=0.696). No statistically significant difference in MCD was observed between the four histological types observed (p-value=0.892). The majority of the tumours were of grade 2 category (n=37), followed by grade 3 (n=11) and grade 1 (n=3). No significant difference in MCD was observed between the three histological grades (p-value=0.785). The MCD was significantly higher in patients without lymphnode metastasis compared to the group with lymphnode metastasis (p-value=0.0023). The MCD in invasive carcinoma of breast, postchemotherapy group was significantly higher than that in invasive carcinoma of breast pre-chemotherapy group (p-value=0.0064).

Conclusion: The current study shows significantly increased MCD at the periphery of the carcinoma breast tissue in patients without lymphnode metastasis compared to those with lymphnode metastasis. Hence, a potential antitumourigenic and beneficial role of mast cells in invasive primary breast carcinoma could be inferred and may serve as one of the prognostic indicators for patient stratification for various treatment options including immunotherapy.

Keywords: Metastasis, Toluidine blue, Tumour microenvironment

INTRODUCTION

Breast cancer is the most common cancer and one of the leading causes of death among women in India and worldwide [1]. It is a multifactorial, hormone-dependent process that can be initiated by a variety of risk factors and progress of the tumour varies from patient to patient. Breast cancer has been found to be more prevalent in Indian women at premenopausal stage with more aggressive, high grade, and treatment-resistant disease, the reasons for which are not well understood [2]. Hence, it is imperative to understand the tumour biology in detail in breast cancer in Indian populations, especially the tumour-host interactions in the microenvironment. Mast cells are potent effector cells of the immune system that infiltrate the tumoural stroma and periphery of the tumours along with other inflammatory cells like cytotoxic T-cell subsets, macrophages, and fibroblasts [3-5]. The diverse mediators derived from mast cells are reported to have both pro-tumourigenic and antitumourigenic effects. The balance between these opposing mechanisms determines their net effect on the progression or regression of the tumour at any given stage.

A pro-tumourigenic effect of mast cells has been found in prostatic adenocarcinoma melanoma, pancreatic adenocarcinoma, pulmonary adenocarcinoma, cholangiocarcinoma, hepatocellular carcinoma, thyroid cancers, basal cell carcinoma, and neurofibroma [6-8].

Mast cells and invasive carcinoma of breast: Mast cell accumulation in mammary adenocarcinoma was first demonstrated in rats and was one of the earliest reports of mast cell association with cancers. The presence of stromal mast cells were found to have a favourable prognosis in some studies including a large study sample of more than 4000 cases of breast carcinoma [9,10]. A general correlation of stromal mast cells to lower histological grades have been found but correlation to hormone receptor expression has not been consistently observed [11,12]. A correlation between stromal mast cells and small size of the tumour, tubular differentiation and hormone receptor expression, molecular subtyping, and microvessel density has been reported [13-17].

However, the exact role of mast cells as part of the tumour microenvironment in breast cancer is not yet completely understood. Hence, this study was taken up as a novel effort to analyse the tumour microenvironment in breast cancers in Indian populations where there is an increasing incidence in younger populations and presentation as more aggressive tumours. Hence, it is imperative to understand the tumour biology in detail to identify and validate therapeutic targets and for patient stratification and personalised treatment. The study aimed (i) To objectively and quantitatively assess MCD in the tumoural compartment of invasive breast carcinoma in South Indian population, and (ii) To compare MCD with

clinicopathological parameters and to infer their biological role in the tumour microenvironment and their prognostic and therapeutic significance.

MATERIALS AND METHODS

The study was a retrospective cross-sectional study carried out in the Department of Pathology at SRM Medical College Hospital and Research Centre, SRMIST, Kattankulathur, Chennai, India on cases of invasive carcinoma of breast received between January 2011 to July 2013 and study conducted between August to November 2013 after obtaining approval from the Institutional Ethics Committee (312/IEC/2012).

Inclusion criteria: (i) Cases represented by resection (mastectomy) specimens with tissue blocks and Haematoxylin and Eosin (H&E) slides representing invasive carcinoma of breast received in the laboratory between January 2011 to July 2013 were included in the study. (ii) Cases with adequate clinical and demographics data of the patient.

Exclusion criteria: (i) Cases without adequate representation of the tumour tissue in sections (ii) Cases with inadequate area of tissue sections for mast cell counting (iii) Cases with incomplete clinical and demographics data were excluded from the study.

