

**“STUDY OF STROMAL EXPRESSION OF CD-10 AND ITS
CORRELATION WITH CLINICOPATHOLOGICAL PARAMETERS IN
CARCINOMA BREAST”**

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ABSTRACT:

Carcinoma breast is the most commonly prevailing neoplasm among women having no geographical variations and the 2nd most prevalent neoplasm all over the world. With the introduction of Triple test approach a more accurate evaluation was made possible which allows a well-planned management from the consultant.^[1,2] Because of the variability of the epithelial component, the histological grade of invasive breast cancer is frequently underestimated in core needle biopsy. The stroma is typically homogeneous throughout the tumour. Also, a significant CD10 stromal positivity has been linked with a higher tumor grade. CD10 is a metallo-proteinase showing its expression in the stroma of innumerable epithelial neoplasms, being associated with the biological-aggressiveness of the tumour. CNB is the preferred approach for assessing breast masses prior to surgery.^[3] However, because of the variability of the epithelial component, CNB frequently underestimates the histological grade of invasive breast cancer.^[4] There may be false-negative results also. Tumor stroma may contain more predictive information than the tumor's epithelial component and can help in determining prognosis.^[5] Cells of the stroma in breast carcinoma may express CD10 which is a zinc-dependent metalloproteinase. It can cleave the matrix and help in tumor invasion and metastasis. CD10 can also cleave doxorubicin leading to resistance to doxorubicin.^[6] An association of strong stromal positivity for CD10 with high grade of the tumour has been found.^[7] Assessment of stromal CD10 positivity in small biopsies may thus aid in assessment of prognosis and deciding the treatment.

KEY WORDS: Breast Carcinoma, Core Needle Biopsy, CD10.

BACKGROUND:

Breast carcinoma has been identified as the most commonly prevailing malignancy in females as also the 2nd most frequent neoplasm all over the world, with no geographical variations. Two types of epithelial cells make up the female breast: 1. Myo-epithelial 2. Luminal (secretory) cells, organized into lobules that contain the acini. The intralobular stroma is more vascular and hormone sensitive, with fibroblast-like cells. The interlobular stroma is not affected by hormones.^[8]

The process of spread of the tumor is variable and it involves multiple intra-cellular molecular changes and genetic abnormalities, like mutation or over-expression of receptors which are hormone dependent, growth-factors, onco-proteins, and tumor suppressor genes, which typically regulate cell proliferation and differentiation.^[8]

Metastatic disease is responsible for the majority of breast cancer deaths, and a greater knowledge regarding the molecular mechanisms of disease with metastasis would also have clinical consequences in the field of diagnosis, management as well as prognosis.

Over the last decade, researchers have discovered and validated the removal of CD10 which is being expressed by the myo-epithelial cells in malignant neoplasms. Recent research relates to some of the studies that found CD10 stromal expression in the stromal cells of carcinoma breast, linking CD10 expression in carcinoma breast stromal cells with the other prognostic variables.

The hypothesized aetiology of expression is how the tumour cells interact with the stromal cells as well as with the extracellular matrix which results in the stromal expression of CD10, which

further proceeds to breakdown the collagen and the extracellular matrix, which helps to create milieu conducive for metastasis and invasion.^[8]

Breast cancer spreads via direct invasion, hematogenous route, as well as through lymphatic route, with hematogenous and lymphatic routes being the most common. Local invasion can also be found in the nipple, skin, fascia, and pectoralis muscle.^[9]

Attempts to anticipate the clinical fate of all patients based on commonly acknowledged variables like size as well as grade of the tumor and the total no. of axillary lymph-nodes which are positive have been partly successful, yet failed in precisely predicting the inherent the potential of cancerous cells to metastasize in each of the individual patients. Various studies have demonstrated the different groups of patients having different survival rates, demonstrating the variety of breast tumors and the need for more molecular research and better patient classification. As a result, the quest for new prognostic markers that can better predict metastasis and thus be included as an extra prognostic factor in the management algorithm of breast tumors continues to be an important focus of current research.

Thus, newer research is gaining pace in order to crack down on and shed light on molecular pathways that promote invasion as well as metastasis, further incriminating aggressiveness of the tumour and the development of products or medications targeting these molecules, thus helping to reduce mortality and thus assisting patients in living disease-free lives, reducing morbidity, and improving quality of life.^[9]

Recent research has focused on the stromal characteristics and molecular signatures like fibrosis, the involvement of the metallo-proteinase, and the presence of fibers with relation to

invasiveness and metastatic potential, and to see if it influences the long term outcome of patients, but this remains unknown.

