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Original Research Article

EXPRESSION OF CD10 IN INVASIVE BREAST CARCINOMA AND ITS CORRELATION WITH OTHER CLINICOPATHOLOGICAL PARAMETERS

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Abstract

Background: Breast cancer represents one of the most prevalent malignancies and a leading cause of mortality in the female population. While characterized as an epithelial malignancy, stromal components are recognized for their significant role in influencing tumor invasion and disease progression. Despite this, the investigation of stromal markers remains relatively limited. The present study aims to establish correlations between the expression of CD10 and well-established markers, including ER, PR, Her-2/neu, tumor grade, and lymph node metastasis. The objective of this research was to investigate the presence of stromal CD10 expression in invasive breast carcinomas and its association with various prognostic indicators, including histological grade, lymph node status, age, menopausal status, estrogen receptor (ER), progesterone receptor (PR), and HER-2/neu. **Materials and Methods:** The study examined 50 cases of invasive breast carcinomas. Tissue sections obtained from representative areas underwent staining with H&E and subsequent examination. Immunohistochemistry was conducted to assess ER, PR, Her-2/neu, and CD10 expression. Statistical analysis involved the chi-square test performed using SPSS version 20.0. **Result:** CD10 exhibited positivity in 96% (n=48) of cases, with 66% displaying strong immunoreactivity and 30% showing weak immunoreactivity. The stromal expression of CD10 demonstrated a significant correlation with tumor grade, lymph node metastasis, and increasing Nottingham's Prognostic Index. No significant correlation was discerned between ER, PR, Her-2/neu, and CD10 overexpression. **Conclusion:** The study revealed that the presence of stromal CD10 in invasive breast carcinoma is correlated with higher tumor grade, an elevated risk of lymph node metastasis, and a worsened prognosis.

INTRODUCTION

Breast cancer stands as the most frequently diagnosed cancer in women and represents the primary cause of cancer-related mortality on a global scale. In 2022, it ranked as the second most diagnosed cancer among women worldwide, second only to lung cancer. Approximately 2.3 million new cases of breast cancer were identified, constituting about 11.6% of all cancer cases. Furthermore, it held the position as the fourth highest cause of cancer-related deaths globally.[1] The early detection of breast cancer has shown significant improvement in recent years. However, the prognosis for this disease remains discouraging due to the occurrence of metastases and recurrences, which often result in treatment failure.

Although breast cancer is classified as an epithelial malignancy, it is important to acknowledge the significant role of the stroma in modulating tumor invasion and metastasis. Recent research has substantiated the impact of stromal involvement in driving the progression and aggressiveness of a diverse range of cancers, including melanoma, colorectal cancer, and nasopharyngeal carcinoma.[2] Stromal factors, particularly extracellular matrix components, are increasingly identified as novel prognostic markers.[3] Extracellular matrix-degrading matrix metalloproteinases (MMPs) play a crucial role

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in carcinoma progression and are associated with tumor angiogenesis, invasion, and metastasis.[4] Recent research has focused on the role of CD10, a stromal marker, in this context.

The cell surface zinc-dependent metalloproteinase, CD10, also known as Common Acute Lymphoblastic Leukemia Antigen (CALLA), has a molecular weight of 90-110 kDa. It is commonly expressed in bone marrow lymphoid stem cells, Pro-B lymphoblasts, mature neutrophils, various lymphoma subtypes, renal cell carcinoma, and endometrial stromal sarcoma.[5] In epithelial cells, the loss of CD10 through methylation induces heightened cell migration, proliferation, and viability, thereby contributing to the initiation and advancement of neoplastic growth.[6] Various studies in the literature have demonstrated that the presence of CD10 in stromal cells is correlated with heightened biological aggressiveness in epithelial malignancies, such as gastric carcinoma, colon carcinoma, and hepatocellular carcinoma.[3,7]

Aim & Objectives

The study aimed to investigate the role of CD10 expression in invasive breast carcinoma and its prognostic significance. Additionally, it examined its correlation with tumor grade, ER, PR, and HER-2/neu.