A total of 51 cases of breast carcinoma were included in this study. The number of samples received as in the study period were analysed, which was above the sample size calculated as per statistical requirements for this study.

Study Procedure

Formalin Fixed Paraffin-embedded (FFPE) tissue blocks and H&E stained sections representing malignant tumour tissue from surgically resected mastectomy specimens were analysed. Clinical parameters including age, gender, history of chemotherapy etc., were obtained from the referring departments and retrieved from the Medical Records Department. Mastectomy specimens were routinely sampled for histopathology analysis. H&E stained tissue sections were evaluated microscopically (OLYMPUS-CX-21; Field area of 0.196 mm^2). Routine microscopic parameters in carcinoma breast including the following were recorded: tumour size, histological type, histological grade, surgical margin involvement, and axillary lymphnode status. A summary of clinicopathological parameters is provided in [Table/Fig-1]. Mast cells were demonstrated histochemically on tissue sections by staining with 1% acidified toluidine blue solution at pH 2.3 [18]. Microscopy-grade toluidine (Loba Chemie; CI no: 52040; Lot no: S26701111; Dye content-80%; Solubility-0.1%) was used for preparing a water clear solution. An electronic pH meter (Eutech Instruments: Catalog No: 35624-02) was used to control the pH.

Control tissue: Tissues from non neoplastic breast tissue were used as controls (as baseline value), to assess significance of MCD

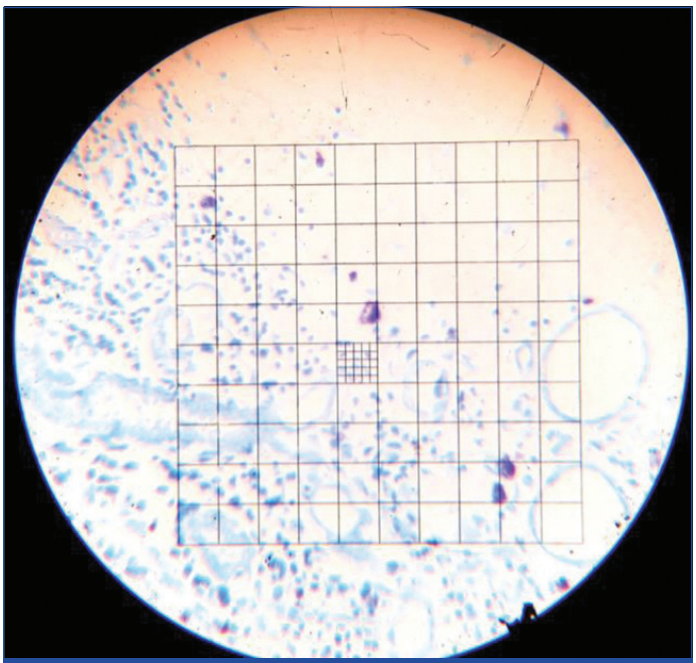
S. No.	Age (years)	Laterality	Quadrant involved	Tumour size (cm)	Tumour size (pT)	Histological type	Histological grade	Surgical margins-involvement by tumour	Lymphnode status (pN)	No. of regional lymphnodes with metastatic deposits
1	32	Right	Upper outer	4.5	T2	IDC-NOS	3	Negative	pN1	2
2	59	Left	Central	3.5	T2	IDC-NOS	2	Negative	pN0	0
3	60	Right	Lower inner	5.5	T3	IDC-NOS	3	Negative	pN0	0
4	41	Left	Upper outer	4	T2	Invasive lobular carcinoma	2	Negative	pN1	2
5	40	Left	Upper outer	3.5	T2	IDC-NOS	2	Negative	pN1	2
6	44	Right	Central	3.5	T2	Mucinous carcinoma	2	Negative	pN0	0
7	69	Left	Lower inner	6	T3	IDC-NOS	1	Negative	pN0	0
8	64	Left	Upper outer	6.5	T3	IDC-NOS	3	Negative	pN2	5
9	65	Left	Lower inner	4	T2	Metaplastic carcinoma	2	Negative	pN0	0
10	57	Right	Outer inner	3	T2	IDC-NOS	2	Negative	pN0	0
11	50	Left	Central	3	T2	IDC-NOS	2	Negative	pN0	0
12	54	Right	Upper inner	3.5	T2	IDC-NOS	2	Negative	pN0	0
13	45	Right	Upper outer	5.3	T3	IDC-NOS	2	Negative	pN0	0
14	43	Left	Upper inner	2	T2	IDC-NOS	1	Negative	pN0	0
15	64	Left	Upper outer	3.5	T2	IDC-NOS	1	Negative	pN0	0
16	45	Right	Upper outer	3.5	T2	IDC-NOS	2	Negative	pN2	4
17	65	Right	Upper outer	3	T2	IDC-NOS	3	Negative	pN1	1
18	65	Right	Central	5.5	T3	IDC-NOS	2	Negative	pN1	1
19	42	Left	Central	5.5	T2	IDC-NOS	2	Negative	pN1	2
20	69	Right	Central	4.5	T2	IDC-NOS	2	Negative	pN1	1
21	32	Right	Upper inner	3.5	T2	IDC-NOS	3	Negative	pN2	7
22	58	Right	Upper outer	6	T3	IDC-NOS	2	Negative	pN0	0
23	57	Left	Upper inner	2.5	T2	IDC-NOS	3	Negative	pN0	0
24	45	Left	Upper inner	7.5	T3	IDC-NOS	2	Positive- DRM	pN3	10
25	40	Left	Central	4	T2	IDC-NOS	2	Negative	pN0	0
26	56	Left	Lower outer	6	T3	IDC-NOS	2	Negative	pN1	1
27	36	Right	Central	5	T3	IDC-NOS	2	Negative	pN2	4
28	49	Right	Upper outer	3	T2	IDC-NOS	2	Negative	pN1	1
29	55	Left	Lower outer	5.5	T3	IDC-NOS	3	Positive- DRM	pN3	11
30	50	Right	Upper outer	3	T2	IDC-NOS	2	Negative	pN2	8
31	37	Right	Lower outer	5	T3	IDC-NOS	2	Negative	pN2	7
32	55	Left	Upper outer	4.5	T2	IDC-NOS	2	Negative	pN2	7

