Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/15022
DOI URL: http://dx.doi.org/10.21474/IJAR01/15022

RESEARCH ARTICLE

ANALYSIS OF CORRELATION OF STROMAL CD10 EXPRESSION INCARCINOMABREASTNOSTYPEWITH HER2/NEU

S. Ulaganathan, Abu Arshad A. and R. Duraisamy
Assistant Professor, DepartmentofPathology,Government Mohankumaramangalam Medical College,Salem,/TamilNaduDr.MGRMedicalUniversity,Chennai,India.

Manuscript Info

Manuscript History
Received: 10 May 2022
Final Accepted: 14 June 2022
Published: July 2022

Key words:-
Breastcarcinoma NOS Type, Prognosticmarker, Stromal CD10, Stromalmarker

Abstract

Background: Breastcancerisoneofthemostcommoncanceramongwomen .Stromaplaysanimportantpathogeneticroleincarcinomaofbreast.Stromal markercouldbeusedforassessingtheprognosisofbreastcancer.
Methods:30invasiveductalcarcinomaofbreastNOStypewereselected.He matoxylinandeosinstainingwasdone.Immunohistochemistrywasdonewit hCD10,andHER2.CD10expressioninstromawasstudiedandstatisticallya nalyzedwithHER2.
Results:strongpositivityforstromalCD10wasobservedin46%(14outof30)ofcases.10outof14(71%)CD10positivecasesshowedHER2/neu positivity.CD10expressionwassignificantlyassociatedHER2/neupositivi ty.
Conclusions: StromalCD10expressionisdirectly correlatedwithHER2receptorpositivity.CD10couldbeusedasnew prognosticmarkerincarcinomaofbreast.

Introduction:-

Worldwide among non- skincancerbreastcarcinomaisthemostcommon carcinoma inwomen.[1]Mortalityrateforbreastcarcinomain India is11.1per 10,000.[2]Chemicalmediatorsbetweentumorcellsandstromalcells impact the growth ofcancerbreast.[3] CD10isa myoepithelialmarker.[4]High gradeinvasiveductalcarcinomaofbreastisassociatedwithlossofCD10 expressioninmyoepithelialcellsandexpressionofCD10instroma.[3]Genetic changesinstroma promote cancer growth.[5]Onlyfewstudieshighlightimportanceofthestomalexpressionof CD10ingrowth andprognosisofbreastcancer.

AsastemcellregulatorinthebreastCD10inhibitsuncontrolledproliferationofstemcells.[6]Apartfrom breastmyoepithelialcellsCD10also expressedinlymphoidstemcells,neutrophils,andotherepithelialcells.[7]CD10also expressedinstromaofprostate, and lung.Instomachcancer,CD10positivestromalcellsarecorrelatedwithvascularinvasionandmetastasis.[8]Chemotherapeuti cdrugs which targettheepithelialcellswhilestromalcellsaresparedwhichmayresultinrecurrence.

Thisstudyaimstoanalyzethecorrelationofstromalexpressionof CD10inbreastcarcinomaNOS type with HER2/neu

AimandObjective:-

Toanalyzethe correlationofstromalexpressionofCD10 inbreast cancerwithHER2/neu

Corresponding Author:- S. Ulaganathan
Address:- Assistant Professor,DepartmentofPathology,Government Mohankumaramangalam Medical College,Salem,/TamilNaduDr.MGRMedicalUniversity,Chennai,India.

Methods:-

Studydesign
Prospective study

Studypopulation
Specimen with invasive ductal carcinoma of breast

Sample size
30patientswith invasive ductal carcinomaofbreast diagnosedbyhistopathological study

Inclusion criteria
1. Agefrom18 to75 years.
2. PatientswithInvasiveductalcarcinomaofbreastnototherwisespecified(NOS)type,stageI,IIandIIIdiagnosed byhistomorphologicalstudies.

