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Stromal Expression Of CD10 In Invasive Breast Carcinoma And Its Correlation With ER, PR, HER2/neu.

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ABSTRACT

Breast cancer (BC), a major health burden both in the developed and developing countries, is the foremost cause of death in women worldwide with more than one million cases occurring annually. There has been sufficient evidence in the literature that supports tissue microenvironment as having a vital role in controlling cell survival, proliferation, migration, polarization, and differentiation.The prognostic role of novel stromal marker such as CD 10 is less studied in literature. To estimate the frequency of stromal CD10 expression in invasive carcinoma of breast. To assess the correlation of CD 10 with known prognostic markers (ER, PR, HER2/neu) of breast carcinoma. Total number of 599 breast specimens had been received in our department during this period. Out of these 287 cases were benign and 199 were reported as malignant. A total of 50 cases of invasive breast carcinoma diagnosed from the specimens of both modified radical mastectomy and lumpectomy procedures are randomly selected for this study. Newly diagnosed patients with unilateral presentation and no previous H/O neoadjuvant therapy are included in the study. Out of 199 cases reported as malignant, 182 cases are Invasive ductal Carcinoma-NOS type, 6 cases are reported as Mucinous carcinoma, 4 cases are Papillary carcinoma, 2 cases are Medullary carcinoma, 1 case of Invasive lobular carcinoma and Mixed ductal and Lobular carcinoma each, and two cases are Malignant phyllodes. PR negativity is seen in 36 cases (72%) and positivity in 14 cases (28%), of which 8 cases (16%) show weak positivity, 5 cases (10%) show intermediate positivity and 1 case (2%) shows strong positivity. Out of 50, 30 cases (60%) show negative for HER2/neu expression while 20 cases (40%) show positive expression for HER2/neu in which 7 cases (14%) show positivity with 2+ score and 13 cases (26%) show positivity with 3+ score. From the above inference, CD10 is documented to be associated with well-established prognostic factors such as higher histological grade, lymph node metastases and hormonal receptor negativity indicating CD10 can be used as a predictive marker of poor outcome in invasive carcinoma of breast.

Keywords: Breast cancer, CD10, oestrogen receptor, HER2/neu, Ki67, progesterone receptor

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INTRODUCTION

Breast carcinoma is a major cause of death among females imposing a global health problem [1]. Among the Indian women, carcinoma of the breast and cervix account for 60% of total cases, of which breast carcinoma accounts for 10.4%. It is more than twice the occurrence of carcinoma in females at any other site [2]. In South India, breast cancer is the second most common cancer among women. The incidence of the disease had been increasing in both developed and developing countries until 1980, but still continues to increase in the developing countries. The mean age of occurrence is 42 years [3]. The approach to the management of breast carcinoma has undergone enormous changes over the last 20 years. Such changes are accompanied by increasing range of systemic, hormonal and cytotoxic drugs used in both adjuvant and neoadjuvant settings [4]. Choice of treatment modalities and outcome of the patient is influenced by the classic variables such as histological type and grade, tumour size, lymph node status, Estrogen, Progesterone receptor status and HER2/neu over expression [5]. Identifying the expression of biomarkers plays a critical role in the management and prognosis of breast carcinoma. At the time of diagnosis, determining the expression of hormonal status (Estrogen and Progesterone receptor status) is essential to plan optimal treatment for breast cancer [6]. Estrogen receptor is a well-established predictive factor in breast cancer. Patients with ER positive/PR positive tumours have a better prognosis than patients with ER negative/PR negative tumours. Hormone receptor test is done routinely in breast cancer since hormone treatment has fewer side effects and it prevents recurrence in 25% of cases. HER2/neu overexpression became clinically relevant with the demonstration that HER2/neu positive tumours have a worse prognosis than HER2/neu negative tumours. It has been recognized that HER2/neu overexpression serves both as a marker of aggressive disease and a target for treatment [7]. With these prognostic implications, the need for accurate and precise assessment of ER, PR, and HER2/neu expression in breast carcinoma is critical in the determination of patients appropriate for treatment with these drugs [8]. Tissue microenvironment has major contribution in tumour progression, invasion and spread to distant site. Studying the biology of local environment around the tumour helps to identify molecular signals that favour proliferation of tumour cells, stromal and vascular invasion [9]. A better understanding of such molecular signalling pathways leads a pavement for new therapeutic approaches. Thus study of CD10, an emerging stromal marker in breast cancer will be of prognostic significance and therapeutic target in near future [10]. Immunohistochemistry is an important tool in precise histopathological diagnosis. Immunohistochemistry (IHC) is the most common method that is practiced in testing ER, PR, HER2/neu status and also in CD10 expression. Survival and response to hormone therapy are most favourable among women who are receptor positive, intermediate for tumours discordant on receptor status and least favourable for receptor negative patients [11]. The interrelationship of Estrogen, Progesterone receptor status and HER2/neu overexpression has an important role in management of breast carcinoma.[13] It has been shown that patients with HER2/neu overexpression do not respond to tamoxifen therapy, while they serve as a candidate for trastuzumab therapy [12].