MATERIALS AND METHODS

A prospective observational analytical study was executed in the Department of Pathology at the Northern Railway Central Hospital in New Delhi from August 2021 to March 2023. Before the initiation of the study, approval was obtained from the institutional ethics committee and informed written consent was obtained. The study encompassed 50 histologically confirmed cases of infiltrating carcinoma of the breast. All Modified Radical Mastectomy and lumpectomy specimens diagnosed with infiltrating carcinoma of the breast were submitted to the Department of Pathology from the Surgery department during the stipulated study period. Pertinent data such as historical information, age, family history, and menopausal status were recorded. Post-chemotherapy cases were excluded from the study. After fixation of the specimens in formalin, representative sections were extracted following a thorough gross examination. Subsequently, H&E staining was conducted, and this was followed by immunohistochemistry.

The breast carcinoma was graded using Nottingham's combined histologic grade, an adaptation of the Scarff–Bloom–Richardson grading system by Elston and Ellis.[8] Subsequently, Nottingham's Prognostic Index (NPI) was computed, and patients were stratified into six NPI groups based on the recommendations of Blamey et al.[9]

NPI = (S x 0.2) + N + G, where

S-Size of the lesion in centimeters

N-No. of involved lymph nodes (scoring1-3)

G-Tumor grade, based on the modified Bloom-Richardson grading system (score: 1-3).

(EPG) Excellent Prognostic group - 2.08 to 2.4

(GPG) Good Prognostic group - >2.42 to = <3.4

(MPG I) Moderate I Prognostic group - >3.42 to </ = 4.4

(MPG II) Moderate II prognostic group - >4.42 to = <5.4

(PPG) Poor prognostic group - >5.42 to = <6.4

(VPG) Very poor prognostic group - >6.5 to 6.8

IMMUNOHISTOCHEMISTRY (IHC) FOR ER, PR, HER-2/NEU AND CD10

The most suitable paraffin blocks with tumor were selected for the study. Antigen retrieval was performed using the Citrate Buffer Antigen Retrieval Protocol with a pressure cooker as the heating source. Immunohistochemistry was manually carried out for ER (Rabbit monoclonal antibody against human estrogen, Dako Anti-Human ER α, EP1-clone, Ready to use-RTU), PR (mouse monoclonal antibody against human PgR, Dako Anti-Human PgR Receptor, PgR 636- clone, RTU), HER-2/neu (Rabbit monoclonal antibody against human Her2, BioGenex Anti-ErbB2/Her2, EP1045Y, RTU), and CD10 (mouse monoclonal antibody against human CD10, Dako Anti-Human CD10, 56C6clone, RTU). Negative control sections were processed by omitting the primary antibody. The periductal stromal cells and non-neoplastic myoepithelial cells in Fibroadenoma were used as a positive control for CD10 expression. A section from endometrial tissue was used as a positive control for ER and PR. Previously known positive cases of Her2/neu-positive breast cancer were used as a positive control for Her2/neu.

Immunohistochemical Analysis

Evaluation of ER, PR and HER-2/neu was done according to CAP (College of American Pathologists). CD10 scoring was done as negative, weak, and strongly positive [Table 1].

The slides were examined using H&E staining, and scores obtained from immunohistochemistry were correlated with various clinicopathological parameters to study prognosis.

Statistical Methods: Statistical analysis was performed using the SPSS 20.0 statistical package for the social sciences. Pearson's chi-square test, or the chi-square test of association, assessed the relationship between CD10 and tumor grade and its correlation with other markers, including ER, PR, and HER2/neu, in breast carcinoma. A p-value of less than 0.05 was deemed to indicate statistical significance.

RESULTS

The mean age of the study cohort was 57.38 years, with 90% of the female participants being postmenopausal. The predominant histological subtype observed was Infiltrating Ductal Carcinoma, NOS, representing 90% of the cases, followed by

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invasive lobular carcinoma (4%), pure mucinous carcinoma (4%), and medullary carcinoma (2%). The distribution of the breast cancer cases by tumor grade revealed that the majority were grade 2 tumors (60%), followed by grade 3 (34%) and grade 1 (6%) tumors.

Immunohistochemical Status

CD10 immunostaining was conducted on all 50 cases. No stromal expression was detected in normal breast tissue. Out of the 50 cases studied, stromal CD10 expression was strongly positive in 33 (66%) cases, weakly positive in 15 (30%) cases, and negative in 2 (4%) cases. [Table 2].

