The Gulf Journal of Oncology

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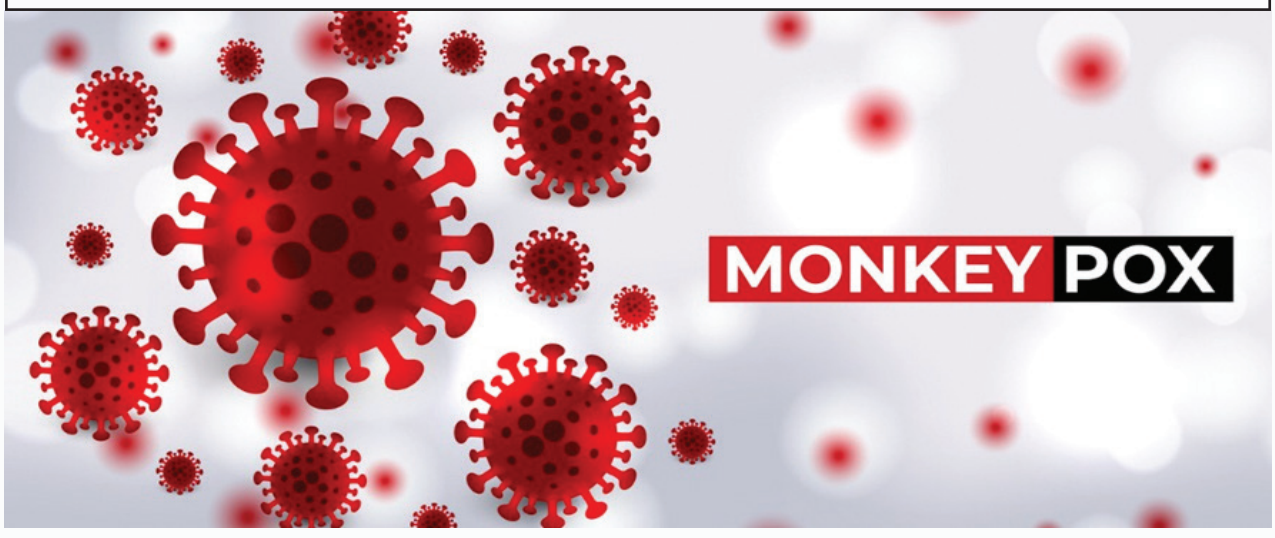
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Original Article

Immunohistochemical Expression of Calretinin in Invasive Breast Carcinoma and its Correlation with Clinicopathological Parameters

Gargi Madhukar Patil, Siddhi Gaurish Sinai Khandeparkar, Shital Subhash Gosavi, Chaitnya D. Khillare, Bageshri P. Gogate, Avinash R. Joshi, Ketki Ghanekar, Asmita S. Pawar

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Abstract

Introduction: Breast cancer (BC) is the most common cancer and foremost cause of death in women.

Aim: This study was conducted to study the calretinin expression in BC and its correlation with other clinicopathological parameters such as tumor size, histological grade, lymph node status, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2/neu), Ki67 status and molecular subtypes in Indian setting.

Materials and methods: Fifty cases of BC diagnosed between 2017 and 2019 were included in the study. A technique of manual tissue microarray was employed for the analysis of expression of IHC markers such as calretinin, ER, PR, Her2/neu, Ki67, CK5/6 and EGFR in all cases. Results were subjected to statistical analysis.

Results: Calretinin positivity was seen in 66% (33/50) cases of BC of which 45.45% (19/33) were triple negative BC (TNBC) and 21.21% (7/33) were of basal like BC (BLBC) molecular subtype. Calretinin expression was significantly associated with higher grade and negative ER and PR expression. Maximum cases expressing calretinin showed lymphovascular invasion (LVI), positive lymph node status, higher stage, Ki67 and HER2/neu positivity.