MATERIALS AND METHOD

This is a retrospective study on cases of breast carcinoma reported during the period of 2014-2016, in the Department of Pathology, Thanjavur Medical College, Thanjavur. Total number of 599 breast specimens had been received in our department during this period. Out of these 287 cases were benign and 199 were reported as malignant. A total of 50 cases of invasive breast carcinoma diagnosed from the specimens of both modified radical mastectomy and lumpectomy procedures are randomly selected for this study. Newly diagnosed patients with unilateral presentation and no previous H/O neoadjuvant therapy are included in the study. All the specimens received are properly sliced and fixed in 10% neutral buffered formalin for 12-16 hours. Detailed gross examination including size of the specimen, appearance of skin, nipple and areola, margins and nodal status is done. Tumour size, consistency and distance from cut margins are also noted. Representative sections are taken from the tumour proper, nipple, resected margins and palpable lymph node. Tissue slices are processed in various grades of alcohol and the tissue sections are paraffin embedded. Paraffin sections are cut to 3-5 µm thickness and subjected to Hematoxylin and Eosin staining. Histological diagnosis of tumour is made and assessment of tumour grade is done by Nottinghan grading scoring system. Nodal status and margin involvement of each case is also reported.Immunohistochemical analysis of Hormone receptors(ER/PR), HER2/neu overexpression and stromal expression of CD10 are done using immunoperoxidase method. Deparaffinised sections for immunostaining are subjected to heat induced antigen retrieval with a pressure sterilizer using Trisodium Citrate buffer (pH 6). Sections are then incubated with peroxidase block to reduce the non-specific antigen binding and then incubated with primary antibodies (Anti-ER, Anti-PR, Anti-HER2, Anti-CD10) for 1hour

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30 minutes. After three washes with Tris buffer, secondary antibody was added for 30minutes. After three washes with Tris buffer, DAB substrate was applied for 5 minutes and counterstained with haematoxylin, dehydrated with ethanol and xylene and mounted with DPX.Positive controls are Proliferative endometrium for ER, Secretory endometrium for PR, Previous known positive case for HER2/neu and Periductal basal cells in fibroadenoma for CD10.Immunohistochemically stained slides are evaluated for the presence of reaction, cellular localization (nuclear or cytoplasmic or membrane bound), pattern of staining (focal or diffuse) and intensity of staining (strong or weak) in individual tumour cells.

Scoring of Estrogen and Progesterone receptor status is done by using ALLRED/QUICK scoring system.[13] HER2/neu overexpression is scored according to guideline published by Ellis *et al*.,[12] CD10 staining has been scored as negative, weak and strong according to Makretsov study.[13]Statistical analysis is done to correlate ER, PR, HER2/neu status with CD10 and P value less than 0.05 is considered as statistically significant.

RESULTS

Chart 1: Year-Wise Incidence Of Benign And Malignant Breast Tumours

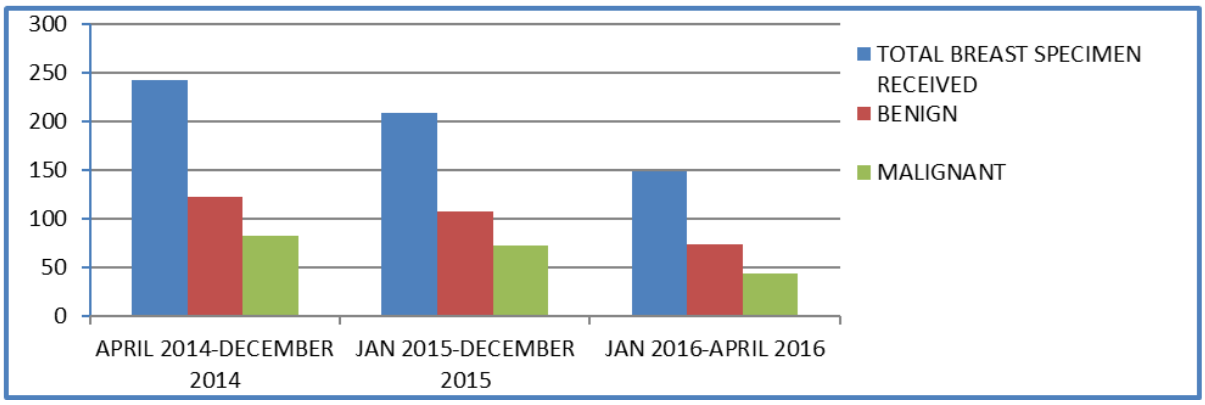

Chart 2: Distribution Of Histological Variants In Malignant Breast Tumours

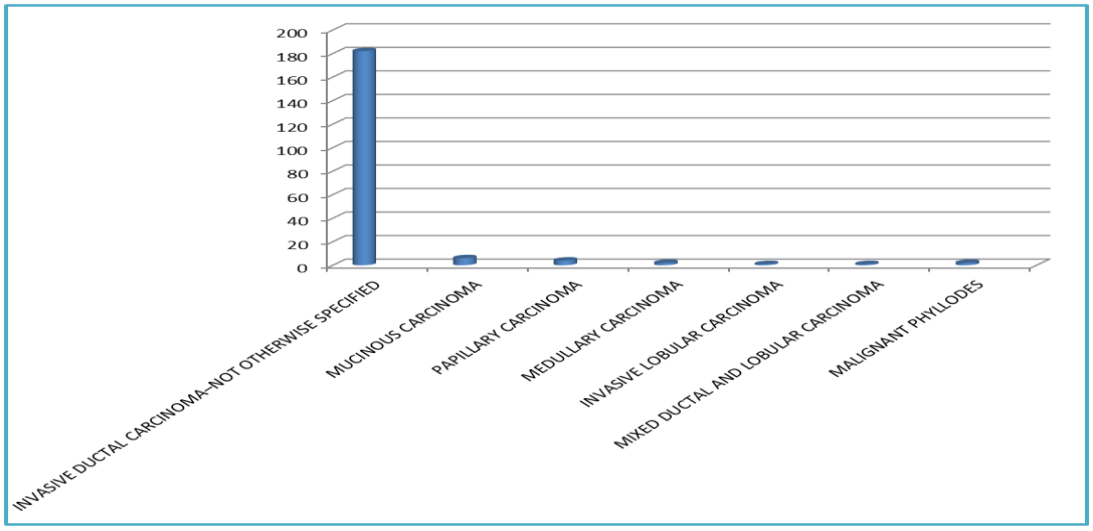

Chart 2 shows the distribution of malignant tumours. Out of 199 cases reported as malignant, 182 cases are Invasive ductal carcinoma-NOS type, 6 cases are reported as Mucinous carcinoma, 4 cases are Papillary carcinoma, 2 cases are Medullary carcinoma, 1 cases of Invasive lobular carcinoma and Mixed ductal and Lobular carcinoma each, and two cases are Malignant phyllodes.