In this study, 84% of cases exhibited positive estrogen receptor expression, while 16% showed a negative estrogen receptor status. Regarding progesterone receptors, 32% of cases demonstrated positive expression, with 68% displaying a negative status. Furthermore, Her-2/Neu receptor positivity was observed in 14% of cases, while negativity was 86%. [Table 3] elucidates the correlation between stromal CD10 expression and clinicopathological factors.

The expression of stromal CD10 demonstrated a statistically significant correlation with higher tumor grade (p=0.000), an increased number of involved lymph nodes (p=0.001), and a more severe prognosis as indicated by the Nottingham Prognostic Index (NPI) (p=0.004). Conversely, there was a non-significant negative correlation with estrogen receptor (ER) and progesterone receptor (PR) expression. No statistically significant correlation was observed between stromal CD10 expression and HER-2/neu overexpression, patient age, or menopausal status.

Table 1: Scoring of CD10 immunohistochemical staining in the stroma.

SCORE	CD10 STAINING
Negative	<10% stromal positive cells/score
Weak positive	10-30% stromal positive cells/score
Strong positive	>30% stromal positive cells/score

Table 2: Distribution of the cases according to stromal CD10 expression

CD10 Expression	Frequency	Per cent
Negative	2	4.0
Weakly positive	15	30.0
Strongly positive	33	66.0
Total	50	100.0

Table 3: Correlation between stromal CD10 expression and Clinicopathologic parameters in breast cancer

Clinic pathological Factor		Number of Cases	Per cent	CD10 Immunostaining			p-value
				Negative	Weak Positive	Strong Positive	
Age	<40yrs	04	8.0	00	02	02	0.729
	40-60yrs	26	52.0	00	07	19	
	>60yrs	20	40.0	02	06	12	
Menopausal	Premenopausal	05	10	00	02	03	0.935
Status	Postmenopausal	45	90	02	13	30	
Lymph Node	Negative	30	60	02	15	13	0.001
Status	1-3	11	22	00	00	11	
	>3	9	18	00	00	09	
Tumor Grade	Grade 1	3	6.0	01	01	01	0.000
	Grade 2	30	60.0	00	12	18	
	Grade 3	17	34.0	01	02	14	

Table 4: Distribution of the cases according to Nottingham's prognostic index with CD10 receptor

Nottingham Prognostic index	CD10	
	Positive N (%)	Negative N (%)
Excellent Prognostic group	2 (4.2)	1 (50.0)
Good prognostic group	19 (39.6)	0
Moderate I Prognostic group	7 (14.6)	1 (50.0)
Moderate II Prognostic group	5 (10.4)	0
Poor prognostic group	3 (6.2)	0
Very poor prognostic group	12 (25.0)	0
Total	48 (100)	2 (100)
p value=0.004		

DISCUSSION

Breast cancer stands as a prominent contributor to cancer-related mortality among women on a global scale. In India, it is the most prevalent form of cancer, constituting 14% of all cases. Notably, breast cancer exhibits heterogeneity morphologically, immunohistochemically, and at the molecular level, irrespective of race or geographical location.[10] Well-established prognostic factors, such as histological grade, lymph node status, ER/PR status, and HER-2/neu, are consistently examined in each instance of breast cancer.

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Breast cancer is a malignancy that originates in the epithelial cells of the terminal ductal lobular unit. However, it is important to recognize the significant role of the stromal microenvironment in the evolution and metastasis of breast cancer.[11] The concept of the microenvironment is continually evolving and elucidates that the behaviour of cancer stems not only from the genetics of the tumor cells alone (cell-autonomous), but also from the surrounding stimuli that tumor cells utilize for their survival, growth, proliferation, and metastasis.[12]

The extracellular matrix (ECM) plays a vital role in the tissue microenvironment, comprising components increasingly recognized as novel prognostic markers. The degradation of the ECM is a significant factor in the development, morphogenesis, tissue repair, and remodeling. Matrix metalloproteinases (MMPs) represent the primary group of enzymes responsible for protein degradation within the ECM.[13] MMPs, also known as matrixins, are members of the metzincin protease superfamily of zinc-dependent endopeptidases.[13] MMP plays a critical role in the progression of tumors and in delineating the influence of the stromal microenvironment on tumor invasion and metastasis.[14]