BREAST CARCINOMA:

Breast carcinomas are classified into two categories based on invasion: Invasive and non-invasive carcinoma. Non-invasive breast carcinoma includes DCIS and LCIS, whereas invasive breast carcinoma including Infiltrating ductal carcinoma, Infiltrating Lobular carcinoma, Mucinous Carcinoma, Medullary carcinoma, Paget's disease, etc.^[10]

Adenocarcinomas account for nearly all (more than ninety-five percent) of breast cancers. They begin as cancer in situ in the duct/lobular system. The majority (at least seventy percent) will have crossed the basement membrane and entered the stroma at the time of clinical identification. The cells now have the ability to penetrate the vessel walls and so reach regional lymph nodes and faraway places.^[11]

Metastatic breast carcinoma is an uncommon kind of cancer accounting for fewer than one percent out of all the breast carcinomas with adenocarcinoma, mesenchymal, and epithelial components.^[12]

Carcinoma breast is often caused because of a combination of inherited as well as environmental factors. The RAS/MEK/ERK and PI3K/AKT pathways shield the normal cells from apoptosis. When the genes encoding these defensive processes change, the cells' ability to commit suicide is lost when they are no longer required, as a result of which cancer develops. Breast tissue histological features such as proliferative benign illnesses, atypia, and in situ carcinoma enhance the likelihood of developing invasive carcinoma in the future.^[13]

Histological grading for breast carcinoma:

Bloom-Richardson grading system is the most widely used grading system.^[14] It comprises of three morphological features; tubule formation in the tumour, mitoses and nuclear pleomorphism. Score ranging from three to nine.^[15]

In recent years, aggressive surgical methods such as modified radical mastectomy have been developed to improve patient prognosis.^[16]

Diagnostic mammography remains the gold standard of care in the initial diagnosis and treatment of carcinoma breast.^[17]

Breast cancer medical therapy using anti-estrogens such as raloxifene or tamoxifen may prevent the disease in people who are predisposed to it. In females with a greater risk to develop carcinoma, surgery of both breasts is an additional preventive measure. Patients with carcinoma breast are treated with a variety of treatments which includes hormone therapy, targeted therapy, radiation therapy, surgery, and chemotherapy. The majority of treatment options for patients with distant metastases aim at improving the quality of life as well as the survival rate.

CNB is the preferred approach for assessing breast masses prior to surgery. However, because of the variability of the epithelial component, CNB frequently underestimates the histological grade of invasive breast cancer.^[18,19] There may also be false-negative outcomes. Tumor stroma may contain more predictive information than the tumor's epithelial component. CD10, a zinc-dependent metalloproteinase, may be expressed by stromal cells in breast cancer.^[20]

EPIDEMIOLOGY:

According to GLOBOCON 2019, carcinoma breast is the commonest diagnosed cancer, which accounts for 2.086 million of all emergent cases (11.6 percent of total cases), and the major cause of cancer related mortality, accounting for 627000 of all cancer deaths (6.6 percent of all cancer fatalities) worldwide, trailed by carcinoma lung as the 2nd most cause of all cancer related mortality.^[21]

Carcinoma breast is a crucial cause of fatality in Indian females, with an age-adjusted mortality rate of 12.07 per one lakh women and an age-adjusted rate of 25.08 per one lakh women. The incidence rate of age-adjusted breast carcinoma in Delhi was forty one per one lakh women, followed by Chennai (37.19 per one lakh), Bangalore (34.14 per one lakh), and Thiruvananthapuram District. The mortality:incidence was found higher (about sixty six) in rural areas, whereas lower (about eight) in the urban region.^[22]

PREDISPOSING FACTORS:

The reproductive years are the age group in which the majority of breast cancers are discovered. The incidence curve begins to rise from puberty, rises steeply until menopause, and then levels out. Breast cancer, on the other hand, can strike at any age, from infants to the elderly.^[23]

The primary cause is the inheritance of a susceptibility gene or genes, which accounts for around 12 percent of all breast cancers. BRCA1 and BRCA2 germline mutations account for around three percent of all breast cancers.^[24]

Lower menarche age, older age at first conception, fewer births, shorter or no breastfeeding periods, and later menopause all contribute to an increase in incidence in most nations. Increased weight, alcohol intake, inactivity and All of these risk factors for carcinoma contribute to its development.^[25]