33	38	Right	Central	7	T3	IDC-NOS	2	Positive- DRM	pN2	6
34	64	Right	Lower inner	3	T2	IDC-NOS	2	Negative	pN2	4
35	45	Right	Upper inner	4.5	T2	IDC-NOS	2	Negative	pN3	11
36	56	Right	Central	4	T2	IDC-NOS	2	Negative	pN3	12
37	40	Left	Lower inner	4.5	T2	IDC-NOS	2	Negative	pN0	0
38	49	Right	Upper outer	3.5	T2	IDC-NOS	2	Negative	pN0	0
39	26	Right	Central	4	T2	IDC-NOS	2	Negative	pN0	0
40	28	Right	Lower outer	2.5	T2	IDC-NOS	2	Negative	pN0	0
41	65	Left	Upper outer	3.5	T2	IDC-NOS	3	Negative	pN2	6
42	40	Left	Central	2.5	T2	IDC-NOS	2	Negative	pN0	0
43	43	Left	Upper outer	3	T2	IDC-NOS	2	Negative	pN2	4
44	48	Right	Uuper outer	3.5	T2	IDC-NOS	2	Negative	pN1	1
45	43	Left	Upper outer	5.5	T3	IDC-NOS	3	Negative	pN2	5
46	55	Right	Lower outer	6	T3	IDC-NOS	2	Negative	pN0	0
47	49	Right	Upper outer	5.5	T3	IDC-NOS	2	Negative	pN0	0
48	51	Left	Central	4	T2	IDC-NOS	3	Negative	pN0	0
49	62	Right	Upper outer	6	T3	IDC-NOS	2	Negative	pN0	0
50	47	Left	Upper outer	5	T3	IDC-NOS	3	Negative	pN2	5
51	58	Left	Lower inner	6.5	T3	IDC-NOS	2	Negative	pN3	11

[Table/Fig-1]: Distribution of cases of invasive carcinoma breast (female) with clinicopathological parameters.
IDC-NOS: Infiltrating ductal carcinoma-Not otherwise specified; DRM: Deep resected margin

within the tissue compartments of invasive carcinoma breast. Non neoplastic breast parenchyma 5 cm away from the outermost margin of the tumour was selected as control tissue. A total of 21 controls were used in the study.

Mast cells were identified on tissue sections due to the violet-purple metachromatic staining of their granules against the blue orthochromatic background. Mast cells were counted quantitatively in sections using an eyepiece grid (model WF-18) [Table/Fig-2]. Each side of the large square represented one millimeter (mm) on the tissue section. A minimum of 10 high power fields were used for counting mast cells and the average density was expressed as: Mast cell density (MCD)=Number of mast cells/sq. mm area of the tissue section.



