ORIGINAL ARTICLE DOI:https://doi.org/10.52206/jsmc.2023.13.4.801 OPEN ACCESS

Stromal CD10 Expression in Invasive Breast Carcinoma in Correlation with ER, PR and Her2 Status and Tumor Grade.

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ABSTRACT

Background: Increasing prevalence of breast cancer in our population is a leading cause of morbidity and mortality.Association of the tumor markers with the behavior of tumor cells may pave a way to better outcomes.
Objectives: To investigate the frequency of Stromal CD10 expression in invasive breast carcinoma in correlation with ER, PR and Her2 status and tumor grade.
Material and Methods: A total of 102 diagnosed cases of breast carcinoma who underwent mastectomies were examined. Immunohistochemistry was performed for Cluster of differentiation 10 (CD10), Estrogen receptor(ER) Progesterone receptor (PR) and Human epidermal receptor factor 2(HER2)for all the samples. Demographic characteristics and immunopathological variables were recorded.
Results: Mean age of the participants was 54.05 ± 8.58 years. Immunohistochemical analysis revealed 83 (81.3%) cases as CD10 positive out of which 15 (14.7%) specimens were weak positive and 68 (66.6%) were strong positive. The expression of CD10 was significantly greater for patients with higher tumor grades (p-value 0.014). Significant association of stromal CD10 expression and ER negativity was observed (p-value < 0.01). Out of 83 (81.3%) specimens that revealed positive CD10 expression, 64 (62.7%) were found HER2 positive and 19(18.6%) were HER2 negative signifying a positive correlation with p-value of <0.01.
Conclusion: Frequency of stromal CD10 expression is significantly associated with increasing tumor grade, HER2 positivity and ER negativity. It employs a prognostic role in predicting the aggressiveness of tumor as indicated by higher tumor grade and preemptive therapy with anti CD10 antibody may be beneficial in such candidates.
Keywords: Breast carcinoma, CD10, ER, PR, HER2.

This article may be cited as: Javaid F, Sajjad A, Basharat S, Safdar A, Khattak MT, Khan M, et al. Stromal CD10 Expression in Invasive Breast Carcinoma in Correlation with ER, PR and Her2 Status and Tumor Grade. J Saidu Med Coll Swat 2023;13(4):152-156. DOI:https://doi.org/10.52206/jsmc.2023.13.4.801

INTRODUCTION

Breast cancer is a globally prevalent pathological condition with more than 2 million new cases reported by the Globocan 2020 survey carrying a high risk of morbidity and mortality.[1] A number of variants have been described for invasive breast carcinoma however the most prevalent invasive breast carcinoma reported in our country was invasive ductal carcinoma with a prevalence of 91% among all the patients diagnosed with breast cancer.[2] It is a wide term coined for a set of breast tumor subtypes with distinct molecular and cellular origins, clinical behavior and patient outcomes. The diversity of presentation, clinical course, variable response to treatment and outcome of breast cancer poses a great challenge to health care workers. Its prognosis remains poor because of high probability of metastasis and local recurrences, which are the main causes of therapeutic failure however identification of early-stage breast cancer is a highly curable with more than 90 percent 5 years survival rate.[3]

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Received: August 08th, 2023 - 1st Revision: August 08th 2023
2nd Revision: October 17th 2023 - Accepted: October 23th, 2023

Although it is a malignancy arising from the epithelial elements of breast, the stroma has an important role in its origin and pathogenesis.[4] The stromal cells in the tumor microenvironment (TME) can influence the progression of multiple types of cancer and is associated with worse outcomes.[5] The matrix provides nourishment for the developing buds of cancer cells as well as it also aids in tumor invasion and distant spread. A better understanding of stromal contributions to cancer progression may identify specific signals that promote growth, de-differentiation, invasion, ectopic survival, and eventually result in the identification of new therapeutic targets for future treatments.[6] Recent advances have led to identification of several prognostic markers which can be utilized to predict the course and severity of the disease. Such markers can also be used as tools for therapy guidance and better outcomes in breast cancer. Expression of progesterone receptor (PR), estrogen receptors(ER) and human epidermal growth factor 2(HER2) receptors have been widely used in breast carcinomas. In addition to these markers' other markers like CD10, antigen Ki67, E-cadherin, Mib1 and others are widely used to predict the aggressiveness and hence the behavior of tumors earlier during the course of disease.[7,8] The rationale of this paper is to evaluate the strength of CD10 expression in patients diagnosed with

invasive breast cancer and its clinicopathological outcome in correlation with ER, PR, HER2 and tumor grade. This may prove beneficial for targeted therapies commenced preemptively to reduce the morbidity and mortality in these patients.

