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Original Article

Pathology Section

Stromal Mast Cells in Invasive Ductal Carcinoma of Breast and its Relationship with Tumour Grade and Hormonal Receptor Status: A Cross-sectional Study

SRI SUGHANYA CHANDRA SEKARAN[1], P ARUNALATHA[2]

ABSTRACT

Introduction: Tumour prognosis depends upon both the tumour cells as well as the stromal cells of the tumour microenvironment. Mast cells are immune cells which are basically involved in allergic reactions. But its role in breast cancer still remains controversial.

Aim: To identify the stromal mast cells in Invasive Ductal Carcinoma (IDC) of breast and its association with tumour grade and hormonal receptor status.

Materials and Methods: The present cross-sectional study was conducted in Department of Pathology, Government Stanley Medical College and Hospital, Chennai, Tamil Nadu, India with a sample size of 108 cases who had underwent Modified Radical Mastectomy (MRM) procedure for breast cancer between the period of November 2016 to April 2017. Patient age and sex was obtained from the histopathology requisition form. Histological grading of tumour based on Elston-Ellis modification of Scarff-Bloom Richardson grading system was done in Haematoxylin and Eosin (H&E) stained tissue sections. Giemsa stain was used to assess the stromal mast cells. All the 108 cases were screened for receptor status of Estrogen and Progesterone as well as Human Epidermal Growth factor receptor 2 (HER2neu) status through immunohistochemical staining. Results were analysed by Independent sample t-test and Chi-square test using Statistical Package for the Social Sciences (SPSS) software version 18.0.

Results: Of 108 study subjects, mean age of the subjects with mast cell positivity was 52.13 years and mast cell negativity was 53.01 years. Grade I tumour had higher proportion of stromal mast cell positivity whereas Grade III had higher proportion of mast cell negativity. Estrogen Receptor (ER) positive tumour showed association with mast cell positivity. There was no significant association between Progesterone Receptor (PR) positivity, Her2neu positivity and mast cell positivity.

Conclusion: Stromal mast cells in higher proportion were observed in low-grade tumour (Histological Grade I) when compared with high-grade tumour (Histological Grade III). Since stromal mast cells were associated with low-grade tumour, its presence suggested better prognosis. In this study only ER positivity were associated with the mast cell positivity. To conclude stromal mast cells has association with low-grade tumour and ER positive tumour which in turn suggested good prognosis.

Keywords: Breast cancer, Giemsa stain, Immunohistochemistry, Prognosis, Tumour microenvironment

INTRODUCTION

Increase in the incidence of breast carcinoma is being seen among the Indian women [1]. In India, IDC is the most common histologic subtype of breast cancer [2]. From the last few decades various researches had been focussed predominantly on the tumour cells. However recent researches indicates that both the tumour cells as well as the stromal cells interact with each other to promote the tumour growth. Stromal cells of breast carcinoma comprised of Cancer Associated Fibroblasts, Lymphocytes, Eosinophils and Mast cells [3]. Among the stromal cells the mast cells has gained interest among the researchers because of its controversial role in breast cancer [4]. Various studies proved the presence of stromal mast cells in other tumours like Malignant melanoma, Hodgkin's Lymphoma, Pancreatic cancer, Oesophageal cancer and Prostatic cancer [5].

Paul Ehrlich in 1878 first described about the mast cells in his thesis. Mast cells are immune cells derived from bone marrow, which are involved in allergic reaction [6]. Mast cells are found in skin, mucosa, stromal tissue, in vicinity of blood vessels and nerve endings. Mast cells on activation releases numerous mediators like heparin, protease, histamine, chemokines and growth factors which together contribute to the wound healing, tissue repair and angiogenesis. These cells also infiltrate the cancer and they can either suppress or promote the cancer growth [7].

Various studies on mast cells in breast cancer carried over in western women by Aaltomaa S et al., Syrjänen KJ et al., Hartveit F et al., Fisher ER et al., and Heidarpour M et al., suggested that the peritumoural stromal mast cells are associated with low tumour grade and hence good prognosis [8-12]. In addition to the routine hormonal study, mast cell identification using special stain may also be included in future to identify the tumour subset with better prognosis and survival. Hence the present study was carried over to study the presence of stromal mast cells in breast cancer and to find its association with the tumour grade, ER, PR and HER2neu receptor status.

MATERIALS AND METHODS

The present cross-sectional study was conducted in Department of Pathology, Government Stanley Medical College and Hospital, Tamil Nadu, India during October 2017 to December 2017 with 108 mastectomy specimens received between November 2016 to April 2017. This study was approved by Institutional Ethical Committee of Stanley medical college dated 25/10/17. Informed consent was not obtained since it was waived by the Institutional Ethical Committee.

