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Stromal Expression of CD10 in Breast Carcinoma and Its Association with Known Prognostic Factors—A Tissue Microarray-Based Study

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Abstract

Background Breast cancer is an epithelial malignancy; however, stroma plays a key role with its stimulatory and inhibitory factors in modulating tumor invasion and metastasis. CD10, a matrix metalloproteinase, is known to regulate cell adhesion, migration and helps in determining the progression of tumor. This knowledge helps to identify specific signals that promote growth, dedifferentiation, invasion, metastasis and serve as target for better therapeutic management.

Objectives The aim of this study was to estimate frequency of expression of stromal CD10 and assess its prognostic significance in breast carcinomas by correlating with known prognostic factors.

Materials and Methods Morphological parameters of 62 cases of carcinoma breast were studied on H&E (hematoxylin and eosin) stained sections and expressions of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2/neu), and CD10 on manually constructed tissue microarray sections by immunohistochemistry (IHC). Staining pattern, percentage of stained cells, and intensity of stains were evaluated and IHC scoring of all markers was done. CD10 scores were correlated with the known prognostic factors (ER, PR, and HER2/neu). A *p*-value less than 0.05 was considered as significant.

Results Stromal expression of CD10 was found in 82.3% of cases and it was significantly associated with increasing tumor size ($p = 0.012$), increasing tumor grade ($p = 0.001$), lymph node metastasis ($p = 0.018$), necrosis ($p = 0.008$), lymphovascular invasion ($p = 0.008$), ER negativity ($p = 0.001$), PR negativity($p = 0.007$), HER 2 positivity ($p = 0.012$), triple-negative molecular subtypes ($p = 0.001$), and poor prognostic groups ($p = 0.01$).

Conclusion CD10 can be used as an independent prognostic stromal marker and this will help to envisage new therapeutic strategies.

Keywords
- breast
- carcinoma
- immunohistochemistry
- prognosis

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Introduction

In India, breast cancer accounts for 18.5% of all newly diagnosed cancers.[1] As it is an epithelial malignancy, various epithelial prognostic factors have been extensively studied.[2,3] Cancer cells interact with stromal cells and involve stimulatory and inhibitory factors that regulate cell adhesion and migration. Recent studies suggest that extracellular proteinase regulates growth factors and cytokines contributing to cancer invasion and metastasis.[4] The matrix molecules play an important role in malignancies and knowledge of such stromal markers will help identification of potential therapeutic targets.[2,5,6]

The continuous and bilateral molecular crosstalk between normal epithelial cells and stromal cells is affected by several factors like growth factors, chemokines, extracellular matrix (ECM) molecules as well as ECM-modifying enzymes, including matrix metalloproteinases (MMPs) secreted by tumor cells or stromal cells and they represent the most prominent group of proteinases associated with tumor progression.[2]

MMPs are a family of metallopeptidases that cleave protein components of ECM and thereby play a central role in tissue remodeling.[7] They also play an important role in secretion of active transforming growth factor β that promotes tumorigenesis. The cleavage products of matrix components (e.g., collagen, laminin) also have chemotactic activity for tumor cells, and thus help in tumor cell migration.[2]

CD10 is a 90 to 110 kDa zinc-dependent metalloproteinase, also called as "common acute lymphoblastic leukemia antigen". It is expressed in normal tissues like myoepithelial cells of breast and salivary glands and pulmonary alveolar epithelial cells, but it is not expressed in stroma of normal breast tissue.[8–10] Stromal CD10 is expressed with higher frequency in malignancy as opposed to borderline and benign phyllodes tumor of breast.[7,11–13] A knowledge of CD10 role in breast cancer will thus help in identifying specific signals that promote growth, dedifferentiation, invasion, angiogenesis, metastasis, and can serve as target for better therapeutic plan and management.[2,5,6]

Materials and Methods

A prospective study of prognostic indicators in 62 cases of carcinoma breast was undertaken from August 2015 to June 2017 at a tertiary care hospital in South India with the approval of Institutional ethical committee (JSSMC/PG/1435/2015-16). The formalin fixed paraffin embedded sections of modified radical mastectomy specimens of invasive breast carcinoma (No Special Type) were studied extensively for all the prognostic factors and were correlated with the clinical details (collected with patient's consent).