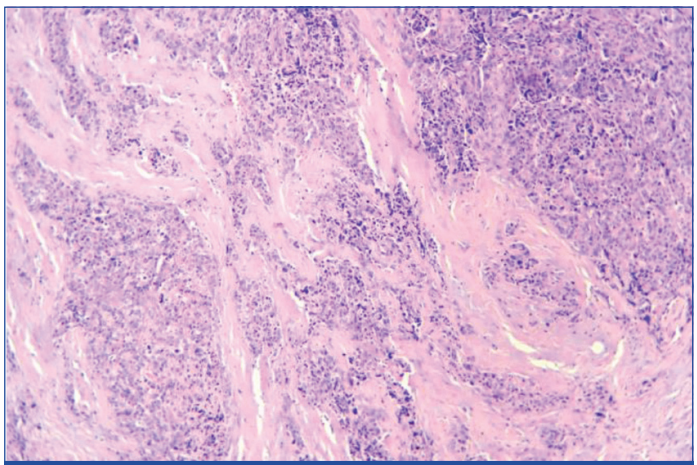
[Table/Fig-2]: Mast cell density (Toluidine blue; pH 2.3) quantitatively assessed on tissue section within tumoural compartment using an eyepiece grid.

STATISTICAL ANALYSIS

Statistical analysis with SPSS software (version 17.0) was done to analyse association of MCD with clinicopathological parameters. For determining statistical significance between two groups, the p-value was obtained using the two-tailed Student t-test. One-way Analysis of Variance (ANOVA) was used when comparing across three or more groups. The statistical data was tabulated for analysis and inference. A p-value of less than 0.05 was considered significant.

RESULTS

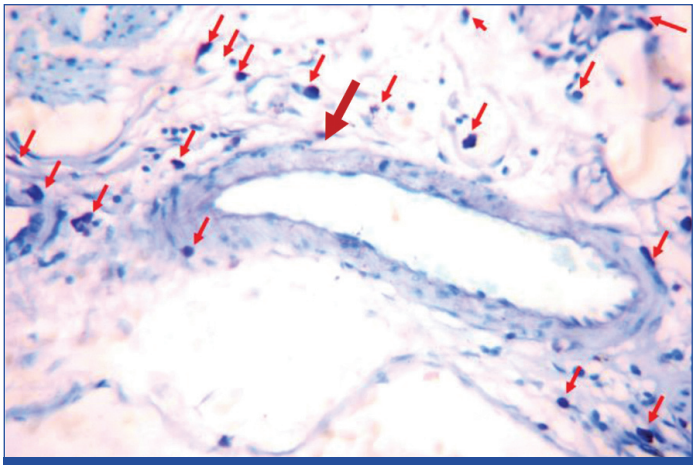
MCD in non neoplastic and malignant breast tissues: Controls representing non neoplastic breast tissue were used to compare with cases of carcinoma breast included in the study. Mast cells were visualised and density assessed in tissue sections representing primary breast carcinoma and correlated with histopathological features [Table/Fig-3-5]. MCD in breast carcinoma tissue was found to be significantly higher compared to MCD in non neoplastic breast tissue (p-value <0.0001; [Table/Fig-6].



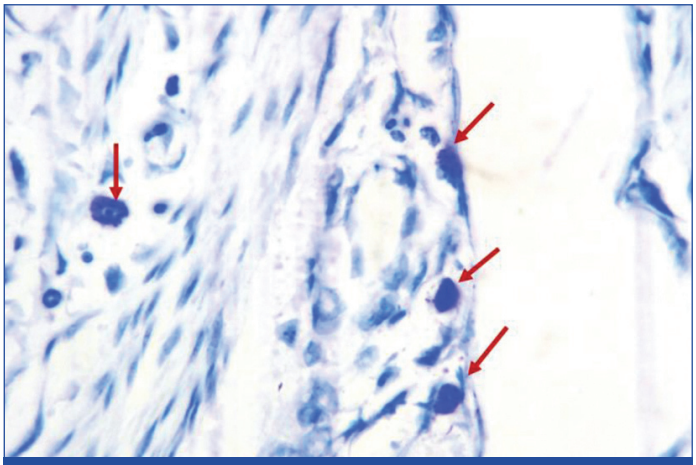
[Table/Fig-3]: Invasive ductal carcinoma- No Special Type (NST); grade 3 H&E; x100.