Sample size calculation: Taking the proportion of breast cancer cases exhibiting stromal mast cell positivity as 50% [12], sample size was calculated based on the formula $N=4pq/d^2$.

p-prevalence=50 [12], q=100-p i.e.100-50=50,

d-precision =20%of p, d=10

Sample size calculated is N=100

Inclusion criteria: 108 cases of varying age (30-80 years) who had underwent MRM procedure with the trucut biopsy report of IDC were included in this study.

Exclusion criteria: Histological variants other than invasive ductal carcinoma of breast and the cases who had undergone neoadjuvant chemotherapy, radiotherapy for breast cancer were excluded from this study.

Study Procedure: Patient's age and sex was obtained from the histopathology requisition form. Formalin fixed paraffin embedded tissue blocks were made from MRM specimens. Tissue sections of five micron thickness were made with semiautomated rotatory microtome and were stained using H&E stain. The histological grade were assigned (Grade I, Grade II, and Grade III) by two pathologists based on Elston-Ellis modification of Scarff-Bloom Richardson grading system which comprised of three factors: Tubule formation, Nuclear size and Mitotic count. Each component were given a score ranged from 1 to 3. Combined score of all three factors were used for assigning the histologic grade. Scores of 3 to 5 were assigned as Grade I, score of 6 and 7 were assigned as Grade II and score of 8 and 9 were assigned as Grade III [Table/Fig-1] [13].

Modified Scarff-Bloom-Richardson Histologic Grading [13]			
Criteria	**Score 1**	**Score 2**	**Score 3**
Tubule formation	>75% of tumour shows tubules	10-75% of tumour has tubules	<10% of tumour has tubules
Nuclear size	Similar to normal ductal cell nuclei	1.5-2 times larger	>2 times larger
Mitotic count	0-7 mitoses/10HPF	8-14 mitoses/10HPF	≥15 mitoses/10HPF
Nottingham Combined Histologic Grade [12]			
Score 3-5	Grade I		
Score 6-7	Grade II		
Score 8-9	Grade III		

[Table/Fig-1]: Modified Scarff-Bloom-Richardson histologic grading [12,13].

With the chrome alum coated glass slides, tissue sections of three micron thickness were cut using Leica HistoCore Multicut-Semi automated rotatory microtome for manual immunohistochemical staining. The tissue sections were deparaffinised using xylene and then rehydrated in graded alcohol (100%, 90% and 70%) three minutes each. After distilled water rinse the sections were kept in Tris-EDTA (pH 9.2) buffer solution and subjected to antigen retrieval using pressure cooker for 30 minutes. After gentle tap water wash and Tris buffer wash for five minutes each, the sections were incubated with Horseradish Peroxidase (HRP) for 10 minutes to inhibit the endogenous peroxidase activity in the tissue. After a Tris buffer wash for five minutes, sections were covered with primary antibodies (ER, PR, Her2neu) for 45 minutes. Antibodies (primary antibody) used were ER (Estrogen Receptor clone EP1,Source–Rabbit Monoclonal, Cat#PR042-3 mL RTU), PR (Progesterone Receptor clone EP2, Source–Rabbit Monoclonal, Cat#PR068-3 mL RTU), Her2/Erb2 (clone EP3, Source –Rabbit Monoclonal, Cat#PR047-3 mL RTU). Then again a Tris buffer wash was given for five minutes, which was followed by the application of super enhancer for 15 minutes which enhances the final reaction product by increasing the sensitivity of antigen antibody reaction. Sections were washed in Tris buffer and subjected to secondary antibody from the goat with the tagged HRP enzyme for 15 minutes. Following the buffer wash for five minutes, Diaminobenzidine (DAB) chromogen was applied for five minutes which give the coloured product at the antigen sites. Sections were rinsed in distilled water, counterstained with haematoxylin, air-dried and mounted with Distyrenedibutyl Pthalidein Xylol (DPX). Normal breast tissue was taken as internal positive control for ER and PR stain whereas Her2neu positive breast cancer were used as positive control for Her2neu stain.

ER, PR receptors were scored by two pathologist individually based on Allred Scoring system which has two components i.e., Proportion score and Intensity score. Proportion score ranges from 0-5 based on the number of tumour cells exhibiting nuclear positivity of ER, PR stains and Intensity score ranges from 0-3 based on the intensity of the stain. Sum of the proportion score and the intensity score gives the final Allred Score. Allred score of zero to two was considered as negative and three to eight was considered as positive [14].