Nottingham combined histological grading (Elston–Ellis modification of Scarff–Bloom–Richardson grading system)[14] and tumor, node, metastasis staging according to American Joint Committee on Cancer (AJCC) classification (8th edition) [15] were followed. Nottingham's Prognostic index (NPI) was calculated using the formula: NPI = 0.2 x $S + N + G$, where, S is the size of the index lesion in centimeters, N is the node status: 0 nodes = 1, 1-4 nodes = 2, >4 nodes = 3 and G is the grade of tumor: Grade I =1, Grade II =2, Grade III =3. Based on the score, the patients were divided into six NPI groups (►**Table 1**).[16]

Table 1 Nottingham's Prognostic Index (NPI) groups[16]

Prognostic groups	NPI
Excellent prognostic group (EPG)	2.08 to 2.4
Good prognostic group (GPG)	> 2.42 to ≤3.4
Moderate prognostic group I (MPG I)	> 3.42 to ≤ 4.4
Moderate prognostic group II (MPG II)	> 4.42 to ≤5.4
Poor prognostic group (PPG)	> 5.42 to ≤6.4
Very poor prognostic group (VPG)	> 6.5 to 6.8

Manual Tissue Microarray Construction

Hematoxylin & eosin (H&E)-stained sections of formalin fixed paraffin embedded tumor tissue were screened to identify representative areas of malignancy. The corresponding areas on the paraffin blocks were marked and tissue cores of 4 mm were punched out using tissue punch. For each case, two cores were taken from the area of interest. Tissue microarray (TMA) blocks were constructed manually in rows and columns with the tissue cores. Sections from TMA blocks were stained with H&E and immunohistochemical (IHC) stains and studied to verify tumor cell content and to note IHC expression profile.[17–19] The sequence of steps in construction of a manual TMA paraffin block is illustrated in ►**Fig. 1**.

Immunohistochemical Staining

–Three to four µm thick TMA sections were fixed on poly-L-lysine coated slides, deparaffinized, and rehydrated. Antigens were retrieved with Tris buffer and following peroxide block the sections were incubated with primary antibodies (CD10, estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor 2 [HER2]/neu Monoclonal mouse antihuman antibody, clone 56C6, Dako), for 30 minutes, washed with wash buffer and further incubated with labeled polymer – HRP (Horse radish peroxidase) (DakoEn Vision + Dual Link System – HRP, DAB +, Code K4065). The bound antibodies were visualized using a DAB- (3,3' Diaminobenzidine) chromogen, counterstained with hematoxylin and mounted.[19]

The staining pattern, percentage of stained cells, and intensity of stains were evaluated by two independent observers. CD10 IHC scoring was done based on extent of cytoplasmic and membrane staining (►**Table 2**)[7] and the scores were correlated with known prognostic factors of carcinoma breast. The myoepithelial cells of normal breast tissue were taken as the positive control and primary antibody was omitted for negative control. The nuclear staining of ER/PR was evaluated based on Allred scoring system, while HER2 was evaluated based on the extent and intensity of membrane staining.