MCD and age: The age of patients with breast carcinoma ranged from 26 to 69 years with a mean age of 49.65 years. No statistically significant difference was noted between the two groups in our study (p-value=0.523).

MCD and tumour size: When the tumors were grouped based on their size using TNM staging parameters, most cases of invasive breast carcinoma belonged to the T2 group (n=33; 64.7% of cases) and 18 cases belonged to T3 (35.3% of cases). None of the cases were reported as T1. No significant difference in MCD was observed between these two groups [Table/Fig-7].



[Table/Fig-4]: Increased Mast cells at the periphery of the tumour within the stroma in invasive breast carcinoma (Toluidine Blue; x100).



[Table/Fig-5]: Mast cells within the tumoural stroma in invasive carcinoma breast (toluidine blue; x400).

Type of breast tissue	No. of cases	Mean MCD±SD	p-value
Control non neoplastic breast tissue	21	0.4±0.25	<0.0001*
Invasive carcinoma of breast prechemotherapy	51	8.7±5.58	

[Table/Fig-6]: Mast cell density in non neoplastic breast tissue and malignant breast tissue.
**p-value <0.05 considered statistically significant; (Student t test method, two-tailed)

Tumour size (in greatest dimension)	No. of cases	Mean MCD±SD	p-value
T2	33	9.75±5.44	0.6967
T3	18	9.75±7.5	

[Table/Fig-7]: Invasive carcinoma of breast: mast cell density and tumour size (T). (Student t test method, two-tailed)

MCD and histological types: Invasive Ductal Carcinoma- Not Otherwise Specified (NOS) accounted for the majority of the tumours (n=48; 94.1%). One case each of invasive lobular carcinoma, mucinous carcinoma and metaplastic carcinoma (1.96% each) were also diagnosed. No significant difference in MCD was observed between the four histological types [Table/Fig-8].

Histological type	No. of cases	Mean MCD±SD	p-value
Invasive ductal carcinoma-NOS	48	8.29±5.24	0.892
Invasive lobular carcinoma	1	5	
Mucinous carcinoma	1	22	
Metaplastic carcinoma	1	13	

[Table/Fig-8]: Invasive carcinoma breast: mast cell density and histological type. One-way ANOVA test

MCD and histological grade: Histological grading of Invasive ductal carcinoma-NOS was performed based on Nottingham's modification of Bloom-Richardson's system [11]. The majority of the tumours were of grade 2 category (n=37; 72.5%), followed by grade 3 (n=11; 21.6% and grade 1 (n=3; 5.9%) [Table/Fig-9]. No statistically significant difference in MCD was observed between the three histological grades.

Histological grade	No. of cases	Mean MCD±SD	p-value
Grade 1	3	7±4.24	0.785
Grade 2	37	8.28±5.46	
Grade 3	11	8.25±5.06	

[Table/Fig-9]: Invasive ductal carcinoma: mast cell density and histologic grade. One-way ANOVA test

MCD and surgical margin involvement by tumour: Only three cases (5.88%) out of 51 cases showed involvement of surgical margins (deep resected margin) by tumour cells [Table/Fig-1]. No statistically significant difference in MCD was observed between the two groups (p-value=0.782).

MCD and regional lymphnode status: Total 28 out of 51 cases showed metastatic deposits from breast carcinoma to regional axillary lymphnodes. The mean MCD as measured in the primary breast tumours of patients without axillary node metastasis was significantly higher compared to mean MCD in primary breast tumours with axillary node metastasis. This difference was found to be statistically significant (p-value=0.0023) [Table/Fig-10]. When lymphnode positive cases were grouped as pN1, pN2, and pN3 according to the number of positive lymphnodes, no statistically significant difference in MCD of primary tumours was observed between the groups pN1, pN2, and pN3 (p-value=0.294) [Table/Fig-11].