Exclusioncriteria
1. BreastcarcinomaotherthaninvasiveductalbreastcarcinomaNOStype.
2. PatientswithStageItumorwhoreceivedneoadjuvantchemotherapy.
3. PatientswithStageIVtumorwhoreceivedchemotherapyandradiotherapy.
4. Malepatients
5. Illfixedspecimen

Data Collection
Breast carcinoma patient were investigated with complete blood count, blood urea,bloodsugar,Xraychest,ECG,andEchocardiogramforsurgicalfitness.Thepatientsunderwent modified radical mastectomy procedure after obtaining informed consent.Specimenswere fixedin10%neutral bufferedformalin.

Histopathologicalexamination
30 breast carcinoma specimens were fixed in 10% neutral buffered formalin for twenty four hours.Specimensweregrossedandbitsfrom representative areasweresampled.HematoxylinandEosin stained microscopic slides of the primary tumors were reviewed to confirm the diagnosis, to definetumorsubtype .

Immunohistochemistry(IHC)forCD10
Four micron sections were cut. Sections were deparaffinized in xylene followed by hydration indescending grades of ethanol. Antigen retrieval was performed by heating sections at 95°c 4 cycles of 5 min eachfor CD10 in Tris–EDTA buffer (pH 9.0), for HER2/neu in citrate buffer(Ph 6.0). Sections wereincubated with power block for 10 min, followed by incubation with primary antibodies for one hour.Mousemonoclonal antibody against human CD10 was used. After two washes with trisphosphate buffer solution secondary antibody was added for 30 min. After two washes with trisphosphate buffer solution, 3, 3'-diaminobenzidine substrate (DABtetra hydrochloride) was applied to the sections for 10 min and sections were counterstained with EhrlichHematoxylin,dehydratedwithethanoland xylene andmountedwithDPX.

Qualitycontrol
As part of quality control positive control slide from fibro adenoma were used forCD10.

Evaluationofstaining
CD10 scoring was done as per the following table (TABLE 1). [9] Pattern of staining for CD10 iscytoplasmic and membranous positivity in stromal cells. Both negative and weak expressionswereconsideredas negative. Only strong CD10 expression was considered as positive for statistical purpose (Figure 1&2). HER2/neu scoring was done as perTABLE2.

Table1:- CD10 scoring.

SCORE	RESULT	CD10STAINING
0	Negative	<10%stromalpositivecells(cytoplasmicandmembrane positivity)

1	Weak	10%-30%stromalpositivecells
2	Strong	>30%stromalpositivecells

Table2:- HER2-neuscoring.

STAININGPATTERN	SCORE	HER2NEU OVEREXPRESSION
Nostainingormembranestaining<10%tumorcells	0	Negative
Faint/perceptible membrane stainingin>10%cells	1+	Negative
Weaktomoderatecomplete membranestainingin>10%cells	2+	Weak
Strongcompletemembranestainingin>30%cells	3+	Strong

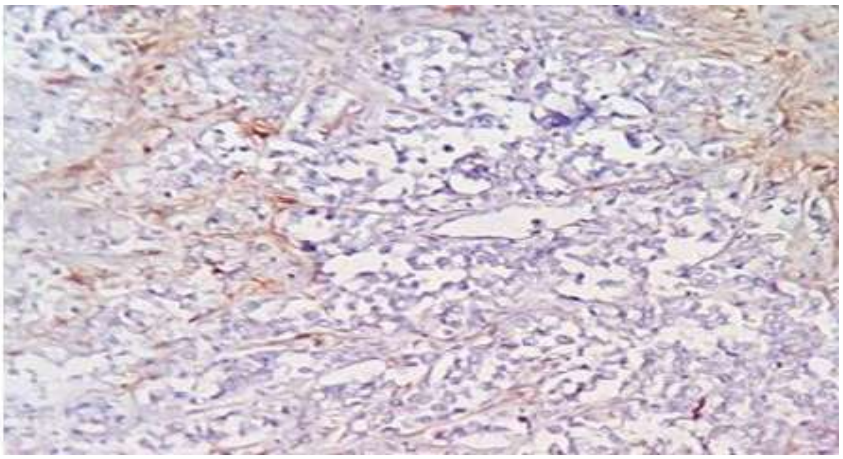

Figure1:-StromalCD10positivityinIDCBreast1+(10%-30%stromalpositivecells)(10x).