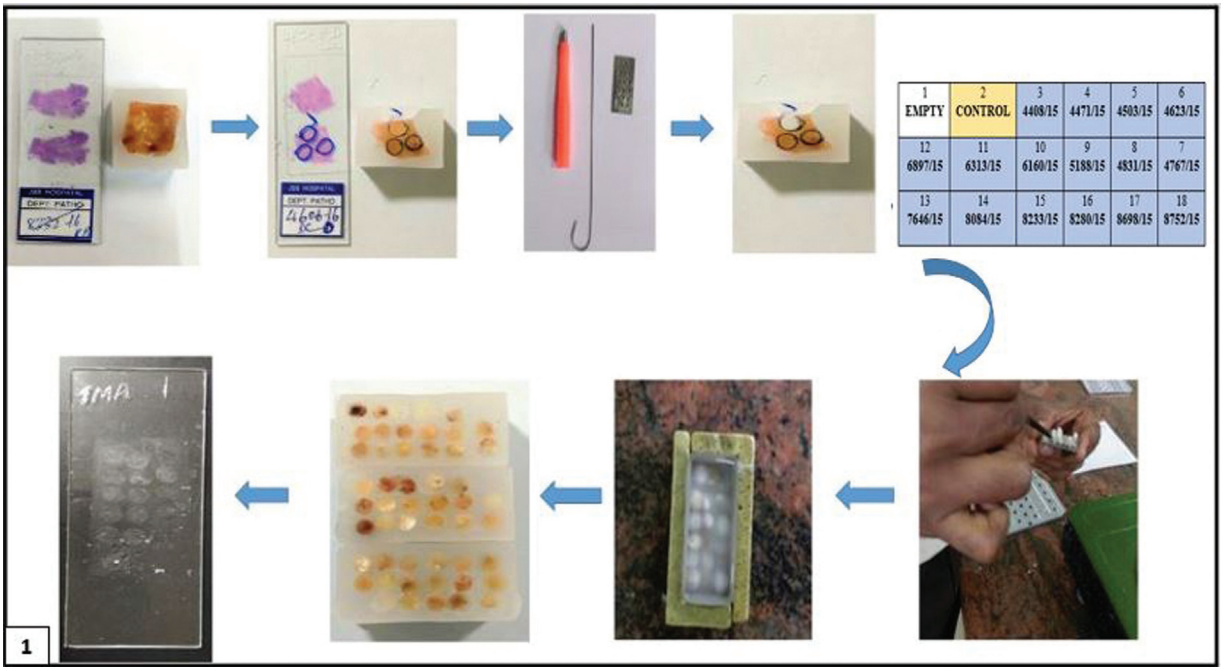

Fig. 1 The sequence of steps in construction of a manual tissue microarray paraffin block.

Statistical analysis was performed using contingency table analysis by SPSS for Windows (version 24.0) and correlation between stromal CD10 expression and clinicopathological features were evaluated using chi-squared test. A *p*-values less than 0.05 were considered statistically significant.

Results

A total of 62 cases of breast carcinoma were included in the study. Most commonly affected patients were in their fifth decade (32.2%) with a mean age of 51.3 years. Tumors were predominantly of grade III (56.5%) and grade II (40.3%) with only 3.2% of grade I tumors. Tumor necrosis, peritumoral lymphocytic infiltration, lymphovascular invasion (LVI), desmoplasia, and perineural invasion were seen in 58.1, 62.9, 80.6, 85.5, and 17.7% of cases respectively.

Pathological staging (based on AJCC system of classification) of majority of tumors was pT2 (67.7%) followed by 22.6% cases of pT3 and 9.7% cases of pT1. About 66.1% of tumors were ER and PR positive, while 56.5% showed HER2/neu overexpression and 19.4% were triple negative. Based on molecular subtyping, majority (41.9%) were of luminal B type, while there were 24.2% of luminal A, 19.4% of triple negative, and 14.5% of Her2 types. NPI showed 46.8% of cases under Moderate prognostic groups (MPG I & MPG II), 27.4% of very poor prognostic group (VPG), 22.6% of poor prognostic group (PPG), and 3.2% of cases of good prognostic group (GPG).