MATERIALS AND METHODS

After approval of the hospital ethical review committee vide certificate no RMI/RMI-REC/ article approval/72dated 12 October, 2022. Simple observational cross-sectional study was conducted at Histopathology department from 1st November 2022 to 30th April 2023.

A sample size of n=93 was calculated with a 19 %[9] reported prevalence of breast carcinoma in our population, employing a 8% margin of error and a confidence level of 95%. Non-probability consecutive sampling technique was used for 102 patients included in the study.

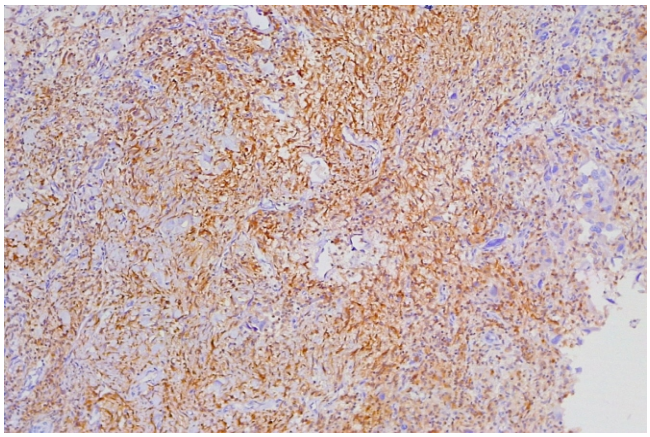
Female patients of any age group diagnosed as Invasive breast carcinoma who underwent mastectomies were included in this study.

Patient who underwent neoadjuvant therapy (Chemotherapy, radiotherapy or hormonal therapy) or diagnosed with invasive lobular carcinoma, medullary carcinoma, metaplastic variant and inflammatory variant, lymphoma and metastatic carcinoma were excluded from this study.

Mastectomy specimens of patients with prior diagnosis of Invasive Breast Carcinoma were received in the histopathology laboratory. Demographic characteristics (age, menopausal status, tumor size) of the patients were recorded and grossing of the specimens were carried out according to the guidelines of college of American pathologists.[10] Grossing, formalin fixation, paraffinization and Hematoxylin and Eosin staining was performed according to the standard protocol. After establishing the grade of tumor, immunohistochemical analysis was done for Estrogen receptor ER (Monoclonal Rabbit Anti Human Estrogen Receptor a Clone EP1), Progesterone receptor-PR (Monoclonal Mouse anti human Progesterone receptor clone (PgR 636), HER2 (Rabbit Monoclonal Primary antibody EP3) and CD10 (Monoclonal Mouse Anti 6666 human CD10 clone 56C6). Using labeled streptavidin biotin (LSAB) kit antigen detection was performed. Expression of stromal CD10 markers was assessed and recorded as strong expression if stromal cells staining was seen in greater than 10 percent cells. Positive CD10 expression was further graded into weak positive if stromal cell staining was >10% and <30% while strongly positive CD10 expression was recorded for specimens with cell staining >30%. For expression of ER Allred scoring[11] was used and for specimens with a score of 3-8 positive ER status was recorded. For immunoreactivity if the percentage of stromal cells staining was >10% ER and PR were considered positive. HER2 staining was considered positive if the cancerous cells revealed moderate to strong staining in >10% of the cells as per the guidelines of college of American pathologist's guidelines. Data analysis was performed using SPSS version 23. Frequency and percentages were computed for categorical variables while continuous variables were computed using Mean ± S.D. Interrelationship of qualitative variables i.e clinic pathological variables and number of cases revealing CD10 positivity/CD10 negativity was performed by applying chi square test keeping a p-value of =0.05 as significant.