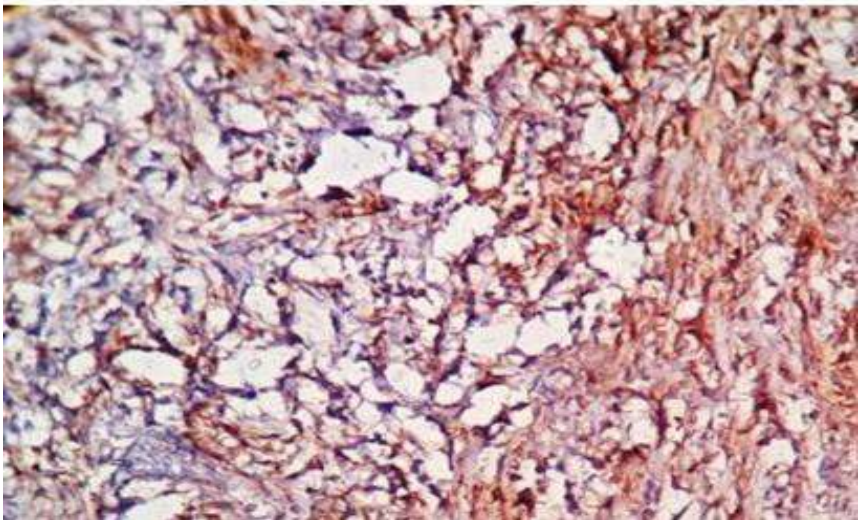

Figure2:-Stromal CD10positivityinIDCBreast2+(>30%stromalpositivecells)(10x).

Statisticalanalysis:

The collected data was analyzed. Statistical correlations between stromal expression ofCD10 and HER2/neu was performed as per Chi square test. P values of less than 0.05 wereconsideredassignificant.

Humanparticipantprotection

Study was undertaken after obtaining institutional ethical committee clearance. The procedures werecarriedoutwithinformedconsentfromthe patients

Results:-

Mostofinvasiveductalcarcinomaofbreastcases in this studybelongto41-50age group(36.7%).73% (22 out of 30) of the cases showed positivity for CD10 in the stroma, of which 46 %(14) caseswerestronglypositiveand27 %(8)wereweaklypositive(TABLE 3),(Figure 1&2).71% (10/14) of the stromal CD10 positive Invasive ductalcarcinomaof breast showedHER2/neupositivity.Theassociation is statistically significant,pvalueis lessthan0.05(pvalue 0.0009,Chi-square test)(TABLE 4).

Table3:- StromalexpressionofCD1Oinbreastcarcinoma.

STROMALCD10EXPRESSION	NEGATIVE	WEAKPOSITIVE	STRONGPOSITIVE	TOTAL
Breastcarcinoma	8(27%)	8(27%)	14(46%)	30

Table4:- CorrelationOfStromalCD10ExpressionWith HER2/neu.

CD10				
HER2/neu	**NEGATIVE**	**WEAKPOSITIVE**	**STRONGPOSITIVE**	**TOTAL**
NEGATIVE	8	7	4	19
POSITIVE	0	1	10	11
TOTAL	8	8	14	30

Discussion:-

Stromal cells play a critical role in breast cancer. Tissue microenvironment has akeyroleincontrollingcellsurvival, proliferation,migration, anddifferentiation.[10],[11]

CD10 is a stem cell regulator in the breastand controls proliferation of stem cells. [6] In the normal breast tissuefew of stromal cells onlyexpress CD10.[12],[13]In gastriccarcinoma,CD10expression in stromalcells is associatedwith vascularinvasionandmetastasis.[8]Innasopharyngealcarcinoma,CD10instromacorrelateswithtumorprogression.[14]