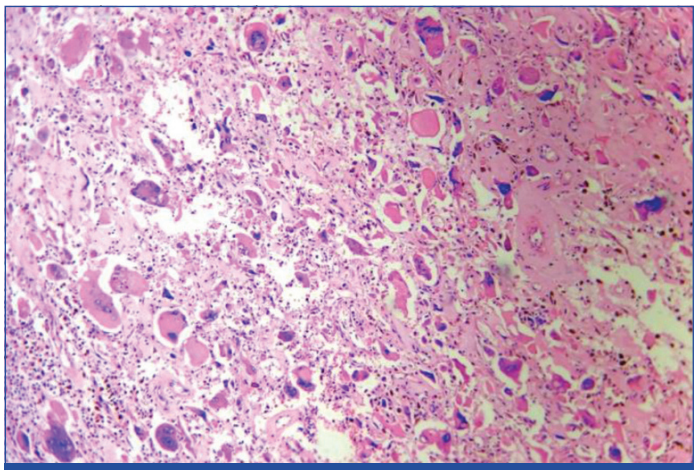
Axillary lymphnode nodal status in carcinoma breast	No. of cases	Mean MCD±SD	p-value
Nodal metastasis absent	23	12.36±6.79	0.0023*
Nodal metastasis present	28	6.33±3.54	

[Table/Fig-10]: Mast cell density in invasive carcinoma of breast and axillary lymphnode metastasis status.
*p-value <0.05 considered statistically significant (Student t test method, two-tailed)

Nodal stage	No. of cases	Mean MCD±SD	p-value
pN1	10	5.38±2.67	0.294
pN2	13	7.45±4.01	
pN3	5	4±2.83	

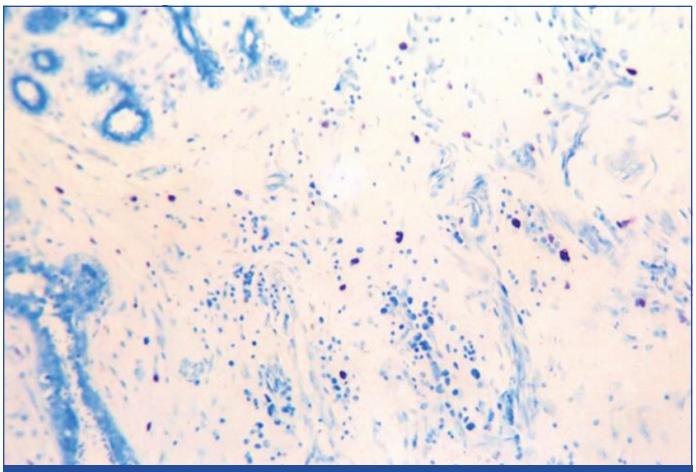
[Table/Fig-11]: Mast cell density in cases of invasive carcinoma of breast and stage of lymphnodes with metastatic tumour deposits (n=28). One-way ANOVA test

MCD in Postchemotherapy cases: MCD in seven cases of invasive breast carcinoma, post-chemotherapy status [Table/Fig-12,13] was significantly higher than MCD in invasive carcinoma of breast prechemotherapy (p-value=0.0064). This was an observation being



[Table/Fig-12]: Postchemotherapy induced changes in invasive carcinoma breast. Many bizarre nuclei, tumour giant cells and necrosis noted (H&E x100).

reported here towards the understanding of mast cell biology and not included in the correlation to clinicopathological parameters.



[Table/Fig-13]: Numerous mast cells distributed within the tumour in invasive carcinoma breast with chemotherapy induced changes (Toluidine Blue; x100).

DISCUSSION

Mast cells were clearly demonstrated in tissue sections using toluidine blue staining method and MCD was found to be significantly higher in the malignant tumour compartment compared to normal breast tissue tissue, the difference being statistically significant. This highlights their potential interaction with tumour cells and the stroma in the tumour microenviroment.

Mast cell density and invasive carcinoma of breast: Dabiri S et al., [9] and Rajput AB et al., [10] have shown that the presence of mast cells in stroma is associated with a favourable prognosis in carcinoma breast and that the presence of mast cells and not necessarily a high MCD is necessary to render this favourable outcome. Fakhrjou A et al., [11] have shown the interaction of mast cells in breast cancer and Tamma R et al., [12] have reported the importance of spatial distribution of mast cells and clinicopathological parameters.

Age: A previous study by Sang J et al., [17] has analysed MCD within two age groups (<50 and >50 years) and observed a higher MCD in patients <50 years compared to patients >50 years. Sang J et al., [17] have described that the demarcation of 50 years of age was to differentiate premenopausal reproductive age group and postmenopausal group. In the present study, no statistically significant difference in the mean MCD between patients in these two age groups was found (p-value=0.523).