CD10 and its role in normal breast –

CD10, also known as common acute lymphoblastic antigen, is a Zn-dependent metallo-proteinase that found in BM lymphoid stem cells, mature neutrophils, proB lympho-blasts, renal cell cancer, numerous lymphoma subtypes and endometrial stromal sarcoma.^[26]

CD10 is a Zn-dependent endo peptidase,a metallo-proteinase type which controls the physiological role of innumerable peptides by reducing their extra-cellular level accessible for binding with the receptors. By leading to the cleavage of the signalling proteins which normally lead to differentiation of Early Common Progenitors to Luminal Epithelial Progenitors or Myoepithelial Progenitors, CD 10 protease maintains the human mammary lineage's early progenitor population, resulting in luminal and myoepithelial cells. As a result, CD10 works as a Progenitor cell regulator in the breast, through its enzymatic activities(together with the support of 1-integrin), it inhibits the uncontrolled proliferation of mammary SC.

Significance of CD10 in breast carcinoma -

Several studies have discovered a link between stromal CD10 expression and biological aggressiveness in a range of epithelial malignancies.

It has the ability to break the matrix and aid in tumor invasion and metastasis. CD10 can potentially cleave doxorubicin, resulting in doxorubicin resistance. Strong CD10 stromal positivity has been linked to a higher tumor grade. Evaluation of stromal CD10 positivity in tiny biopsies may thus aid in prognosis and therapy decision-making.

CD10 has recently emerged as a key player in diseases such as endometrial stromal sarcoma, cannalicular pattern hepatocellular carcinoma, renal cell carcinoma, and Acute Lymphoblastic Leukemia (CALLA).^[27]

CD10 expression in the stroma is caused as the malignant cells interact with the stromal cells and extracellular matrix causing degradation of extracellular matrix and collagen, establishing an environment conducive for invasion and metastasis.

CD10 expression appears to have conflicting results in breast cancers. On one side, DCIS progresses to invasive malignancy because to its absence in basement membrane and the myoepithelial cells. CD10 expression by stromal cells around a breast tumor, on the other side, has been linked to a higher grade of tumor, ER negative status and thus a poor survival rate. This is explained by Maguer-Satta et al. concept, which states that CD10-enzyme expression in transformed cells or the nearby cellular environment is affected by early oncogenic processes in stem cells. A reduction in the enzymatic function of CD10 during malignant transformation of early common-progenitors or progenitors can lead to an accumulation of unprocessed peptides in

the stem cell milieu, which results in lineage commitment and malignant proliferation. This is the proposed progression of ductal carcinoma in situ to invasive cancer with CD10 deletion.

However, in invasive breast carcinoma, an increase in mutant CD10 enzymatic activity contributes to the buildup of local CD10-cleaved peptides, which inhibit epithelial cell differentiation and maintain cancer stem cells, explaining why higher CD10 expression is found in undifferentiated (high histological grade anaplastic) carcinomas.

Relation of CD10 with mitotic rate, prognosis and chemotherapy -

Normally, CD 10 binds to PTEN which is a tumor suppressor, and it results in decreased phosphorylation of Phosphatidylinositol 3, 4, 5-tris-phosphate, restricting Akt pathway activation (important in tumor cell growth) and cell apoptosis (through MDM-2 pathway). Also, CD10 leads to the cleavage of growth-factors like fibroblast growth-factor 2, promoting endothelial cell proliferation and angiogenesis by activating Akt signaling. CD10 inhibits migration of the neoplastic cells (via PI3K-FAK pathway) as well. CD10 signaling in cancer progenitors or SCs could be altered in breast cancer, regardless of the activity of the enzymes. These signaling alterations may affect PTEN activity, leading to apoptotic suppression, cell growth and angiogenesis through the Akt pathway. This could explain why CD10 positive is linked to an increase in mitotic grade (increased cell proliferation) and a bad long term outcome. Furthermore, the poor response to chemotherapy drugs in some CD10 positive individuals may be connected to this altered CD10 signaling system, which results to decreased apoptosis and thus chemotherapy resistance.

