A Histopathological Study on Invasive Ductal Carcinoma Breast with Respect to ER/PR Status and Mast Cell Distribution

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Abstract

Introduction: When a carcinoma develops our immunity plays a major role in fighting against tumor cells. Mast cells which play a major role in our innate immunity are also found to get activated in a developing tumor. So far only few studies have been conducted on the role of mast cell in carcinoma breast which have shown the cytolytic activity of these on tumor cells and their relationship in response to hormone receptor status.

Aim: To study the histopathological characteristics of invasive ductal carcinoma breast, and mast cell count in them and their relationship with Estrogen & Progesterone receptor status.

Materials and Methods: We did a descriptive histopathological study on the specimens of modified radical mastectomy received in the Department of Pathology, Government Medical College, Thiruvananthapuram from 1st January 2012 to 2014. Histopathological characteristics of each case with respect to their ER/PR status was studied. Mast cell were stained using special stains and counted. Data was statistically analysed with SPSS software using Univariate analysis and chi square test to detect the significance of mast cell presence with receptor status in invasive ductal carcinoma breast.

Results: Out of total 150 cases the mast cells were present in 56 cases (37.3%) and were absent in 94 cases (62.7%). The relationship between presence of mast cells and estrogen and progesterone receptor positivity was found to be statistically insignificant as the p-value was more than 0.05. Thus there was no significant relationship between estrogen and progesterone receptor status with the presence of mast cells.

Conclusions: The present study showed that there is no significant relationship between presence of mast cells in peritumoral tissue and the hormonal status of the patient. So as per this study mast cell presence cannot be suggested as a definitive cheap easily assessable prognostic factor in carcinoma breast. Newer modalities for detection of new prognostic indicators can help in implementation of adjuvant therapies in a patient with ductal carcinoma breast.
Introduction
Among the various cancers carcinoma breast is the most common cancer among women in developed countries and is the second most common cancer among Indian females. Developmentally, the female breast is under the control of estrogen and progesterone. So these hormones play a strong role in the causation of breast cancer. It can be of 2 types- ductal and lobular of which Invasive Ductal Carcinoma (IDC) is the commonest form.

When a carcinoma develops our immunity plays a major role in fighting against tumor cells. Mast cells which play a major role in our innate immunity are also found to get activated in a developing tumor. So far only few studies have been conducted on the role of mast cell in carcinoma breast which have shown the cytolytic activity of these on tumor cells and their relationship in response to hormone receptor status. Various studies have been conducted to find out the relationship between the hormone receptor status and cellular status in tumor microenvironment.

The invasive breast carcinomas is graded histologically as per the Nottingham modification of the Scarff-Bloom-Richardson grading system which grades breast carcinomas by adding up scores for tubule formation, nuclear pleomorphism, and mitotic count. The scores for each of these are added together to give an overall final score and corresponding grade for IDC.

The Clinical Grading is using TNM staging. Lower the stage betters the prognosis. ER and PR status is assessed as per Allred score. Positivity for these receptors favors good prognosis.

A study is being planned to find out histopathological characteristics of invasive ductal carcinoma breast in our setup and to find out the relationship of mast cell distribution in invasive carcinoma breast with respect to various grades and their ER/PR status.

Materials and Methods
Study Design: Descriptive study

Study Setting: Department of Pathology, Government Medical College, Thiruvananthapuram.

Study Period: January 2012 to January 2014

Study Population:

Inclusion Criteria
All the specimens of modified radical mastectomy received in the Department of Pathology, Government Medical College, Thiruvananthapuram from 1st January 2012 to 1st January 2014.

Exclusion Criteria
- Histopathological diagnosis other than invasive ductal carcinoma
- carcinoma breast in males

Methodology
- Evaluation of clinical features
- Evaluation of Morphological Factors

In hematoxylin and eosin stained sections, various parameters namely tumour grade, histological type, mitosis, peritumoral tissue, venous invasion, host response and the number of lymph nodes involved by the tumour were studied.

Sections from tumor were also assessed for hormone receptor status namely estrogen and progesterone receptor status and graded using ALLRED scoring system.

Sections from peritumoral tissue were taken and stained with toluidene blue and giemsa for studying the distribution of mast cells.