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Chart 3: Age-Wise Distribution Of Invasive Ductal Carcinoma-Nos Type

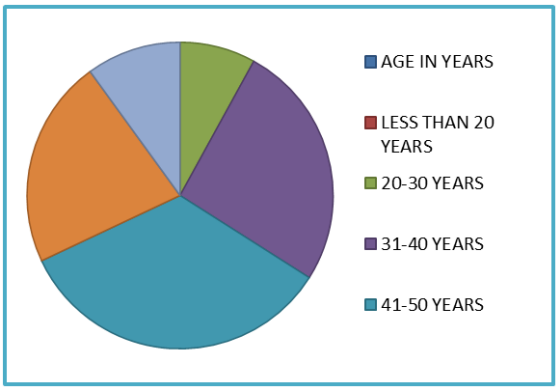

Table 4 shows the distribution of histological grading according to Modified Bloom Richardson grading system. Among the 50 cases included in this study, 23 cases (46%) are grade 2, 16 cases (32%) are grade 3, 12 cases (22%) are grade1.

Table 1: Expression Of Estrogen Receptor In This Study

S.NO	ER STATUS	NO OF CASES	PERCENTAGE
1	NEGATIVE	38	76
2	WEAK POSITIVE	5	10
3	INTERMEDIATE POSITIVE	4	8
4	STONG POSITIVE	3	6

Table 1 shows the distribution of ER negative and ER positive cases in the 50 cases under study. Most of the cases 38 (76%) are ER negative, remaining 12 cases show weak positivity in 5 cases (10%), intermediate positivity in 4 cases (8%) and strong positivity in 3 cases (6%).

Table 2: Expression Of Progesterone Receptor In This Study

S.NO	PR STATUS	NO. OF CASES	PERCENTAGE
1	NEGATIVE	36	72%
2	WEAK POSITIVE	8	16%
3	INTERMEDIATE POSITIVE	5	10%
4	STRONG POSITIVE	1	2%

Table 2 shows the distribution of PR positive and PR negative cases in this study. PR negativity is seen in 36 cases (72%) and positivity in 14 cases (28%), of which 8 cases (16%) show weak positivity, 5 cases (10%) show intermediate positivity and 1 case (2%) shows strong positivity.

Table 3: Correlation Of ER/PR Status

S.NO	HORMONE STATUS	NO. OF CASES	PERCENTAGE
1	ER+/PR+	8	16%
2	ER-/PR+	6	12%
3	ER+/PR-	4	8%
4	ER-/PR-	32	64%

Table 3 shows the correlation of Estrogen and Progesterone receptors. Among the 50 cases under study, 8 cases (16%) show both ER and PR positivity, 6 cases show PR positivity with ER negativity, 4 cases show ER positivity with PR negativity and 32 cases (64%) show both ER and PR negativity

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Table 4: Expression Of HER2/neu In This Study

S.NO	HER2/neu	NO. OF CASES	PERCENTAGE
1	NEGATIVE	30	60%
2	EQUIVOCAL	7	14%
3	POSITIVE	13	26%

Table 4 shows the expression of HER2/neu among 50 cases in this study. Out of 50, 30 cases (60%) show negative for HER2/neu expression while 20 cases (40%) show positive expression for HER2/neu in which 7 cases (14%) show positivity with 2+ score and 13 cases (26%) show positivity with 3+ score.ER, PR and HER2/neu are routine immunohistochemical markers used for prognostication in breast carcinoma. CD10, a new stromal marker is taken for the study and its expression is correlated with routine markers. Out of 50 cases in this study, 30 cases are selected for assessing the CD10 expression.

Table 5: Expression Of Cd10 In This Study

S.NO	CD10 EXPESSION	NO.OF CASES	PERCENTAGE
1	NEGATIVE	9	30%
2	WEAK POSITIVE	3	10%
3	STRONG POSITIVE	18	60%

Table 5 shows the expression of CD10 among the 30 cases selected. Out of 30 cases 18 cases (60%) show strong positivity, 3 cases show weak positivity and 9 cases (30%) show negative expression.

Table 6: Correlation Of Histological Grade With CD10

S.NO	HISTOLOGICAL GRADE	NO OF CASES	CD10 POSITIVE	CD10 NEGATIVE
1	GRADE 1	6	3	3
2	GRADE 2	14	12	2
3	GRADE 3	10	6	4

Table 6 shows CD10 expression and its comparison with histological grade. In this study, out of 14 cases of grade 2 tumours, 12 cases show CD10 positivity. Also 6 out of 10 grade 3 tumours show CD10 positivity. Thus CD10 expression is seen in tumour with higher grade.