DISCUSSION:

The study titled 'Stromal expression of CD10 in breast carcinoma and its correlation with clinic-pathological parameters' by **Ashish Nitin Dhande et al**, which included 60 cases of breast carcinoma over a two-year period from 2013 to 2015, found that CD10 stromal expression was linked to greater tumour grade, higher number of positive lymph nodes, HER2neu positivity, ER negativity, and Ki67 positivity. CD10 can be utilized as a prognostic marker on its own and should be included in routine histopathology reports. CD10 could be employed as a therapeutic target in the future.^[28]

Study conducted by **Vandana Puri et. al.** titled '**Stromal Expression of CD10 in Invasive Breast Carcinoma and Its Correlation with ER, PR, HER2-neu, and Ki67**' conducted for a period of 2 years from 2007 to 2009 **concluded that** CD10 expression was dynamically linked with well-established unfavourable prognostic indicators, such as HER2-neu and ki67 positivity, Estrogen Receptor/Progesterone Receptor negativity, and greater tumor grade, demonstrating that CD10 can be utilised as an independent marker signalling bad outcome.^[29]

CD10 expression by stromal cells in carcinoma of the breast and its correlation with ER, PR, HER2neu, and Ki67-A tissue microarray study in a tertiary care hospital' by **Monideepa Chattopadhyay et al.** was found to be positively correlated with Ki67 and increasing tumour grade, but inversely correlated with ER and PR status in a two-year study conducted from

September 2015 to August 2017. No correlation was found between CD10 and lymph node status or HER2-neu status.^[30]

Keiichi Iwaya et al had forty-seven out of a total of one hundred and ten patients with histopathological grade II, of which thirty-seven had positive CD10 expression, although statistical analysis proved inconsequential.

Nikita A Makretsov et al. found 139 cases with histopathological grade II out of 258. 100 of them had CD10 expression that was positive. The researchers discovered that stromal CD10 was more common in invasive breast cancers than noninvasive breast cancers, and that stromal CD10 expression was associated with higher tumour grade and oestrogen receptor negative status. There was no link between CD10 and lymph node status, tumour size, histological subtype, progesterone receptors, or Her2 status, according to the study. In lymph node negative patients, but not lymph node positive patients, long-term disease-specific and overall survival were found to be worse in people who expressed stromal CD10. It determined that stromal CD10 expression in invasive breast cancer was linked to ER negativity, greater tumour grade, and shorter survival, and that it might be used as a prognostic marker and a target for new therapeutics.

Fereshteh Mohammadizadeh et al. showed twenty five out of forty nine patients with grade two carcinoma showing CD10 expression. The analysis was found to be statistically significant.

In their study, **Ali Taghizadeh-Kermani et al** had fifty out of a hundred patients with tumour grade 2, with thirty one out of fifty demonstrating positive immunoreactivity with CD10. The relationship between CD10 expression and tumour grade was found to be statistically significant.

In their study, **Hala N. Hosni et al** reported 19 out of 50 patients with tumour grade two and eighteen out of nineteen cases with CD10 immunopositivity. The association between CD10 expression and tumour grade was discovered to be statistically significant.

Conclusion –

Carcinoma breast is one of the most commonly occurring malignancy in women throughout the world. Each tumor is distinct in terms of invasion and metastatic propensity, as also its pace of growth. The type and number of oncogenes that are activated have an impact on the prognosis of a certain lesion. To evaluate oncogene expression or amplification, many markers have been used. The clinical manifestations of the malignancy can be modified by targeting over-expressed oncogenes with treatment. In all cases of breast cancer, well-established prognostic markers such as tumor stage, histological grade of the tumour, number of positive lymph nodes, hormone receptor status and HER2-neu are regularly assessed.

Stromal markers have been recently emerging as novel predictors of invasive breast cancer prognosis, although they have received little emphasis to date. Stroma is important in controlling tumor invasion and its potential to metastasize. A greater knowledge of the contribution of the stroma to the progression of malignancy will lead to the identification of particular signals that enhance tumour cell proliferation, dedifferentiation, invasion, and ectopic survival, ultimately

leading to the identification of new therapeutic targets for further management. This supports the investigation of CD10, a novel stromal marker, in the prognosis of invasive breast cancer.

The majority of studies discovered a statistically significant connection between stromal CD 10 expression and lymph node metastases, histological grade, and Nottingham's prognostic index.

The majority of the studies found no statistically significant link between age, menopausal status, tumour size, histological grade, or mitotic rate. The majority of the studies found no statistically significant link between age, menopausal status, tumor size, histological subtype, or mitotic rate.

As a result, in conjunction with Nottingham's prognostic index and lymph node stage, CD10 can be used as a prognostic marker.

More research is necessary to determine the role of expression of CD10 in the stroma, predicting overall and disease-free survival rates in IDC breast. To increase molecular understanding, rate of survival, post-chemotherapy modifications, and response to doxorubicin, its pro-drugs, and chemoresistance must be thoroughly investigated, and CD 10 may potentially emerge as a theranostic marker.

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