Various prognostic factors analysed in the study may be defined as follows:
- Age, Tumour location, Tumour size
- Tumour grade: Tumour grading was done based on Modified Bloom Richardson scoring system:
- Histology: only tumors which had histology consistent with IDC-NOS was selected
- Vascular invasion: Vascular emboli were searched in the tumour as well as in adjacent tissues.
- Peritumoral tissue: The host immune response in peritumoral tissue was assessed as to whether there was
lymphocytic infiltration or fibrosis or mast cells.

- **Lymph nodes involved**: ER AND PR STATUS: as per ALLRED SCORING SYSTEM using adequate controls

**Patients were Stratified into 4 groups Based on Average Intensity Score of ER and PR Status**

**Mast Cells**: Sections from peritumoral areas are stained using toluidene blue and giemsa and mast cells are counted per high power field.

A case was taken as mast cell positive only if one or more mast cells were present in stromal areas of specimens in 10 high power fields in both giemsa and toluidene blue.¹

Finally cases were compared with presence of mast cells in each with respect to their ER and PR status.

**Analysis**

Statistical analysis in the present study was performed using SPSS software. Univariate analysis was done using chi square test to detect the significance of mast cell presence with receptor status in invasive ductal carcinoma breast.

**Observations and Results**

The present study was done on the mastectomy specimens done for carcinoma breast received in the department of pathology, Government Medical College, Thiruvananthapuram during a period of two years from January 2012 to January 2014. A total of 150 cases were studied.

**Age Distribution**

In this study all the cases were divided into 3 groups based on age as <40yrs, 40-60yrs and >60 yrs. Majority of the cases were between 40-60 yrs (68%) followed by 23% cases above 60 yrs. The youngest patient was 30 yrs old and oldest was 78 yrs old. (Table 1,Figure 1)

**Table 1 - Age Distribution**

| Age (in years) | Frequency | Percentage |
|----------------|-----------|------------|
| <40            | 13        | 8.7%       |
| 40-60          | 102       | 68.0%      |
| >60            | 35        | 23.3%      |
| Total          | 150       | 100.0%     |

**Tumor Laterality**

Among 150 cases studied, most of the tumors 69(54%) were located on left side and 81 cases (46%) were located on right side. Thus there was a slight predominance for left sided tumors. (Table 2,Figure 2)

**Table 2- Tumor Laterality**

| Tumor Laterality | Frequency | Percentage |
|------------------|-----------|------------|
| Right            | 69        | 46.0%      |
| Left             | 81        | 54.0%      |
| Total            | 150       | 100.0%     |

**Tumor Size**

Tumor size was graded into 3 groups ie.a)Less than or equal to 2 cm size b)more than 2cm to size less than or equal to 5cm and c)more than 5 cm and majority of the cases ie 110 cases (73.4%) had tumor size between 2 to 5 cm. (Table 3,Figure 3)
Table 3 - Tumor Size

| Tumor Size (Cm) | Frequency | Percentage |
|----------------|-----------|------------|
| ≤2             | 14        | 9.3%       |
| >2 - ≤5        | 110       | 73.4%      |
| >5             | 26        | 17.3%      |
| Total          | 150       | 100.0%     |

Figure 3 - Tumor Size

Histological Grade

All the cases were graded using Modified Bloom Richardson grading (MBR) system. Out of the 150 cases studied 123 cases (82%) belonged to grade 2 closely followed by 25(16.7%) cases in grade 3 and 2 cases (1.3%) in grade 1. (Table 4, Figure 4)

Table 4 - Histological Grade

| HISTOLOGICAL GRADE (MBR) | FREQUENCY | PERCENTAGE |
|--------------------------|-----------|------------|
| 1                        | 2         | 1.3%       |
| 2                        | 123       | 82.0%      |
| 3                        | 25        | 16.7%      |
| Total                    | 150       | 100.0%     |

Figure 4 – Histological grade

Number of Lymphnodes Involved by Metastasis

The patients were divided into 4 groups based on lymph node status. Majority of the cases had positive lymph nodes showing tumor (62.7%) while 56 cases (37.3%) had negative nodes. (Table 5, Figure 5)

Table 5 - Lymphnode Involvement

| Number Of Lymphnodes Involved By Metastasis | Frequency | Percentage |
|--------------------------------------------|-----------|------------|
| Nil                                        | 56        | 37.3%      |
| 1-3                                        | 42        | 28.0%      |
| 4-9                                        | 39        | 26.0%      |
| >10                                        | 13        | 8.7%       |
| Total                                      | 150       | 100.0%     |