38% cases were TNBC. Calretinin was found positive in 78.95% of TNBC cases. Calretinin expression was seen in TNBC cases of higher grade and stage with positive lymph node status, presence of LVI and Ki67 positivity.14% cases were BLBC. Calretinin was found positive in 77.78% of BLBC cases. Calretinin expression was seen in BLBC cases of higher grade and stage with positive lymph node status, Ki67 positivity and presence of LVI.

Conclusion: Calretinin can be potentially used as a prognostic marker and could be included in routine IHC workup of BC cases which could aid in development of tailored therapy.

Keywords: Calretinin, breast carcinoma, prognosis

Introduction

Breast cancer (BC) is the most common cancer and foremost cause of death in women. It is a heterogeneous disease encompassing several pathological and molecular subtypes characterized by different outcomes and responses to a given treatment.[1] Tumor size, grade, axillary lymph node metastasis, mitotic rate, hormone receptor status and human epidermal growth factor receptor 2 (HER2/neu) status have traditionally been regarded as prognostic markers in patients with BC.[2] A gene expression analysis has classified BC into subgroups (luminal A, luminal B, HER2/neu rich, and triple negative profile).[3] The recent increased knowledge in molecular mechanisms of this cancer and consequent targeted treatments have attempted to improve its outcome.[1]

Calretinin is a 29–kD, intracellular, vitamin D–dependent calcium binding protein belonging to calmodulin superfamily that has multiple functional roles such as intracellular calcium buffering and message targeting.[4] It is a known mesothelial marker which is expressed in both epithelial and mesenchymal malignancies including BC.[5]

Till date there are hardly any studies in Indian literature that have documented calretinin expression in BC cases and their association with other well established

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prognostic factors. The present study was conducted to evaluate the calretinin expression in BC cases and its correlation with other clinicopathological parameters in the Indian scenario.

Materials And Methods

This cross–sectional study was conducted in the Department of Pathology in a tertiary care hospital. Ethical clearance was obtained from Institute's Ethical Committee. Fifty cases of BC cases operated upon and diagnosed from 2017 to 2019 were included in the study. The available data for all the patients as regards with age, location of tumor, grade, stage and lymph node status was collected from the records of histopathology section of the Department of Pathology.

All the slides were evaluated by two senior histopathologists. The Modified Bloom–Richardson (MBR) system of cancer grading system was used in this study. TNM classification and staging of the cases was done as per American Joint Committee on Cancer (AJCC) guidelines.[6] The most suitable tissue block of BC cases was selected for immunohistochemical (IHC) evaluation. A technique of manual tissue microarray was employed for the study of Calretinin, estrogen receptor (ER), progesterone receptor (PR), HER2/neu, Ki67, cytokeratin (CK)5/6 and epidermal growth factor receptor (EGFR) in all cases with one tissue core taken from each selected BC block.[7] Antigen retrieval was done using Citrate Buffer Antigen Retrieval Protocol. Pressure cooker was used as heating source.

The primary antibodies used were Calretinin (Clone Calret 1, Dako)[8], ER (Clone 6F 11, Novacastra), PR (Clone PGR312, Novacastra), HER2/neu (Clone CB11, Novacastra), Ki67 (Clone MM1, Novacastra), EGFR (Clone 6F 11, Novacastra) and CK5/6 (Clone D5/16 B4, Dako). Negative control (without adding primary antibody) was included in all batches.

Section from normal breast was used as positive control for Calretinin and CK5/6 expression.[9] Section from endometrial tissue was used as positive control for ER and PR.[10] Section from BC, which previously showed unequivocal strong immunoreactivity for HER2/neu, was used as positive control for HER2/neu.[7] Section from skin was used as positive control for Ki67 and EGFR.[1,8] Sections were examined under High Power Field (HPF) to observe the immunoreactivity.