Table 7: Correlation Of CD10 With Lymph Node Status

S.NO	CD10	NODAL STATUS	
		POSITIVE	NEGATIVE
1	NEGATIVE	4	5
2	POSITIVE	13	8

Table 7shows the lymph node metastasis in CD10 expressed cases. In this study, out of 21 CD10 positive cases, 13 cases (61%) show lymph node metastasis.

Table 8: Correlation Of Cd10 With Er

S.NO	CD10	ER POSITIVE	ER NEGATIVE	TOTAL
1	NEGATIVE	3	6	9
2	WEAK	2	1	3
3	STRONG	4	14	18
TOTAL		9	21	30

Table 8 shows the expression of CD10 in cases with ER Positive and Negative status. In 18 cases with CD10 strong expression, 14 cases show ER negativity which is statistically significant (P Value =0.0423).

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Table 9: Correlation Of CD10 With Pr

S.NO	CD10	PR POSITIVE	PR NEGATIVE	TOTAL
1	NEGATIVE	1	8	9
2	WEAK	1	2	3
3	STRONG	5	13	18
TOTAL		7	23	30

Table 9 shows the correlation of CD10 expression in cases with PR Positive and Negative status. In 18 cases with CD10 strong expression in stroma, 13 cases show PR positive status and is statistically significant (P Value = 0.0211).

CHART 4: CD10 With ER, PR, HER2/neu

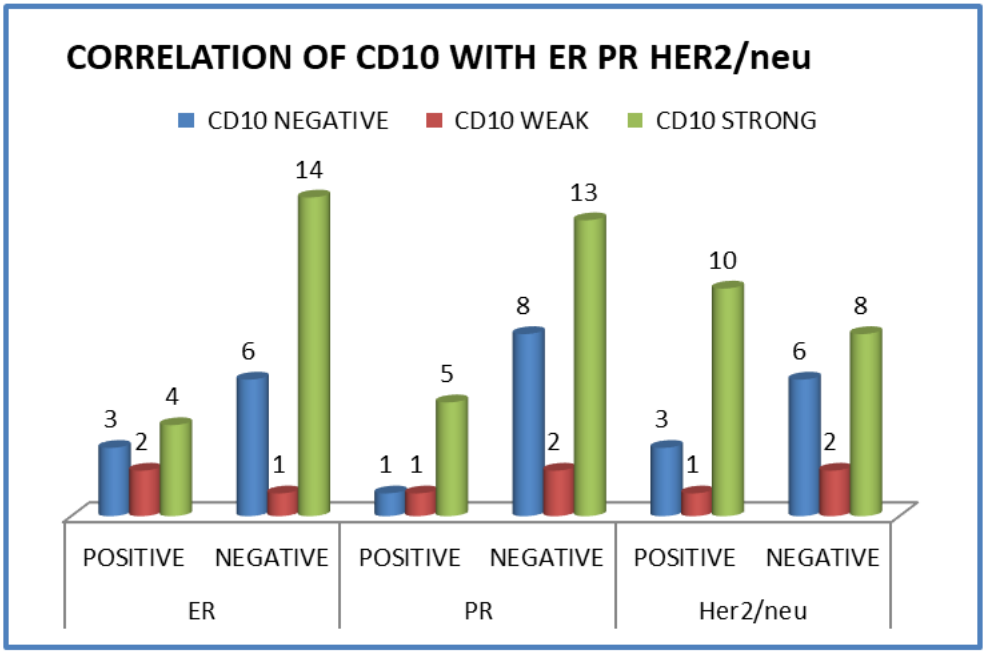

Chart :4 shows the expression of CD10 in cases with HER2/neu negative status and HER2/neu overexpression. In 18 cases with strong CD10 stromal expression, 10 cases show HER2/neu overexpression with score 2+ and 3+ and is not statistically significant with P value 0.421.

Table 10: Correlation Of Cd10 With Triple Negative Carcinoma

S.NO	CD10	NO OF TRIPLE NEGATIVE CASES
1	NEGATIVE	3
2	POSITIVE	5

In this study 8 triple negative cases are assessed for CD10 expression in which 5 out 8 cases show positive CD10 stromal expression.

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Figure 1: Gross Appearance Of Infiltrating Ductal Carcinoma

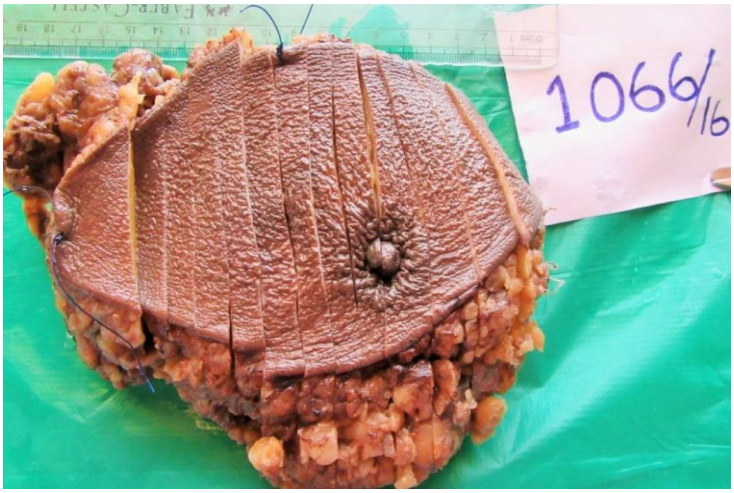

Figure 2: Cut Surface Showing Ill Defined Grey White Mass With Infiltrative Margins