Figure 5 - Lymphnode involvement

Lymphovascular Invasion

Out of 150 cases evaluated only 11 cases (7.3%) showed features suggestive of tumor invading lymphatics or vessels. (Table 6, Figure 6)

Table 6 - Lymphovascular Invasion

| Lymphovascular Invasion | Frequency | Percentage |
|-------------------------|-----------|------------|
| Present                 | 11        | 7.3%       |
| Absent                  | 139       | 92.7%      |
| Total                   | 150       | 100.0%     |
Margin Involvement
Margin involvement was found in only 26 cases (17.3%) while 124 cases (82.7%) showed no margin involvement by tumor cells. (Table 7, Figure 7)

Table 7-Margin Involvement

| Involvement of Margins | Frequency | Percentage |
|------------------------|-----------|------------|
| Present                | 26        | 17.3%      |
| Absent                 | 124       | 82.7%      |
| Total                  | 150       | 100.0%     |

Estrogen Receptor Status
Cases were analysed for Estrogen receptor status and graded using ALLRED scoring system and divided into 4 grades as strong positive, moderately positive, weak positive and negative. Majority of the cases i.e. 87 cases (58%) showed positivity for Estrogen receptor. While 63 cases (42%) showed Estrogen negativity. (Table 8, Figure 8)

Table 8- Estrogen Receptor Status

| Estrogen Receptor | Frequency | Percentage |
|-------------------|-----------|------------|
| Absent            | 63        | 42.0%      |
| Weak              | 47        | 31.3%      |
| Moderate          | 32        | 21.3%      |
| Strong            | 8         | 5.3%       |
| Total             | 150       | 100.0%     |

Progesterone Receptor Status
Progesterone receptor status assessed by ALLRED scoring system showed positivity in 74 cases (49.3%) and 76 (50.7%) cases showing progesterone negativity. (Table 9, Figure 8)

Table 9- Progesterone Receptor Status

| Progesterone Receptor | Frequency | Percentage |
|-----------------------|-----------|------------|
| Absent                | 76        | 50.7%      |
| Weak                  | 40        | 26.7%      |
| Moderate              | 24        | 16.0%      |
| Strong                | 10        | 6.7%       |
| Total                 | 150       | 100.0%     |

Presence of Mast Cells
Presence of mast cells in peritumoral tissue was assessed using special stains. The mast cells were present in 56 cases (37.3%) and were absent in 94 cases (62.7%). (Table 10, Figure 9)
Presence of Ductal Carcinoma in Situ

Presence of ductal carcinoma in situ component in adjacent breast tissue was present in 35 cases (23.3%) while rest 115 cases (76.7%) showed features like fibrosis, adenosis, inflammatory cell infiltrate etc. (Table 11, Figure 10)

Table 11- Presence of Ductal Carcinoma In situ Component

| DCIS     | Frequency | Percentage |
|----------|-----------|------------|
| Present  | 35        | 23.3%      |
| Absent   | 115       | 76.7%      |
| Total    | 150       | 100.0%     |

**Figure 10** Presence of Ductal Carcinoma INSITU

Mast cells and Hormonal Status

The relationship between presence of mast cells and estrogen receptor positivity and progesterone receptor positivity was analysed separately using Chi-Square test. The result was found to be statistically insignificant as the p-value was more than 0.05. Thus there was no significant relationship between estrogen and progesterone receptor status with the presence of mast cells. (Table 12, Table 13)

Table 12- Mast Cells and Estrogen Receptor Status

| ER     | MAST cells | Total |
|--------|------------|-------|
|        | Present    | Absent|       |
|        | No: | %   | No: | %   | No: | %   |
| Absent | 18  | 32.1 | 45  | 47.9 | 63  | 42.0 |
| Weak   | 19  | 33.9 | 28  | 29.8 | 47  | 31.3 |
| Moderate| 15 | 26.8 | 17  | 18.1 | 32  | 21.3 |
| Strong | 4   | 7.1  | 4   | 4.3  | 8   | 5.3  |
| Total  | 56  | 100.0| 94  | 100.0| 150 | 100.0|