For calretinin, both nuclear and/or cytoplasmic staining was required to be considered positive staining. The degree of immunoreactivity was assessed based on a combined score of the extent and intensity of staining. Scores 0–3 were assigned according to the percentage of positive tumor cells (0=0%; 1=<25%; 2=25–50%; 3=>51%) and the intensity of staining in tumor (no staining = 0; mild staining = 1; moderate = 2; marked = 3) as previously described. The two scores were multiplied to give an overall score of 0–9, of which 0 was considered negative and 1– 9 as positive.[8]

Allred score was used to evaluate the ER and PR, and a score of 3 to 8 was considered positive. Immunoreactivity for ER and PR was assessed by estimating the percentage of tumor cells showing nuclear staining. More than 10% of the tumor cells showing immunoreactivity was considered as positive.[9] HER2/neu staining was scored according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. Moderate to strong complete membrane staining of 10% or more of the tumor cells was considered to be positive (2+ and 3+) [10] Ki67 labeling index (KiLI) of equal to or more than 14% was considered to be positive.[3] EGFR stain was considered positive if any (weak or strong) membranous expression in tumor cell was observed. CK5/6 stain was scored positive if any (weak or strong) cytoplasmic and/or membranous staining was detected in the tumor cells. EGFR and CK5/6 were only used for classification of BC into molecular subtypes.[8]

The Primer of Biostatistics 7.0 program was used to calculate the association between the analyzed Calretinin expression and clinicopathological variables by Pearson's Chi–square test or Fisher's exact test whenever appropriate. Quantitative data was presented as mean ±SD. Qualitative data was presented as frequency and percentage. The results were considered to be statistically significant when the p value was ≤ 0.05 and highly statistically significant when p value was ≤ 0.01.

Results

The various clinicopathological features of BC are presented in Table 1. The age of patients ranged from 33 to 79 years, with a mean value of 53.38 years. The highest number of cases (19/50, 38%) was seen in the age group of 41–50 years.

Calretinin expression in BC and its correlation with various clinicopathological parameters is shown in Table 2 (Figure 1). Calretinin positivity was seen in 33/50 (66%) cases of invasive BC. Calretinin expression was statistically significantly associated with higher grade (Grade III;26/50,52%) ($\chi2=14.286$, $p<0.01$) and absent ER and PR expression ($\chi2=5.353$, $p<0.05$). Maximum cases showing HER2/neu expression expressed calretinin (15/21,71.43%) Maximum cases showing calretinin expression showed Ki67 immunopositivity (30/50,60%), positive lymph node status (24/50, 48%), presence of lymphovascular invasion (LVI) (21/50,42%) and were of

Clinicopathological characteristics	Number of tumours 50 BC cases (%)	Number of tumours 19 TNBC cases (%)
Laterality		
Right	17(34)	07(36.8)
Left	33(66)	12(63.2)
Menopausal status (48)		
Premenopausal	11(22)	05(26.3)
Post–menopausal*	39(78)	14(73.7)
Histopathological types		
IDC (NST)	35(70)	09(47.4)
Medullary	8(16)	08(42.1)
Metaplastic	2(4)	02(10.5)
IDC + Mucinous	2(4)	–
IDC + Lobular (Mixed)	1(2)	
Mucinous carcinoma	1(2)	–
Invasive Cribriform	1(2)	–
Status of lymphovascular invasion		
Present	30(60)	11(57.9)
Absent	20(40)	8(42.1)
Tumour Size (pT)		
pT1	7(14)	01(05.3)
pT2	27(54)	11(57.9)
pT3	13(26)	7(36.8)
pT4	3(6)	–
ALN metastasis		
N0	15(30)	06(31.6)
N1	18(36)	06(31.6)
N2	11(22)	05(26.3)
N3	6(12)	02(10.5)
MBR Grade		
Grade I	06(12)	0(0)
Grade II	14(28)	1(2)
Grade III	30(60)	18(36)
Stage		
I	3(6)	0(0)
II	20(40)	9(18)
III	27(54)	10(20)
IHC markers		
Calretinin	33(66)	–
ER	10(20)	–
PR	10(20)	–
HER2/neu	21(42)	–
Ki67	46(92)	–
Molecular subtype		
Luminal A	3(6)	–
Luminal B	7(14)	–
Her2 Positive	21(42)	–
TNBC	19 (38)	–
BLBC	9(18)	–
NCBC	10(20)	–