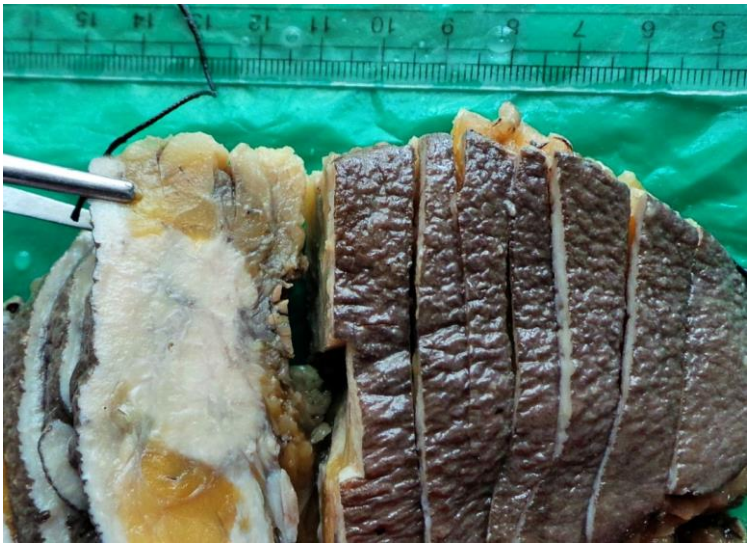

Figure 3: Microscopic Picture Of Infiltrating Ductal Carcinoma-Nos Type Grade 2 (H&E Under 10x)

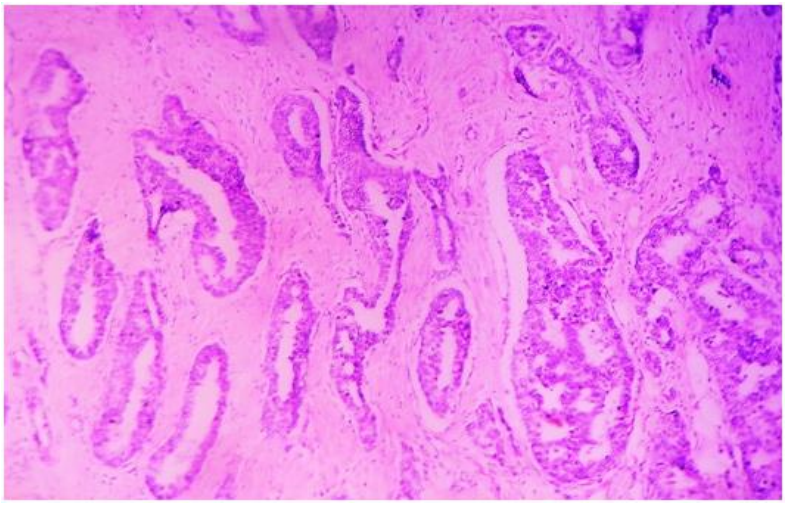

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Figure 4: Microscopic Picture Of Infiltrating Ductal Carcinoma- NOS Type Grade 3 (H&E Under 40x)

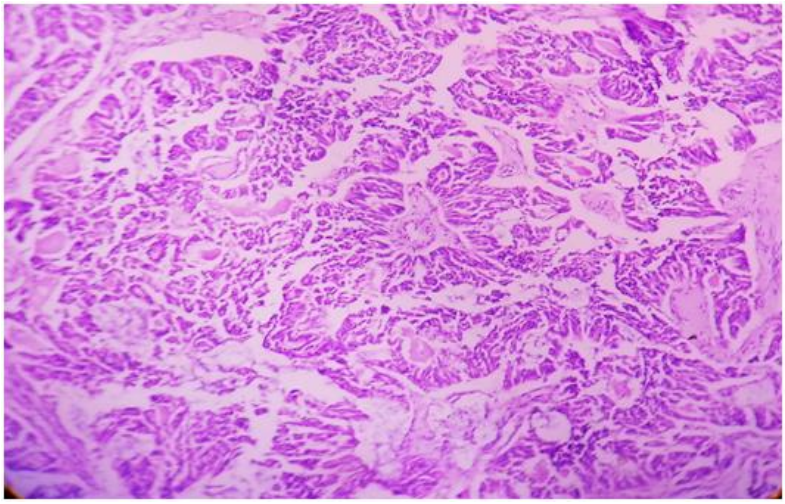

Figure 5: Expression Of ER In IDC NOS Type, Showing Weak Positivity (IHC Under 40X)

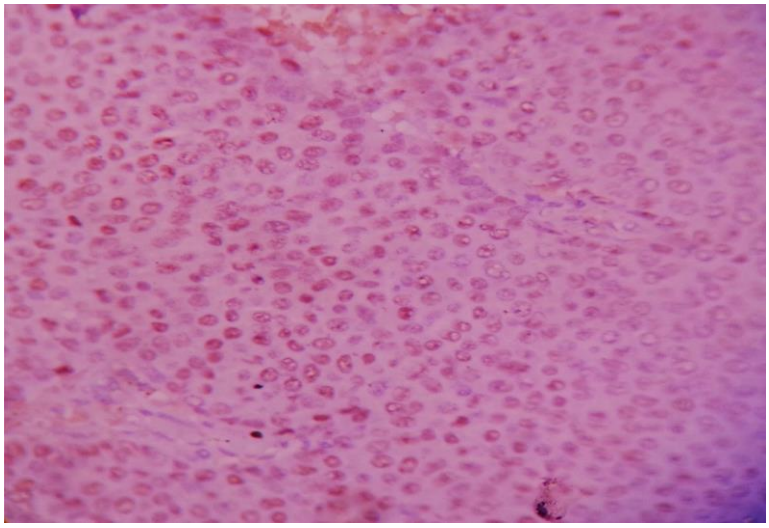

Figure 6: Expression Of ER In IDC NOS Type Showing Strong Positivity (IHC Under 40X)