χ² = 4.053 df = 3 p=0.256

Table 13- Mast Cells and Progesterone Receptor Status

| PR     | MAST cells | Total |
|--------|------------|-------|
|        | Present    | Absent|       |
|        | No: | %   | No: | %   | No: | %   |
| Absent | 26  | 46.4 | 50  | 53.2 | 76  | 50.7 |
| Weak   | 16  | 28.6 | 24  | 25.5 | 40  | 26.7 |
| Moderate| 11 | 19.6 | 13  | 13.8 | 24  | 16.0 |
| Strong | 3   | 5.4  | 7   | 7.4  | 10  | 6.7  |
| Total  | 56  | 100.0| 94  | 100.0| 150 | 100.0|

χ² = 1.409 df = 3 p=0.703

Discussion

As carcinoma breast is the most common cancer affecting women a clear knowledge regarding the different prognostic factors is very important. The detection of new factors helps us to implement newer treatment modalities which can be advocated as adjuvant treatment mainly to node negative patients. The detection of new factors like mast cells detected by simple techniques are seen to correlate with hormone status and so can be useful both as prognostic and treatment factor. The Present Study Included 150 Cases of Invasive Ductal Carcinoma Over A Period Of 2 Years.
Age
The mean age of patients was 54yrs which was similar to other studies. Comparing with other studies it was found to be comparable to findings by Baxter et al with mean age of 56.88 yrs. The majority of patients belonged to the age range of 40 to 60 yrs.

Table 14-Comparison of Age

| Study                  | Mean Age   |
|------------------------|------------|
| Dueck et al^5          | 58.7 yrs   |
| Baxter et al^6         | 56.88yrs   |
| Chakraborthy et al^4    | 43.21yrs   |
| Present study          | 54yrs      |

Tumor Laterality
Most common side affected by invasive ductal carcinoma breast was found to be leftside. Comparing with other studies it was similar to the findings by Stanec et al^8 but dissimilar to the observations made by Chakraborthy et al^8 and Raychaudhari et al^7 with most common side affected being right side.

Table 15- Comparison of Tumor Laterality

| Study              | Right breast | Left breast |
|--------------------|--------------|-------------|
| Chakraborthy et al^8 | 56.52%       | 43.48%      |
| Raychaudhari et al^7 | 51.7%        | 46.7%       |
| Stanec et al^9      | 45.4%        | 54.6%       |
| Present study       | 46%          | 54%         |

Tumor Size
In the present study it was seen that majority of the cases had tumor size between 2 cm to 5 cm category which was comparable with the observations made by Rojananin et al^11 and Tan PH et al^12. However, Baxter et al^6 found that predominant tumors size was less than 2 cm. Rusby JE et al^13 categorised tumour size into ≤ 2 cm and > 2 cm and observed a higher proportion of tumours in ≤ 2 cm category (63%).

Table 16 Comparison of Tumour Size

| Study               | Tumour size ≤2 cm | Tumour size >2 cm but ≤ 5 cm | Tumour size >5 cm |
|---------------------|-------------------|------------------------------|------------------|
| Rojananin et al^11  | 30.4%             | 56.5%                        | 13.1%            |
| Tan PH et al^12     | 20%               | 60%                          | 20%              |
| Baxter et al^6      | 60.1%             | 27.8%                        | 12.1%            |
| Present study       | 9.3%              | 73.3%                        | 17.3%            |

Histological Grade
On grading invasive ductal carcinoma using Modified Bloom Richardson grading system in the present study, majority belonged to grade 2. The results were in concordance with the published observations by Baxter et al^6, Dueck et al^5, Smith et al^9 and Stanec et al^8. The result was however in contrast with the observations made by De Rosa G et al^10 who observed a predominance of grade 3 tumours. The difference may be due to inter-observer variability in grading the tumours.

Table 17- Comparison of histological grade

| Study               | Grade 1 | Grade 2 | Grade 3 |
|---------------------|---------|---------|---------|
| Baxter et al^6       | 27.3%   | 38.3%   | 34.4%   |
| Dueck et al^5        | 18%     | 42%     | 40%     |
| Smith et al^7        | 10%     | 47%     | 43%     |
| De Rosa G et al^10   | 9%      | 33%     | 58%     |
| stanec et al^9       | 32.1%   | 35.8%   | 32.1%   |
| Present study        | 1.3%    | 82.0%   | 16.7%   |

Lymph Node Involvement
In the present study metastasis from breast carcinoma to axillary lymph nodes was observed in 63.3% of cases. This was found to be similar to the result obtained by De Rosa G et al^10 and Chattopadhyay BK et al^7. However Baxter et al^6, AC Dueck et al^5 and Rusby JE et al^13 noted less proportion of cases with lymph node involvement. In the present study, majority of the cases had between 1 to 3 lymph nodes being involved which was similar to the observations made by Rusby JE et al^13.