Histological type: Variations in MCD between histological types was observed in previous studies by Fakhrjou A et al., [11] and Glajcar A et al., [14]. In the present study there was no statistically significant difference between the mean MCD in different histologic types of breast carcinoma. However, it needs to be noted that the present study had only one case each of metaplastic carcinoma, mucinous carcinoma, and invasive lobular carcinoma. All the other cases were of invasive ductal carcinoma-NOS. Dabiri S et al., [9] have reported a lower number of mast cells in metaplastic carcinoma, which was not observed in the present study.

Histological grade of invasive ductal carcinoma-NOS: Rajput AB et al., [10] and Keser SH et al., [15] found significantly higher number of mast cells in low grade invasive ductal carcinoma-NOS compared to high grade tumours. In the present study, no significant difference in MCD was observed across grades 1, 2, and 3 tumours.

Surgical margins' involvement by tumour: Only three out of 51 cases showed involvement of surgical margins (deep resected margins) by tumour cells. No statistically significant difference in MCD was observed between the two groups (p-value=0.782). Previous studies by Rajput AB et al., [10] and Sang J et al., [17] have not found significant difference between MCD and surgical margin status.

Regional lymphnode status: Axillary lymphnode metastasis is a significant prognostic factor in carcinoma breast. Our results indicate that a higher MCD within the primary breast tumour is seen in patients without lymphnode metastasis compared to those with lymphnode metastasis [Table/Fig-10]; (p-value=0.0023). This was a significant finding correlating with many previous studies including Dabiri S et al., [9], Rajput AB et al., [10], and Pal S et al., [16] suggesting an antitumourigenic role of mast cells in invasive carcinoma breast.

Number of lymphnodes involved by tumour: Fakhrjou A et al., [11] have shown an inverse correlation of MCD to the number of lymphnodes involved by tumour. The present study did not reveal statistically significant difference of MCD between cases with pN1, pN2, and pN3 status.

MCD in carcinoma breast: Postchemotherapy induced changes in tissue. The present study included seven cases of carcinoma of breast, postneoadjuvant chemotherapy to assess their density and distribution pattern (and not included for clinicopathological correlation). The mean MCD was 3-4 folds higher compared to that of cases who did not receive chemotherapy. Mast cells were also distributed equally within the intratumoural and peritumoural areas whereas they were distributed mostly in the peritumoural areas, in those who did not receive chemotherapy.

A variety of inflammatory cells including mast cells are recruited to the breast parenchyma following neoadjuvant chemotherapy. It has been postulated that some of these cells may play a role in rendering chemoresistance. Ruffell B et al., [19] demonstrated that mast cells and neutrophils first infiltrate the tumour cells in higher number compared to those cases who did not receive neoadjuvant chemotherapy. Recent advances in tumour immunobiology have shown a role of antimast cell therapy for tumours where they play a pro-tumorigenic role [20] and a role for immunotherapy for some cancers where augmentation of antitumour immune response could limit the progression of cancers [21,22].

Limitation(s)

The study has a few limitations including a relatively smaller sample size of breast cancer patients who have undergone mastectomy (n=51) and found to be adequate for statistical analysis; however, can be expanded into one with a larger sample size. More diversity of various histological types and tumour size and could shed more light on association of MCD with those clinicopathological parameters and their significance. Immunohistochemical (IHC) staining could be more advantageous to differentiate between functional mast cell subsets (chymase and tryptase positive) to infer their role.

CONCLUSION(S)

Our study on the differential distribution of mast cells within the tumour microenvironmemnt in breast carcinoma in a South Indian population with relation to clinicopathological parameters has shown a statistically significant level of higher MCD within the peritumoural area in the patient group without regional lymphnode metastasis compared to the group with regional lymphnode metastasis. This would suggest an antitumorigenic or beneficial role of mast cells in breast carcinoma compared to other solid organ cancers and could serve as a positive prognostic indicator for patient stratification and specific treatment. Diligent clinical follow-up of these patients and survival rates are required to determine the exact prognostic significance of these findings. The function of mast cells, being a key component of the innate immune system could also be augmented by immunotherapy in cancers where they have an antitumorigenic role. This study could be extended with functional in-vitro studies and IHC analysis of mast cell subsets (tryptase and chymase positive) could further help to establish their exact function at a particular stage of tumour development and help identify mast cell-derived or associated molecular biomarkers, which could serve as

new therapeutic targets for breast cancer in the era of personalised medicine.

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