Scoring of CD10 by IHC and Its Correlation with Known Prognostic Factors

In normal breast tissue, CD10 expression was seen only in myoepithelial cells lining the ducts, while in 82.3% of invasive ductal carcinomas (NST), CD10-positive cells were seen infiltrating surrounding stroma. Of these, 48.4% of cases showed strong positivity (score 2) (►**Fig. 2**), while 33.9% of cases showed weak positivity (score 1; ►**Fig. 3**). CD10 scores were correlated with known prognostic factors like tumor size, grade, necrosis, LVI, perineural invasion, lymph node metastasis, and prognostic markers—ER, PR, HER2, molecular subtypes, prognostic groups. ►**Table 3** shows the correlation and statistical significance of CD10 scores with these prognostic factors.

Tumor Size

There was a significant association of CD10 expression and size of tumor. All tumors more than 5 cm showed CD10 positivity and it was overexpressed not only in 81% of tumors

Table 2 CD10 IHC scoring criteria[11]

Immunoreactivity	Score	Interpretation
No staining	0	Negative
Diffuse light brown or strong dark brown staining in less than 30% of the stromal cells	1	Weakly positive
Strong staining in more than 30% of the stromal cells	2	Strongly positive

Abbreviation: IHC, immunohistochemistry.

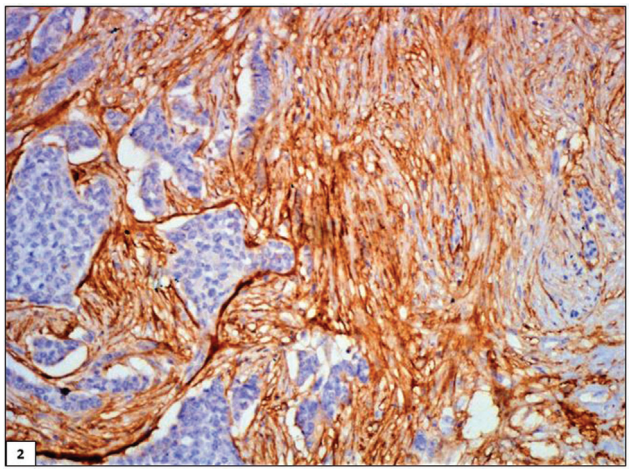

Fig. 2 CD10 immunohistochemistry (IHC) staining displaying strong staining intensity in >30% of stromal cells in invasive breast carcinoma —score 2 (CD10 IHC, x200).

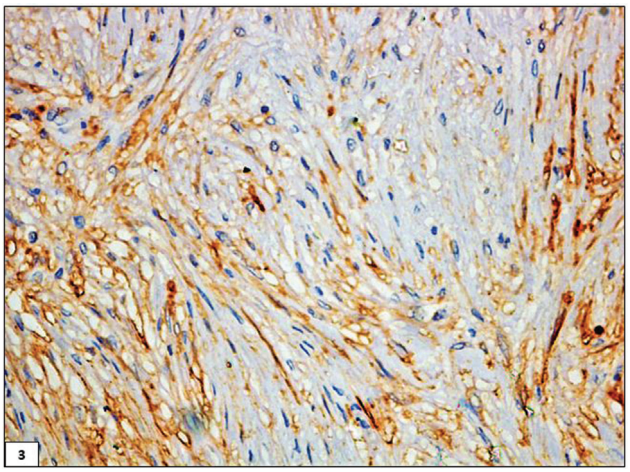

Fig. 3 CD10 immunohistochemistry (IHC) staining showing moderate staining intensity in <30% of stromal cells of invasive breast carcinoma- Score 1 (CD10 IHC, x200).

of 2 to 5 cm but also in 50% of tumors of less than 2cms. It was further observed that the expression was of a higher intensity (score 2) in 78.6% of tumors more than 5cm and 45.3% of tumors of 2 to 5 cm, while tumors less than 2cm had a lower intensity (score 1) of expression.

Histopathological Grade

Overexpression of CD10 in stroma was seen in 76% of grade II tumors and 91.4% of grade III tumors, while it was not expressed in grade I tumors thus signifying a statistically significant higher expression with increasing grade. Also, majority (65.7%) of grade III tumors showed a higher intensity of expression of CD10, while same was noted in 28% of grade II tumors.