The interaction between epithelial cells and stromal cells is influenced by factors secreted by the tumor cells or by stromal cells. [10],[15],[16]The matrix metalloproteinase (MMP) is one ofthemolecularfactor.MMPhas a crucialroleintumorprogression,tumorinvasionandmetastasis.
[17]HigherMMPactivitiescorrelatewithbadprognosisandpromotestumourigenesis,angiogenesis,invasionandmetastasis.
[18]

CD10 is a MMP which controls proliferation of stem cells by cleaving signaling proteins. [19]Loss of CD10 in cancer breast myoepithelial cell leads to proliferation of malignant cells and invasion of insitu cancer. Stromal expression of CD10 in invasive cancer might prevent differentiaon of cancer cells and helpsin maintaining the cancer stem cells. [19] Enhanced expression of CD10 in stroma seen in high gradebreastcarcinomas.[8]

In the present study 73% (22 out of 30) of the cases showed positivity for CD10 in the stroma, of which46%(14) cases were strongly positive and 27%(8) were weakly positive. Only two cases of strong positivity forCD10 were noted in the adjacent normal breast parenchyma. Stromal expression of CD10 had a statisticallysignificantassociationwithbreastcancerthaninparenchymal tissue,p value is0.002.

In a study done by Makretsov et al 79 %(205 out of 258) of invasive ductal carcinoma of breastshowedexpression of CD10 in stroma.[3]Thomas S et al study shows stromal CD10 positivityin 55% (16outof29)ofcases.[20]

In the present study we attained direct correlation between stromal CD10 expression and HER2/neuover expression. 71% (10/14 cases) of stromal CD10 positive invasive ductal carcinoma of breast cases expressedHER2/neu. This correlation is statistically significant with the p value less than 0.05(p value 0.0009).Jana SH et al study also exhibits correlation between stromal CD10 expression and HER2/neu over expression.[6]Purietalstudyshowsstatistically significantcorrelationbetweenstromalCD10expressionandHER2/neuover expression.[21]Makretsovetaldoesnotfindstatisticallysignificantcorrelationbetweenstromal CD10expressionandHER2/neuover expression.[3]

CD10 could be a therapeutic target for treating carcinoma breast since it cleavesdoxorubicinandresults in resistancetochemotherapeuticagent.Experimental studies reveal CPI0004Na, a CD10 cleavablepeptideprodrug of doxorubicin, enhances antitumor efficacy[22]

Conclusion:-

To conclude, expression of CD10 in stroma of invasive ductal carcinoma of breast is directly correlatedwith HER2/neu over expression and higher tumour grade. Thus investigating stromal CD10 expression in all invasive ductal carcinoma of breast especially in triple negativepatients might assist in choosing optimal treatment option. Increased level of stromal CD10 activity leads toinhibition of epithelial cell differentiation. Thus cancer stem cells are maintained and may result in recurrence ofmalignancy. Since CD10 cleaves the drug doxorubicin thereby causes chemo resistance. Thus inhibiting theactivity of CD10 may have an increased response to chemotherapeutic agents and decreases the recurrence.ExperimentalstudiesshowCPI0004Naimprovesantitumor efficacy.

Further researches are neededto identify the source of stromal CD10 expression, its role in epithelial tomesenchymal transition, its role in tumerogenesis of breast cancer, effect of chemotherapeutic agents on CD10,todevelopnewermoleculestargetingCD10andtocorrelatewithchemotherapeuticresponseand prognosis.