Her2neu scoring was done based on American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. Her2neu shows cell membranous positivity and depending upon the intensity of stain, score of zero to three were assigned. Score of 3+ was considered as positive and 0, 1+, 2+ were considered as negative. Score of 2+ was defined as weakly positive/equivocal based on ASCO/CAP guidelines but need confirmation with Fluorescent In Situ Hybridisation (FISH) technique. Due to the non availability of FISH technique in the institute, 2+ Her2neu cases were taken as negative in this study [15].

Tissue sections were again cut at three microns thickness from the formalin fixed paraffin embedded tumour tissue blocks for geimsa staining. Slides were deparaffinised in xylene and hydrated in distilled water. Working Giemsa solution was made by diluting ready-made Giemsa solution (Brand-NICE) with distilled water in 1:20 ratio. Slides were dipped in working Giemsa solution for 30 minutes, then differentiated in 1% acetic acid solution for 3 seconds. Distilled water rinse were given, then dehydrated and mounted. Tissue section of cutaneous mastocytosis were taken as positive control. Mast cells showed violet purple metachromatic stain. Sections were examined by two pathologist separately. Mast cells were examined in the tumour stroma and the case were assigned as mast cell positive if one or more mast cells were present in the peritumoral stroma in 10 high power field. [Olympus microscope CH20i, 40X magnification,18 mm eye piece diameter] [12].

STATISTICAL ANALYSIS

All the collected data were compiled in Microsoft Excel and the SPSS version 18.0 was used for statistical analysis. Analysis was done using independent sample t-test and Chi-square test. The p-value <0.05 was considered significant statistically.

RESULTS

The mean age of the study subjects with mast cell positive tumour was 52.13 years and mast cell negative tumour was 53.01 years. The mean difference of age was -0.880 which was not statistically significant [Table/Fig-2].

Groups	Mean age±SD (years)	Mean difference	95% Confidence interval	p-value
Mast cell positive cases (n=51)	52.13	-0.880	(-4.533-2.77)	0.633
Mast cell negative cases (n=57)	53.01			

[Table/Fig-2]: Comparison of age of the cases which shows stromal mast cell positivity and mast cell negativity using independent t-test.

Out of 108 cases, 57 (52.78%) cases were negative for stromal mast cells and 51 (47.22%) were positive for stromal mast cells [Table/Fig-3].

Average mast cell count	Number of cases (n)	Percentage (%)
Zero/10 HPF	57	52.78
1/10 HPF	3	2.78
2-5/10 HPF	27	25
6-9/10 HPF	17	15.74
10 and above/10 HPF	4	3.7
Total	108	100

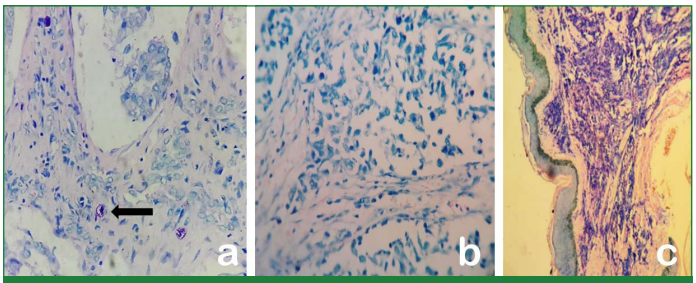
[Table/Fig-3]: Average stromal mast cell count per 10 High Power Field (HPF) (n=108).

Out of 108 cases, 21 (19.44%) cases were of histological grade I, 65 cases (60.19%) were of grade II and 22 (20.37%) were of grade III

tumours [Table/Fig-4]. Of 21 cases (19.44%) with histological grade I, all 21 cases (19.44%) were mast cell positive [Table/Fig-5a]. Out of 65 (60.19%) patients with histological grade II, 27 (25%) were mast cell positive and 38 (35.19%) were mast cell negative. Out of 22 patients (20.37%)with grade III, 3 (2.78%) were mast cell positive and 19 (17.59%) were mast cell negative [Table/Fig-5b]. Grade I tumour had higher proportion of mast cell positive tumours while Grade III tumours had higher proportion of mast cell negativity. This association was statistically significant (p-value <0.01) [Table/Fig-4]. Positive control taken for giemsa stain was cutaneous mastocytosis, in which the infiltration of numerous mast cells was seen [Table/Fig-5c].

Tumour grade	Mast cells (%)			Chi-square value	p-value
	Positive Cases	Negative Cases	Total		
Grade I	21 (19.44)	0	21 (19.44)	34.27	<0.01
Grade II	27 (25)	38 (35.19)	65 (60.19)		
Grade III	3 (2.78)	19 (17.59)	22 (20.37)		
Total	51	57	108 (100)		

[Table/Fig-4]: Comparison between tumour grade and mast cells positivity and negativity.