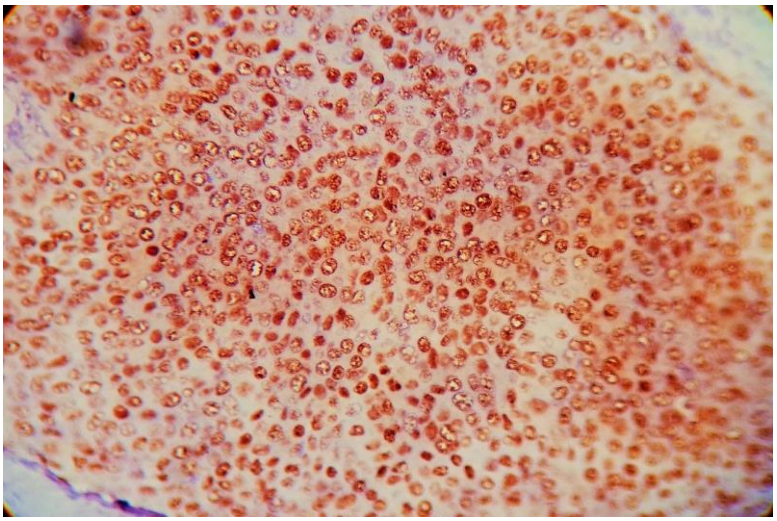

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Figure 7: Expression Of PR IN IDC NOS Type , Showing Weak Positivity (IHC Under 40X)

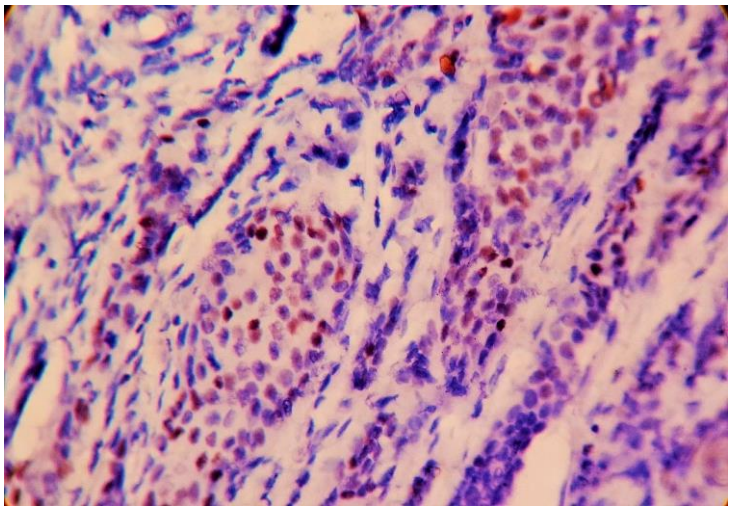

Figure 8: Expression Of PR In IDC NOS Type Showing Strong Positivity (IHC Under 40X)

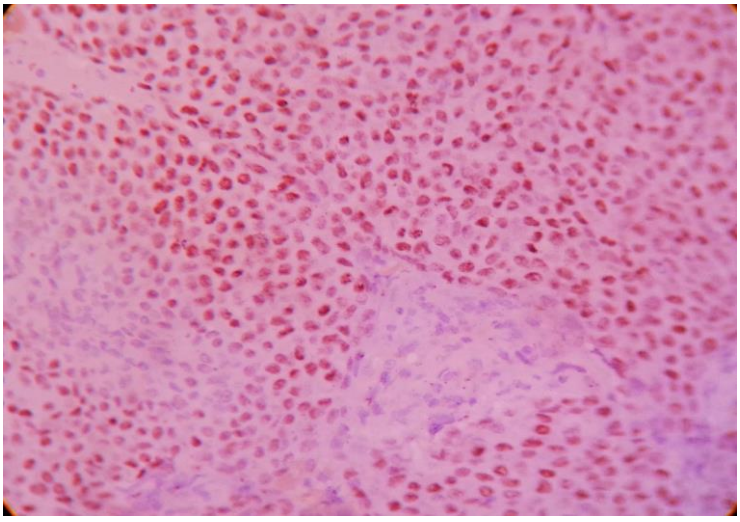

Figure 9: Overexpression Of HER2/neu in IDC NOS Type With Score 2+ (IHC Under 40X)

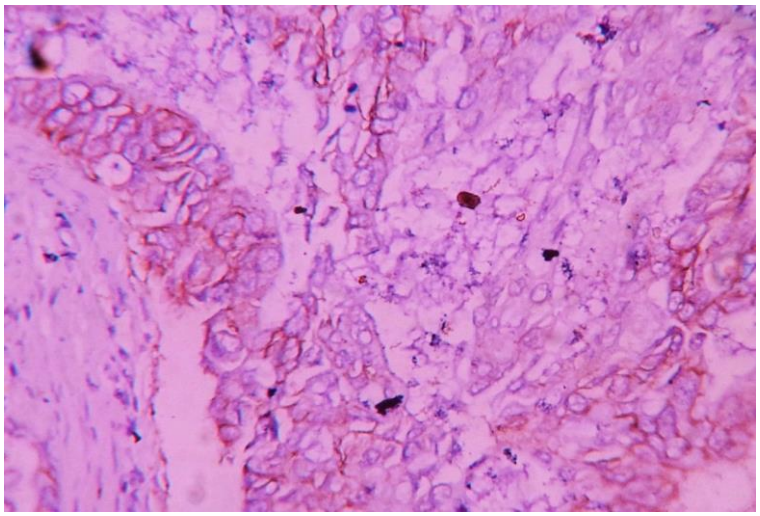

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Figure 10: Overexpression Of HER2/neu in IDC NOS Type With Score 3+ (IHC Under 40X)