LVI, tumor necrosis, desmoplasia, peritumoral lymphocytic infiltration, and perineural invasion: There was a statistically significant correlation between CD10 expression and tumor necrosis ($p = 0.008$), desmoplasia ($p = 0.01$) and LVI ($p = 0.008$) while there was no correlation with stromal lymphocytic infiltration ($p \_= 0.41$) and perineural invasion ($p = 0.29$; ►**Table 3**).

Lymph Node Status

Overexpression of CD10 was seen more often in node positive cases in 70% of N0, 81.3% of N1, 100% of N2, and 81.9% of N3 tumors. The intensity score increased with increase in number of lymph nodes showing metastasis. The N2 and N3 tumors showed higher intensity of score 2 as compared to N0 and N1 tumors (intensity score of 1). This higher intensity staining for CD10 with worsening lymph node (N) status was statistically significant with a p-value of 0.018.

ER, PR, and HER 2 Expression

With 90.5% of ER- and PR-negative tumors showing an overexpression of CD10, there was a statistically significant inverse correlation of CD10 with ER and PR expressions. Contrary to this, there was a statistically significant overexpression of CD10 in HER2/neu positive tumors (94.3%) compared to HER2/neu-negative tumors (66.6%).

Molecular Subtypes

CD10 expression was seen in 13.3% of cases of luminal A, 42.3% of luminal B, 66.7% of triple negative, and 94.3% of HER2 molecular subtypes of tumors. The CD10 expression was of higher intensity in triple negative (66.6%) and HER2 types (100%), while in luminal A (13.32%) and luminal B subtypes (42.3%), the expression was of lower intensity.

NPI Groups

Higher intensity of expression was seen in 28.6% of MPG I, 40% of MPG II, 50% of PPG, and 76.5% of VPG with no expression in Nottingham's GPG.

Follow-Up

Among the 62 cases of invasive carcinoma breast, we could follow-up 41 cases on the recurrence and breast-cancer-associated deaths for a period of 3 years. The remaining cases were lost to follow-up. Two cases succumbed to disease-specific death by the end of 1.5 and 2 years, respectively, and both cases were strongly CD10 positive and belonged to the Nottingham's VPG. Recurrence was recorded in eight cases, of which five belonged to VPG and three to PPG with strong CD10 expression. Thus, this showed a significant trend toward CD10 overexpression and decreased survival as well as disease recurrence in the patients.

Discussion

The structural and functional integrity of breast is maintained by mutual efforts of the epithelial cells and stromal components. Interaction of tumor cells with stromal cells involves various factors that regulate tumor growth, adhesion, migration and thus affects invasiveness and metastatic potential of cancer cells. This modifying effect of matrix molecules gives matrix a cardinal role in cancer proliferation and metastasis.[20] More knowledge regarding the role of stroma in breast cancer development and progression will

Table 3 Correlation of CD10 expression with other known prognostic factors of breast cancer