CD10 is a cell surface zinc-dependent metalloproteinase called Common Acute Lymphoblastic Leukemia Antigen (CALLA). When CD10 is lost from methylation in epithelial cells, it leads to increased cell migration, growth, and survival, which can result in the development and progression of neoplasms. Several recent studies have suggested that the expression of CD10 in the tumor stroma of invasive breast carcinoma is associated with tumor aggressiveness and a worsened prognosis.[15]

The current study observed that CD10 expression in stromal cells was present in 96% of the cases. Among these cases, 66% showed strongly positive immunostaining, and 30% showed weakly positive immunostaining. The stromal cells within the area of invasive carcinoma expressed CD10, while the stromal cells of normal breast did not show CD10 expression. Most of the subjects in our study group had grade 2 tumors, similar to the study by Makretsov et al,[16] whereas Puri et al,[17] had most of the patients with grade 3 tumors.

Correlation of CD10 with Age & Menopausal status

Like other studies, we could not establish a significant association between stromal CD10 immunostaining with age (p=0.729) and menopausal status (p=0.935).

Correlation of CD10 with Tumor Grade

Our study found a statistically significant correlation between stromal CD10 positivity and increasing tumor grade (p=0.000). This finding aligns with several other studies by Dhande et al,[11] H Jana et al,[15] Pradhan et al,[16] Makretsov et al,[17] Kim et al,[19] Emad Sadaka et al [20], Mohammadizadeh et al,[21] B. V. Anuradha Devi et al,[22] and Ahmed Abdel Aziz et al,[23] which also reported a significant correlation between CD10 immunostaining positivity and tumor grade.

However, Puri et al,[18] and Iwaya et al,[24] reported contradictory results, finding an insignificant correlation between CD10 positivity and tumor grade.

Correlation of CD10 with Lymph Node Status

Stromal CD10 was found to have a significant correlation with an increasing number of metastatic lymph nodes (p=0.001). Multiple authors, including Dhande et al,[11] Pradhan et al,[16] Kim et al,[19] Sadaka et al,[20] Mohammadizadeh et al,[21] B V Anuradha Devi et al,[22] Ali Taghizadeh Karmani et al,[25] and Nema et al [26], have reported similar findings.

In contrast to the above results, Makretsov et al,[17] found no correlation between stromal CD10 immunoreactivity and lymph node status.

Correlation of CD10 with Nottingham's Prognostic Index (NPI)

The study showed a strong correlation between stromal CD10 expression and a poorer prognosis, as indicated by NPI (P=0.004). This finding is consistent with the research conducted by Jana et al,[15] Pradhan et al,[16] Mohammadizadeh et al,[21] B V Anuradha Devi et al,[22] and Ali Taghizadeh Kermani et al.[25]

Correlation of CD10 with Hormone Receptor Status

The study found that 84% of cases were positive for estrogen receptors, while 33.3% were positive for progesterone receptors. A negative and non-significant correlation existed between stromal C10 expression and ER/PR status. Puri et al,[18] and Ahmed Abdel Aziz et al,[23] found no significant correlation of CD10 immunostaining with ER and PR status. On the other hand, Dhande et al,[11] Jana et al,[15] Pradhan et al,[16] and Makretsov et al,[17] found a significant correlation between CD10 immunoreactivity and ER negativity. Additionally, Makretsov et al. found no statistical significance between stromal CD10 expression and PR. Dhande et al,[11] and Puri et al,[18] showed a good negative correlation between CD10 and PR; however, it was not statistically significant.

Correlation of CD10 with HER-2/neu status

The study did not find a significant correlation between stromal CD10 expression and HER-2/neu status. This finding aligns with the research of Pradhan et al,[16] Makretsov et al,[17] Mohammadizadeh et al,[21] and Ahmad Abdel Aziz et al.[23] In contrast, Dhande et al,[11] Jana et al,[15] Puri et al,[18] Sadaka et al,[20] and Thomas et al,[27] observed a significant correlation between CD10 immunostaining and Her-2/neu overexpression.

CONCLUSION

The current study found that stromal expression of CD10 is significantly associated with increasing tumor grade, worsening prognosis, and lymph node status. However, age, menopausal status, ER, PR, and

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HER-2/neu showed no correlation with stromal CD10 expression. This study has highlighted important aspects of CD10 expression in breast cancer. Further research in this area can provide more evidence supporting the prognostic significance of CD10 in breast cancer.

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