[Table/Fig-5]: a) Microphotograph of grade I tumour showing mast cell positivity (Giemsa stain 40x); b) Microphotograph of grade III tumour showing mast cell negativity. (Giemsa stain, 40x); c) Microphotograph of cutaneous mastocytosis as positive control (Giemsa stain, 40x).

Out of 108 cases of breast carcinoma, 77 (71.30%) were ER positive and 31 (28.7%) were ER negative. The association was statistically significant (p-value=0.0480). ER positive tumours were more associated with mast cell positivity while ER negative tumours were associated with mast cell negativity [Table/Fig-6].

ER	Mast cells n (%)			Chi-square	p-value
	Positive cases	Negative cases	Total		
Positive	41 (37.97)	36 (33.33)	77 (71.30)	3.9066	0.0480
Negative	10 (9.26)	21 (19.44)	31 (28.70)		
Total	51 (47.23)	57 (52.77)	108 (100)		

[Table/Fig-6]: Comparison of estrogen receptor status and mast cell positivity and negativity.
ER: Estrogen receptor

Out of 108 cases of carcinoma breast, 38 (35.19%) were PR positive and 70 (64.81%) were PR negative. Out of 38 PR positive, 20 (18.52%) were mast cell positive and 18 (16.67%) were mast cell negative. Out of 70 cases, 31 (28.70%) were mast cell positive and 39 (36.11%) were mast cell negative. This association was not statistically significant (p-value=0.407) [Table/Fig-7].

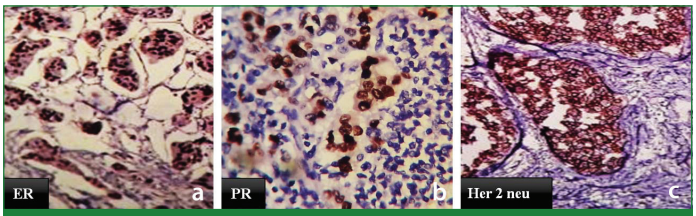
PR	Mast cells n (%)			Chi-square	p-value
	Positive cases	Negative cases	Total		
Positive	20 (18.52)	18 (16.67)	38 (35.19)	0.6883	0.407
Negative	31 (28.70)	39 (36.11)	70 (64.81)		
Total	51 (47.22)	57 (52.78)	108 (100)		

[Table/Fig-7]: Comparison of progesterone receptor status and mast cell positivity and negativity.
PR: Progesterone receptor

Out of 108 cases of carcinoma breast, 30 (27.78%) were Her2neu positive and 78 (72.22%) were Her2neu negative. Out of 30, 13 (12.04%) were mast cell positive and 17 (15.74%) were mast cell negative. Out of 78, 38 (35.18%) were mast cell positive and 40 (37.04%) were mast cell negative. The association was not statistically significant (p-value=0.616) [Table/Fig-8]. Cases with ER, PR and Her2neu positivity showed brown staining of tumour cells infiltrating into the stroma [Table/Fig-9].

Her2neu	Mast cells n (%)			Chi-square	p-value
	Positive cases	Negative cases	Total		
Positive	13 (12.04)	17 (15.74)	30 (27.78)	0.2521	0.616
Negative	38 (35.18)	40 (37.04)	78 (72.22)		
Total	51 (47.22)	57 (52.78)	108 (100)		

[Table/Fig-8]: Comparison of Her2neu receptor status and mast cell positivity and negativity.
Her2neu-Human epidermal growth factor receptor.



[Table/Fig-9]: a) Microphotograph showing tumour tissue with IHC (ER) -Estrogen Receptor positivity (40x), IHC (PR)- b) Progestrone Receptor positivity (40x), IHC (Her2neu)- c) Human epidermal growth factor receptor 2 positivity (40x).

DISCUSSION

With the rise in incidence of breast cancer, there is a need to research, identify novel prognostic markers and their drugs to improve the patient survival. Treatment of breast cancer comprises of surgery, chemotherapy and hormonal therapy depending upon the tumour staging. In addition to the routine treatment guidelines, identifying tumour subset with good prognosis using new prognostic markers can improve the lifetime survival. Few researches demonstrated stromal mast cells as a favourable prognostic marker in breast cancer [8,9].

Age of the cases in the present study varied from 30-80 years, with majority of the cases in 50-60 years. Mean age was 52.13 years with mast cell positivity and 53.01 years with mast cell negativity. Age difference between mast cell positive cases and mast cell negative cases was not statistically significant.