Clinicopathological parameters	Total patients *n* (%)	CD10 expression			*p*-Value	Significance (*p*-value <0.05)
		Negative	Weakly positive	Strongly positive		
Age (in years)						
21–30	1 (1.6)	1 (100)	0 (0)	0 (0)	0.25	Not significant
31–40	14 (22.6)	4 (28.6)	2 (14.3)	8 (57.1)		
41–50	16 (25.8)	3 (18.8)	5 (31.3)	8 (50)		
51–60	19 (30.6)	2 (10.5)	10(52.6)	7 (36.8)		
61–70	9 (14.5)	1 (11.3)	3 (33.3)	5 (55.6)		
71–80	2 (3.2)	0 (0)	0 (0)	2 (100)		
81–90	1 (1.6)	0 (0)	1 (100)	0 (0)		
Menopause						
Postmenopause	36 (58.1)	3 (8.3)	15(41.7)	18 (50)	0.05	Not significant
Premenopause	26 (41.9)	8 (30.8)	6 (23.1)	12 (46.2)		
Histopathological grade						
Grade 1	2 (3.2)	2 (100)	0 (0)	0 (0)	0.001	Significant
Grade 2	25 (40.3)	6 (24)	12 (48)	7 (28)		
Grade 3	35 (56.5)	3 (8.6)	9 (25.7)	23 (65.7)		
Necrosis						
Present	36 (58.1)	6 (16.7)	7 (19.4)	23 (63.9)	0.008	Significant
Absent	26 (41.9)	5 (19.2)	14 (53.8)	7 (26.9)		
Desmoplasia						
Present	53 (85.5)	11 (20.8)	14 (26.4)	28 (52.8)	0.01	Significant
Absent	9 (14.5)	0 (0)	7 (77.8)	2 (22.2)		
Lymphocytic infiltration						
Present	39 (62.9)	5 (12.8)	14 (35.9)	20 (51.3)	0.41	Not significant
Absent	23 (37.1)	6 (26.1)	7 (30.4)	10 (43.5)		
Lymphovascular invasion						
Present	50 (80.6)	7 (14)	14 (28)	29 (58)	0.008	Significant
Absent	12 (19.4)	4 (33.3)	7 (58.3)	1 (8.3)		
Perineural invasion						
Present	11 (17.7)	3 (27.3)	5 (45.5)	3 (27.3)	0.29	Not significant
Absent	51 (82.3)	8 (15.7)	16(31.4)	27(52.9)		
Tumor size						
<2cm	6 (9.7)	3 (50)	3 (50)	0 (0)	0.012	Significant
2–5cm	42 (67.7)	8 (19)	15 (35.7)	19 (45.3)		
>5cm	14 (22.6)	0 (0)	3 (21.4)	11 (78.6)		
Lymph node status						
N0	20 (32.3)	6 (30)	6 (30)	8 (40)	0.018	Significant
N1	16 (25.8)	3 (18.8)	9 (56.3)	4 (25)		
N2	15 (24.2)	0 (0)	2 (13.3)	13 (86.7)		
N3	11 (17.7)	2 (18.2)	4 (36.4)	5 (45.5)		
ER						
Positive	41 (66.1)	9 (22)	19 (46.3)	13 (31.7)	0.001	Significant
Negative	21 (33.9)	2 (9.5)	2 (9.5)	17 (81)		
PR						
Positive	41 (66.1)	9 (22)	18 (43.9)	23 (48.9)	0.007	Significant
Negative	21 (33.9)	2 (9.5)	3 (14.3)	16 (76.2)		
HER2/neu						
Positive	35 (56.5)	2 (5.7)	12 (34.3)	21 (60)	0.012	Significant
Negative	27 (43.5)	9 (33.3)	9 (33.3)	9 (33.3)		
Molecular subtypes						
Luminal A	15 (24.2)	6 (40)	7 (46.7)	2 (13.3)	0.001	Significant
Luminal B	26 (41.9)	3 (11.5)	12 (46.2)	11 (42.3)		
Triple negative	12 (19.4)	2 (16.7)	2 (16.7)	8 (66.7)		
HER 2 positive	9 (14.5)	0 (0)	0 (0)	0 (100)		
Prognosis						
GPG	2 (3.2)	2 (100)	0 (0)	0 (0)	0.01	Significant
MPGI	14 (22.6)	4 (28.6)	6 (42.9)	4 (28.6)		
MPGII	15 (24.2)	2 (13.3)	7 (46.7)	6 (40)		
PPG	14 (22.6)	3 (21.4)	4 (28.6)	7 (50)		
VPG	17 (27.4)	0 (0)	4 (23.5)	13 (76.5)		

Abbreviations: ER, estrogen receptor; GPG, good prognostic group; HER2, human epidermal growth factor receptor 2; MPGI, moderate prognostic group I; MPGII, moderate prognostic group II; PPG, poor prognostic group; PR, progesterone receptor; VPG, very poor prognostic group.

help in identification of new prognostic markers that can serve as potential therapeutic targets.[2,5]