RESULTS

A total of 102 cases were examined and reported after histopathological examination. Mean age of the participants was 54.05 ± 8.58 years. As Table 01 shows, Immunohistochemical analysis for CD10 expression of the specimens revealed 83 (81.3%) cases as CD10 positive out of which 68 (66.6%) were strong positive (Fig 01). CD10 expression for tumors with Grade III was highest (40.1%) (Fig 02) and lowest for Grade I tumors (8.8 %). (Tab 02). The expression of CD10 was significantly greater for patients with higher tumor grades (p-value <0.014). Significant association of stromal CD10 expression and ER negativity was observed with a p-value of <0.01. Out of 83 (81.3%) specimens that revealed positive CD10 expression, 64 (62.7%) were found HER2 positive and 19(18.6%)were HER2 negative signifying a positive correlation with p-value of <0.01. Clinicopathological correlations with CD10 expression are shown in Table 02.



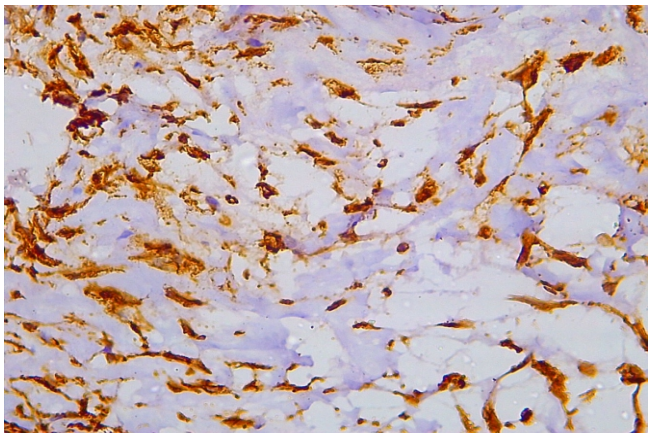


Fig. 01 & 02: Strong stromal CD10 positivity in greater than 10% tumor cells.

Table 01. Stromal expression of CD10 among participants (n=102)

Immunohistochemistry	Weakly Positive n (%)	Strongly Positive n (%)	Total Positive n (%)	Negative n (%)
CD10 stromal expression	15 (14.7%)	68 (66.6%)	83 (81.3%)	19 (18.6%)

Table 02. CD10 expression and clinicopathological correlations (n=102)

Variables		Positive CD10 expression n=83	Negative CD10 expression n=19	p- value
Age (n=%)	<50years	39(38.2%)	07(6.8%)	0.423
	>50years	44(43.1%)	12(11.7%)	
Tumor grading (n=%)	Premenopausal	19(18.6%)	06(5.8%)	0.427
	Postmenopausal	64(62.7%)	13(12.7%)	
Menopause (n=%)	Grade I	09(8.8%)	07(6.8%)	0.014
	Grade II	33(32.3%)	07(6.8%)	
	Grade III	41(40.1%)	05(4.9%)	
Tumor size (n=%)	T1	06(5.8%)	02(1.9%)	0.476
	T2	50(49%)	08(7.8%)	
	T3	15(14.7%)	06(5.8%)	
	T4	12(11.7%)	03(2.9%)	
Tumor stage (n=%)	1	03(2.9%)	03(2.9%)	0.073
	2	38(37.2%)	10(9.8%)	
	3	42(41.1%)	06(5.8%)	
ER status (n=%)	Positive	17(16.6%)	12(11.7%)	<0.01
	Negative	66(64.7%)	07(6.8%)	
PR status (n=%)	Positive	20(19.6%)	07(6.8%)	0.256
	Negative	63(61.7%)	12(11.7%)	
HER2 status	Positive	64(62.7%)	06(5.8%)	<0.01
	Negative	19(18.6%)	13(12.7%)	