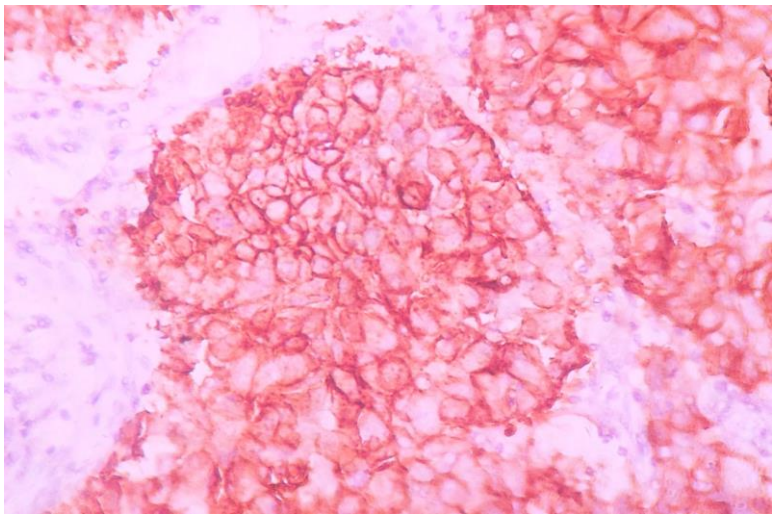

Figure 11: Negative Staining Of CD10 In Stromal Cells Of IDC NOS Type (IHC Under 40X)

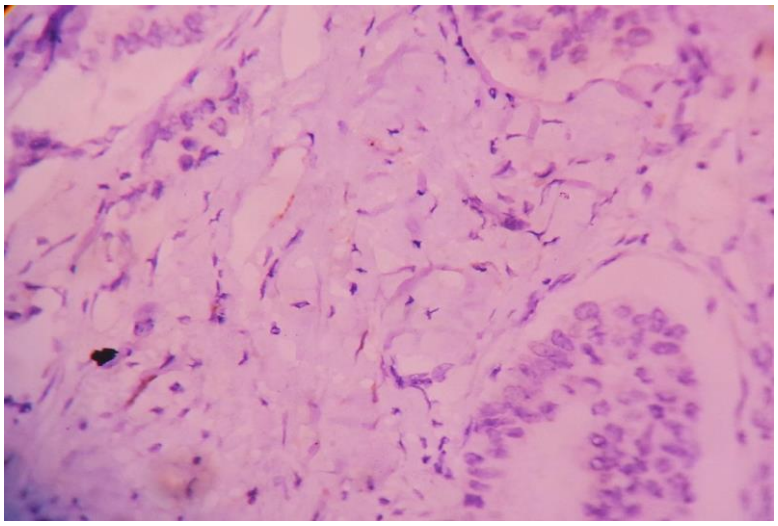

Figure 12: CD10 Weak Staining Less Than 30% Of Stromal Cells In IDC NOS TYPE (IHC Under 40X)

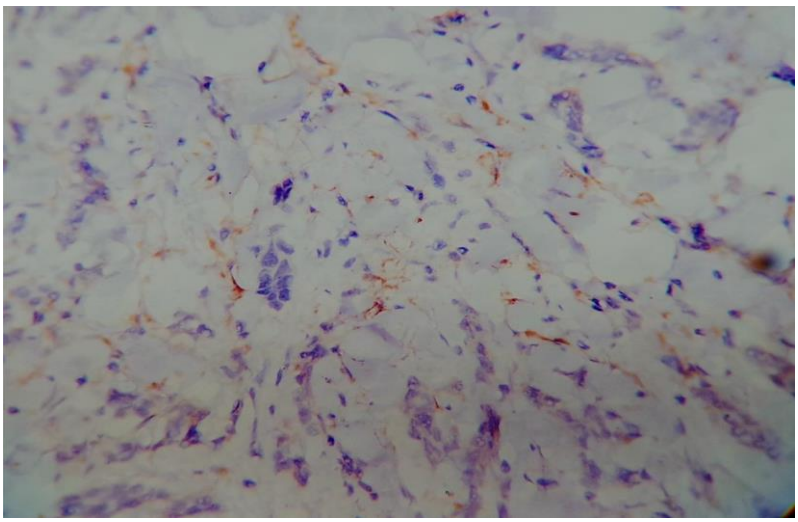

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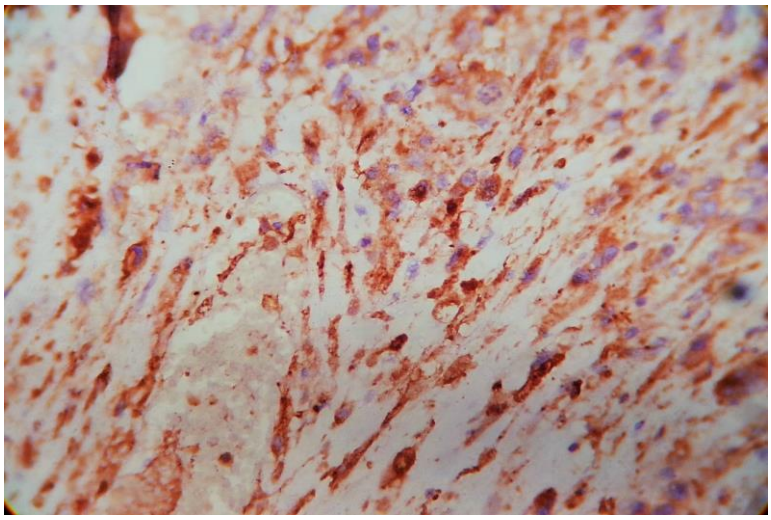
Figure 13: CD10 Strong Positivity In Greater Than 30% Of Stromal Cells In IDC NOS Type (IHC Under 40X)