Table 18- Comparison of Lymph node involvement

| Study               | Lymph node involvement |
|---------------------|------------------------|
| De Rosa G et al^10  | 51%                    |
| Chattopadhyay BK et al^7 | 57.5%         |
| Baxter et al^6      | 38.2%                  |
| Dueck et al^3       | 36%                    |
| Rusby JE et al^13   | 44.1%                  |
| Present study       | 63.3%                  |

Lympho-Vascular Invasion
In the present study the cases showing positivity for lympho-vascular invasion formed a small proportion coming to 7.3%. This was comparati-
vely less than the observations made by Z.Stanec et al., Dueck et al. and Rusby JE et al.

Table 19-Comparison of Lympho-vascular Invasion

| Study                | Presence of lymphovascular invasion |
|----------------------|-------------------------------------|
| Z.Stanec et al.      | 23%                                 |
| Dueck et al.         | 26%                                 |
| Rusby JE et al.      | 41%                                 |
| Present study        | 7.3%                                |

Presence of Ductal Carcinoma in Situ Component
In the present study Ductal carcinoma insitu component was observed in 35(23.3%) cases which was slightly higher compared to the data published by Rojananin et al. However, Rusby JE et al. observed a much higher proportion of cases i.e. 41% with both invasive carcinoma and intraductal component.

Table 20-Comparison for the presence of DCIS component

| Study               | DCIS component + Invasive Carcinoma |
|---------------------|-------------------------------------|
| Rojananin et al.    | 15.6%                               |
| Rusby JE et al.     | 54.7%                               |
| Present study       | 23.3%                               |

Oestrogen Receptor Status
In the present study which was done with control, positivity for oestrogen receptor was observed in 58% of cases. This proportion is comparatively lesser than the observations noted in other studies.

Table 21- Comparison of Oestrogen Receptor Positivity

| Study               | Oestrogen Receptor Positivity  |
|---------------------|-------------------------------|
| Baxter et al.       | 74.4%                         |
| Rusby JE et al.     | 75%                           |
| De Rosa G et al.    | 89.5%                         |
| Present study       | 58.0%                         |

Table 22-Comparison of Progesterone Receptor Positivity

| Study               | Progesterone Receptor Positivity |
|---------------------|----------------------------------|
| Baxter et al.       | 65.7%                            |
| De Rosa G et al.    | 84.5%                            |
| Present study       | 49.3%                            |

Presence of Mast Cells
The presence of mast cells in tumor tissue was assessed using control and was found to be positive in 37.3% cases which was similar to study by M. Heidarpouret al. study by David Hunstman et al. showed mast cell positivity in 26.7% cases. This variation might be due to the difference in techniques employed for the detection of mast cells.

Table 23- Comparison of Mast Cell Positivity

| Study               | Mast Cell Positivity |
|---------------------|----------------------|
| David Hunstman et al| 26.7%                |
| MitraHeidarpouret al| 33.3%                |
| Present study       | 37.3%                |

Comparison of Hormonal Status and Presence of Mast Cell in Breast Carcinoma
In the present study on analyzing the relationship between the presence of mast cells with the estrogen receptor status by chi square test it was found that there is no significant association between presence of mast cells in the peritumoral tissue and estrogen receptor status. This was similar to findings by Shahriar Dabiri et al which showed that there was no significant relationship between estrogen receptor status and mast cells by conducting studies on 348 cases of invasive ductal carcinoma breast. It was dissimilar to findings by Heidrapour et al which showed that stromal mast cells correlated to Estrogen receptor positivity and hence a good prognostic indicator.

The present study showed no relationship between progesterone receptor status with mast cells which was similar to the study findings by Mitra Heidrapour et al and Shahriar Dabri et al which also showed no correlation between the presence of stromal mast cells and PR positivity.

Conclusion
The present study showed that there is no significant relationship between presence of mast...
cells in peritumoral tissue and the hormonal status of the patient. So as per this study mast cell presence cannot be suggested as a definitive cheap easily assessable prognostic factor in carcinoma breast. Newer modalities for detection of new prognostic indicators can help in implementation of adjuvant therapies in a patient with ductal carcinoma breast.

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