DISCUSSION

The cross-sectional study evaluated CD10 expression in invasive breast carcinoma and its correlation with tumor grade, Estrogen and Progesterone receptor status. Immunohistochemical analysis revealed 83 (81.3%) patients with positive CD10 expression while 19 (18.6%) cases were CD10 negative. Positive CD 10 expression was observed with increasing grade of tumor, positive HER2 expression and negative ER. In a similar study when the frequency of CD10 expression in patients was correlated with ER, a negative correlation was concluded. Increase in the frequency of CD10 expression led to decrease in ER expression with a p-value of <0.01.[12] Histological grade of a tumor is a reliable prognostic indicator which can preemptively be used as a sign of tumor invasiveness.[11] Cross sectional study done by Dhande AN et al concluded that the number of cases of invasive breast carcinoma with tumor grade 2 morphology were 24(35%) and 27(38%) had a tumor grade 3. CD 10 expression in grade 2 tumor was found in 21(35%) of the cases while CD10 expression in grade 3 tumor was observed in 24(38%) revealing the increase in the frequency of CD10 expression with increasing tumor grade.[13] CD10-metalloproteinase is known for functions of migration of cells, adhesion and cell division. The expression of CD10 is a potential reliable indicator to predict the behavior and prognosis of breast cancer. In a similar trial the potential prognostic role was proved when CD10 positivity was found to be significantly correlated with nodal metastasis, lymphovascular invasion, PR negativity, HER2 positivity and poor prognostic groups.[14] Another research conducted by Srivastava G et al assessed the prognostic role of CD10 expression in invasive breast carcinoma and results were similar to our study. Frequency of CD10 positivity was significantly related to increase in the grade of tumor, stage of tumor and nodal metastasis.[15] Prevalence of breast carcinoma is on the rise but advances in diagnostics and therapeutic modalities have led to surprising results with a potential to decrease morbidity and mortality. Stromal markers provide a beneficial clue about the progression of the tumor and treatment with systemic, hormonal or cytotoxic drugs can be initiated at an early stage of the disease. This allows for prompt diagnosis and early commencement of treatment in such invasive pathologies.[16] Advances in field of medical sciences have led to meaningful treatments and one research reveals that drugs like trastuzumab, neratinib and tucatinib can potentially target HER2 whichmay lead to decreased invasiveness and mitotic activity of the cancerous cells in patients with HER2 positive breast cancer.[17] The expression of CD10 by invasive breast tumors makes it a viable target for T-cells as they express chimeric antigen receptors and therapies like universal chimeric antigen receptor T cell therapy can prove beneficial in such tumors.[18]

Beneficial role of novel prognostic markers like CD10 and its correlation with tumor grade, PR, ER and HER2 in our study can serve as a guide for commencement of early radiation, systemic or surgical therapies. Adjuvant therapies like hormonal, chemotherapy and anti HER2 can increase the overall survival in such patients by their anticancer role.[19] Hence our study proves that CD10 is a reliable marker which can prognosticate the invasiveness of the tumor. CD10 correlation with ER negativity, Her2 positivity and increasing tumor grade may be helpful in initiating early targeted therapies for better outcomes.

Limitations of the Study

The study was done on a limited population and didn't explore the possibility of geographical variation, further study to establish its clinical utility from a prognostic and therapeutic point of view and stratification of patients for anti CD10 therapy is suggested.

CONCLUSION

Stromal CD10 expression is significantly associated with increasing tumor grade, HER2 positivity and PR negativity. It employs a prognostic role in predicting the aggressiveness of tumor as indicated by higher tumor grade and preemptive therapy with anti CD10 antibody may be beneficial in such candidates. There is a need to work on a larger population for estimation of geographical variation and explore its clinical utility from a prognostic and therapeutic point of view and stratification of patients for antiCD 10 therapy.

Ethical Consideration

This study was approved by the ethical board of Rehman Medical Institute, Peshawar, Pakistan.

Funding

There is no role of any funding agency in this study.

Conflict of Interest
Authors declare no conflict of interest

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DATA SHARING STATEMENT: The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

AUTHOR'S CONTRIBUTION
The following authors full fill authorship criteria as per ICMJE guidelines;

Javaid F, Sajjad A:	Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Basharat S, Safdar A:	Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Khattak MT, Khan M:	Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Khan IM:	Analysis and interpretation of data, critical revision,final approval, agreed to be accountable for all the work.

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