CD10 is metallopeptidase that plays an important role in tissue remodeling by cleavage of protein components of ECM.[7] In normal breast, CD10 is expressed only by myoepithelial cells that line the outer layer of the ducts. In invasive breast carcinoma, enzymatic activity of CD10 is upregulated; this leads to an accumulation of CD10–cleaved peptides that inhibit epithelial cell differentiation and result in epithelial mesenchymal transition and malignant proliferation.[2]

Tumor size is one of the significant prognostic factors in breast carcinoma and there is increased incidence of axillary lymph node metastasis and decreased survival with increasing size of tumor.[21,22] Majority of patients in the present study had large tumors when they sought medical attention and there was a significant positive correlation with the overexpression of CD10 and tumor size[5,17,23] however, Iwaya et al[24] and Arora et al[25] have not noticed this correlation.

Researchers have observed a significant correlation between CD10 expression and increasing grade[25] and lymph node involvement.[4,5,17,23,24] Complimenting this finding, a higher intensity of CD10 expression has been noted more often in grade III tumors, N2/N3 tumors compared to grade II tumors, and N0 / N1 tumors. Studies have reported that factors like necrosis, desmoplasia, and LVI are associated with aggressive nature, poor prognosis, and early recurrence/death.[26–28] The present study has shown a significant association of CD10 expression with these factors, which implies CD10 as a poor prognostic indicator.

Though majority of breast tumors are hormone dependent or express HER2 and have appropriate treatment targeting these pathways, triple-negative tumors form a significant number. Studies have reported a statistically significant correlation between CD10 expression and ER/PR negativity[2–5,7] and HER2/neu positivity,[2,3] but data correlating CD10 expression with molecular subtypes is limited. In the present study, CD10 expression was seen more often in triple negative and HER2 molecular subtypes of tumors compared to luminal A and luminal B subtypes and CD10 expression was of higher intensity in triple negative and HER2 types are the aggressive molecular variants, while in luminal A and Luminal B subtypes, expression was of lower intensity. An increased expression was also noted inPPGs.[2] Studies have reported that a strong positive stromal CD10 expression in breast carcinoma was associated with decreased long-term disease-specific survival and overall survival.[7,17,23,24]

CD10 can be used as a potential target for novel therapies as it is involved in cleavage of doxorubicin, a critical component in many chemotherapy protocols. As doxorubicin is known for its toxicity, CPI0004Na a prodrug of doxorubicin that can be cleaved by CD10 may improve the antitumor efficacy profile with reduced toxicity in tumors that overexpress CD10.[8]

Our study shows a statistically significant correlation of CD10 overexpression with poor prognostic factors including larger tumor size, lymph node metastasis, higher histological grade, necrosis, LVI, ER/PR negativity, HER2/neu positivity, triple-negative molecular subtypes, and the PPGs, signifying that CD10 can be used as an independent poor prognostic marker in carcinoma breast.

Stromal CD10 expression in breast cancer is not static and changes with neoadjuvant anthracycline based chemotherapy. A stable or decrease in CD10 expression indicates complete or partial clinical response, while an increase in CD10 expression appears to correlate with poor clinical response. Thus, incorporating CD10 as a biomarker along with known factors into a prognostic index will not only help to predict clinical outcome more accurately but also help in predicting treatment failure in patients receiving neoadjuvant chemotherapy.

Conclusion

Our results are found parallel with other investigators, but it is necessary to further unveil the complex crosstalk between the cancer cells and other cells of the tumor microenvironment to establish high-quality targeted therapy. Larger prospective clinical studies with a longer duration of follow-up and study of survival are essential to validate our findings and help to envisage new therapeutic strategies.

Authors' Contributions

N.G. contributed to literature search, clinical and experimental studies, data acquisition, data and statistical analysis, and manuscript preparation. J.K. helped in conceptualization, designing, definition of intellectual content, and manuscript editing and review. N.G. has provided guarantee.

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Conflict of Interest

None declared.

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