Heidarpour M et al., conducted a study which included patients with age less than 30 to more than 85 years [12]. Mean age of the study samples was 52.3 years. Similar mean age of study samples were observed in the studies done by Fakhrjou A et al., [16], Divyarani MN et al., [17], and Pyla RD et al., [18]. A study conducted by Amini RM et al., included patients from 27 to 95 years with a mean age of 54 years [19]. A study was conducted by Dabiri S et al., which included patients from 28-87 years with a mean age of 63 years [20]. Rovere FD et al., conducted a study with a mean age of 67.64 years in 2007 [21].

In the present study out of 108 cases, 21 (19.44%) cases were of histological grade I and all these cases showed mast cell positivity in the peritumoural stroma. Out of 65 (60.19%) cases of grade II tumours, 27 (25%) cases showed stromal mast cells and among 22 (20.37%) cases of grade III tumours, only 3 (2.78%) cases showed stromal mast cell positivity. The comparison between tumour histological grade and mast cell positivity was statistically significant (p-value <0.01). Studies by Heidarpour M et al., Amini RM et al., Jana S et al., Glajcar A et al., also showed that the mast cells were associated with low tumour grade [12,19,22,23]. Mast cells secrete Tumour Necrosis Factor (TNF), various cytokines like Interleukin1, 4, 6 which in turn may lead to tumour cell necrosis. Mast cell may prevent the tumour growth by causing fibrosis of the tumour due to the fibroblastic proliferation produced by the mast cell tryptase [24].

In this study, out of 108 cases, 77 (71.30%) cases were ER positive and 31 (28.70%) cases were ER negative. Out of 31 ER negative cases, 10 (9.26%) were mast cell positive and out of 77 ER positive cases, 41 (37.97%) were mast cell positive. Comparison of mast cell positivity with ER positivity was statistically significant in the present study (p-value=0.0480). Studies by Heidarpour M et al., Pyla RD et al., Amini RM et al., Jana Set al., and Rajput AB et al., also showed statistically significant association between ER positivity and mast cell positivity [12,18,19,22,24].

In the present study, out of 108 cases, 38 (35.19%) cases were PR positive and 70 (64.81%) cases were PR negative. Out of 38 PR positive cases, 20 (18.52%) were mast cell positive and out of 70 PR negative cases, 31 (28.70%) were mast cell positive. Comparison of mast cell positivity with PR positivity was not statistically significant (p-value=0.407). Other studies by Heidarpour M et al., and Amini RM et al., also showed statistically insignificance between mast cell positivity and PR positivity [12,19]. But studies by Jana S et al., Glajcar A et al., and Sang J et al., showed significant association between PR positivity and mast cell positivity [22,23,25].

Out of 108 cases 30 (27.78%) cases were Her2neu positive and 78 cases were Her2neu negative. Out of 30 Her2neu positive cases, 13 (12.04%) were mast cell positive and out of 78 (72.22%) Her2neu negative cases, 38 (35.18%) were mast cell positive. Comparison of mast cell positivity with Her2neu positivity was not statistically significant (p-value=0.616). Similar results were observed by the studies done by Heidarpour M et al, Pyla RD et al., Jana S et al, Glajcar A et al., and Sang J et al [12,18,22,23,25].

To summarise this study, presence of stromal mast cells in invasive ductal breast cancer was associated with low tumour grade and ER positivity. Thus study of stromal mast cells in breast cancer may help us to identify the tumour with better prognosis.

Limitation(s)

In this study only Her2neu 3+ cases were taken as positive and its association with mast cell positivity were studied. However Her2neu2+ cases (equivocal cases) can be confirmed only with FISH technique and its non availability was the major limitation of this study. Also in the present study only special stain Giemsa was used for the identification of mast cells and IHC of mast cell (CD-117/Tryptase/Chymase) were not used due to budgetary limitation

CONCLUSION(S)

This study showed the association between stromal mast cells in IDC of breast with low tumour grade and ER positivity. Since low-grade tumour and ER positive tumour have better prognosis, presence of stromal mast cells also indicate better prognosis. Thus in addition to the routine histopathological staining and hormone receptors staining, staining for mast cells can be included to identify the subset of breast cancer which carries better prognosis.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Pathology, Trichy SRM Medical College Hospital and Research Centre, Tiruchirappalli, Tamil Nadu, India.
2. Professor, Department of Pathology, Stanley Medical College and Hospital, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sri Sughanya Chandra Sekaran,
No.17, Rajiv Gandhi Nagar, Edamalaipatti Pudur, Trichy, Tiruchirappalli, Tamil Nadu, India.
E-mail: c.srisughanya@yahoo.com

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