DISCUSSION

Based on National Cancer Registry Programme 2012-2014, Breast cancer is the most common cancer among females in urban India. Incidence of breast cancer varies from 5/1,00,000 females per year in rural areas to 30/1,00,000 females per year in urban areas. In India, the age adjusted incidence rate is lower than the western countries. A few decades of about 30 years back, most breast cancer victims (>69%) are above 50 years of age. Nowadays, increasing number of patient are in the age group of 25 to 40 years (about 48%) Clinically, invasive carcinoma of breast is not a single entity, but composed of a range of phenotypes with widely variable outcome [13]. Management of breast cancer relies on the prognostic and predictive factors to guide patient decision making and reflection of treatment option. Prognostic factors are used to classify patients into three groups namely, those with good prognosis that adjuvant therapy would not be beneficial, those with poor prognosis that adjuvant therapy is warranted and those patients who are likely to be responsive or resistant to a particular type of therapy [14]. The most widely accepted grading system for invasive breast carcinoma is the Nottingham (Elston – Ellis) system which is the modification of Scarf – Bloom – Richardson system, also known as the Nottingham Grading System (NGS). Most pathologists use Elston – Ellis system in practice and the reproducibility of this grading system is well documented [15]. Presence of estrogen receptors in malignant mammary tissue is believed to indicate the potential estrogenic regulation of the cancer that is retained despite malignant change.ER and PR status are most important for guiding selection of hormone treatment than for determining prognosis [16]. About 50 to 60% of patients with invasive breast carcinoma expressing significant amount of Estrogen receptors respond favorably to hormone or endocrine therapy.PR is expressed only after transcriptional activation of its gene by a functional estrogen receptor(ER)-estrogen complex. More percentage of response is seen if ER level is high and if both ER and PR are positive [16]. In a study, with 50 cases of invasive breast carcinoma, ER negativity is seen in 68% and PR negativity in seen in 58% of cases whereas ER positivity is seen in 24% and PR positivity is seen in 32% of cases [17]. Our study is close to the above mentioned study which shows ER expression in 24% of cases and PR expression in 28% of cases. (54.5%) were positive for both ER and PR, 72 patients (38%) were negative for both ER and PR, 10 patients (5.3%) were positive for PR and negative for ER and 4 patients (2.1%) were positive for ER and negative for PR [18]. Close to the above mentioned studies, present study reveals 16% percentage of cases are positive for ER and PR; both ER and PR negative expression is seen in 65% of cases. While 12% of cases are positive for PR and negative for ER; 8% of cases show ER positivity and PR negativity. Though our study is consistent with earlier studies in India, we have higher proportion of ER – ve, PR –ve tumours compared to western studies [19]. Various studies have reported that expression of hormone receptors increases with increase in age of the patient that may be explained by the higher proportion of low grade and more differentiated carcinoma seen in older women. But in our study, significant association is not found between the age of the patient and ER / PR expression. This may be due to increased prevalence of high grade tumours and late diagnosis in our population resulting in more cases showing negativity for both ER and PR status. Epidermal growth factor receptor 2 (ERB2; also known as HER2/neu) has raised more attention as a possible prognostic marker. HER2/neu is a

protooncogene located on chromosome [20]. It is amplified and or its protein is over expressed in 15 to 25% of invasive breast carcinoma. Most studies reported that HER2/neu amplification or over expression is associated with worst outcome. However, HER2/neu status of breast carcinoma has gained clinical importance due to the introduction of trastuzumab, a therapeutic monoclonal antibody against the receptor. This drug helps to prolong the survival of patients with metastatic breast carcinoma. Moreover, HER2/neu may be predictive marker for response to adjuvant chemotherapy and endocrine therapy. Patient with HER2/neu over expression do not respond to tamoxifen therapy. In normal bone marrow, CD10 positive stromal cells induce Pre B cells and myeloblasts to differentiate into B-cell lineage and to accelerate cell proliferation and cell motility [21]. Likewise, CD10 positive stromal cells in breast cancer may interact with cancer cells to accelerate the cell cycle and to activate cell locomotion. In normal breast, CD10 is constantly expressed by the myoepthelial cells during the development and maturation. Thus, CD10 is considered as a specific marker of myoepithelial cells in normal breast tissue and benign tumours. DCIS shows heterogeneous staining pattern of CD10 in myoepithelial cells [22]. Disappearance of CD10 from myoepithelial cells leads to progression of DCIS to invasive carcinoma. In invasive carcinoma, upregulation of mutated CD10 would lead to accumulation of local cleaved peptides that inhibit epithelial cell differentiation and maintain cancer stem cells. This results in lineage commitment and malignant proliferation, which has been the proposed basis for progression of DCIS into invasive malignancy [23]. Only two studies had discussed about the expression of stromal CD10 expression in triple negative invasive breast carcinoma but its statistical significance was not found [24-26].

CONCLUSION

Stromal expression of CD10 was significantly associated with higher tumor grade, lymph node metastasis, HER2neu positivity, ER negativity, and Ki67 positivity. CD10 can be used as an independent prognostic marker and should be included in routine histopathology report. CD10 could act as a potential target for newer drug development.

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