References:-

[1].RobinsandCotranPathologicBasisofDisease.9ed.volumeII.Elsevier;2015:1051
[2].Surakasula A, Nagarjunapu GC, Raghavaiah KV.A comparative study of pre- and post-menopausalbreast cancer: Risk factors,presentation,characteristics and management.JResPharm Pract2014;3:12-8.
[3].Nikita A Makretsov, Malcom Hayes, Beverly A Carter, ShahriarDabiri, C Blake Gilks and David G Huntsman Stromal CD10expression in invasive breast carcinoma correlates with poor prognosis, estrogen receptor negativity, and high grade, ModernPathology(2007)20,84-89.
[4]. A NKalof, D Tam, B Beatty, K CooperImmunostaining patterns of myoepithelial cells in breast lesions: a comparison of CD10and smoothmusclemyosinheavychainJ ClinPathol2004;57:625–629.
[5].CunhaGRetal:Roleofstromalmicroenvironmentincarcinogenesis.IntJCancer107:1,2003.
[6]JanaSH,JhaBM,PatelC,JanaD,AgarwalA.CD10Anewprognosticstromalmarkerinbreastcarcinoma,itsutility,limitations androleinbreastcancerpathogenesis.IndianJ PatholMicrobiol2014;57:530-6.
[7].MohammadizadehF,SalavatiM,AfsharMoghaddamN.CD10expressioninstromalcomponentofinvasivebreastcarcinoma:ApotentialprognosticdeterminantJResMedSci2012;17(Spec2):S194-9.
[8].HuangWB,ZhouXJ,ChenJY,ZhangLH,MengK,MaHH,etal.CD10positivestromalcellsingastriccarcinoma:correlationwith invasionandmetastasis.JpnJClinOncol2005;35(5):245-50.
[9]. VandanaPuri,Manjulajain,andShajiThomasIntJouofBreastCancer,2011,atricleID437957.
[10].MottJD,WerbZ.Regulationofmatrixbiologybymatrixmetalloproteinases.CurrOpinCellBiol2004;16:558-64.
[11].FidlerIJ.Thepathogenesisofcancermetastasis:The'seedandsoil'hypothesisrevisited.NatRevCancer2003;3:453-8.
[12].IwayaK,OgawaH,IzumiM,KurodaM,MukaiK.StromalexpressionofCD10ininvasivebreastcarcinoma;anewpredictorofclinicaloutcome.Virchows Arch2002;440:589-93.
[13]. DewarR, Fadare O, Gilmore H,GownAM. Best practices in diagnostic immunohistochemistry: myoepithelialmarkersinbreastpathology. ArchPatholLabMed2011;135(4):422-9.
[14].BrahamH,TrimecheM,ZiadiS,MestiriS,MokniM,AmaraK,etal.CD10expressionbyfusiformstromalcellsinnasopharyngealcarcinomacorrelates with tumorprogression. VirchowsArch2006;449(2):220-4.
[15].BremnesRM,DønnemT,AlSaadS,AlShibliK,AndersenS,SireraR,etal.Theroleoftumorstromaincancerprogressionandprognosis:Emphasisoncarcinoma-associatedfibroblastsandnon-smallcelllungcancer. JThoracOncol2011;6:209-17.
[16]. DeWeverO,MareelM.Roleoftissuestromaincancercellinvasion.JPathol2003;200:429-47.
[17].CurranCS,KeelyPJ.BreasttumorandstromalcellresponsestoTGFβandhypoxiainmatrixdeposition.MatrixBiol2013;32:95-105.
[18]. JingaDC,BlidaruA,CondreaI,ArdeleanuC,DragomirC,SzegliG,etal.MMP-9andMMP-2gelatinasesandTIMP-1andTIMP-2 inhibitorsinbreastcancer:CorrelationswithprognosticfactorsJCellMolMed 2006;10:499-510.
[19].BachelardCascalesE,ChapellierM,DelayE,PochonG,VoeltzelT,PuisieuxA,etal.TheCD10enzymeisakeyplayertoidentifyandregulatehumanmammarystemcells.Stem Cells2010;28:1081-8.

[20].ThomasS,BabuRJ,AgarwalK,PuriV,JainM,etal.EffectofneoadjuvantchemotherapyonstromalCD10antigensinbreastcancer-Apreliminarystudy.IndianJCancer2013;50:46-51.
[21]. VandanaPuri,Manjulajain,andShajiThomasIntJouofBreastCancer,2011,atricleID437957.
[22].TanDS,MarchioC,ReisFilhoJS.Hereditarybreastcancer:frommolecularpathologytotailoredtherapies.JClinPathol2008,61:1073-1082.