Table 1: Clinicopathological characteristics of Breast carcinoma cases
BC=breast carcinoma, TNBC=triple negative breast carcinoma, IDC–NOS=infiltrating duct carcinoma, not otherwise specified, NEC=neuroendocrine carcinoma, MBR=modified Bloom Richardson grading, IHC=immunohistochemistry, BLBC=basal like subtype, NCBC=non–classified subtype.
*2 cases are males

higher stage (Stage III;19/50,38%). This was however statistically insignificant.

The commonest molecular subtype included in this study was HER2/neu positive (21/50, 42%), followed by triple negative BC (TNBC) (19/50, 38%), luminal B (7/50, 14%) and luminal A (3/50, 6%). TNBC cases included 9/50 (18%) cases of basal like BC (BLBC) and 10/50 (20%) cases of non–classifiable (NCBC) subtype.

Calretinin was found positive in 15/19(78.95%) of TNBC cases. Calretinin expression was seen in TNBC cases of higher grade (Grade III, 14/19,73.68%) and higher stage (Stage III, 8/19,42.10%) with positive lymph node status (11/19,57.89%), presence of LVI (9/19,47.37%) and Ki67 positivity (13/19, 68.42%). This was however statistically insignificant.

Calretinin was found positive in 7/9(77.78%) BLBC cases. Calretinin expression was seen in BLBC cases of higher grade (Grade III, 7/9,77.78%) and higher stage (Stage III, 4/9,42.10%) with positive lymph node status (5/9,55.55%) and positive Ki67 immunoreactivity (6/9, 66.67%). Maximum cases of BLBC showing LVI were calretinin positive. (3/4, 75%) This was however statistically insignificant.

Variables		Calretinin		Chi–square Value	p–value
		Positive (n=33, 66%)	Negative (n=17, 34%)		
Age (Yrs)	≤50 (26)	19 (38)	7 (14)	0.641	0.423
	>50 (24)	14 (28)	10 (20)		
Side	Right (17)	12 (24)	5 (10)	0.031	0.860
	Left (33)	21 (42)	12 (24)		
Menopause status	Pre–menopausal (11)	7 (14)	4 (8)	0.030	0.863
	Post–menopausal (39)	26 (54)	13 (26)		
Tumor size (cm)	T1 (≤2) (7)	4 (8)	3 (6)	2.439	0.118
	T2 (>2 to ≤5) (27)	16 (32)	11 (22)		
	T3 (>5) (13)	10 (20)	3 (6)		
	T4 (3)	3 (6)	0		
Lymph node status	Positive (36)	24 (48)	12 (24)	0.030	0.863
	Negative (14)	9 (18)	5 (10)		
Lympho Vascular Invasion	Present (30)	21 (42)	9 (18)	0.182	0.670
	Absent (20)	12 (24)	8 (16)		
Grade	I (6)	2 (4)	4 (8)	14.286	<0.01
	II (14)	5 (10)	9 (18)		
	III (30)	26 (52)	4 (8)		
Stage	I (3)	2 (4)	1 (2)	0.551	0.759
	II (20)	12 (24)	8 (16)		
	III (27)	19 (38)	8 (16)		
Estrogen receptor	Positive (10)	3 (6)	7 (14)	5.353	0.021
	Negative (40)	30 (60)	10 (20)		
Progesterone receptor	Positive (10)	3 (6)	7 (14)	5.353	0.021
	Negative (40)	30 (60)	10 (20)		
HER2/neu	Positive (21)	15 (30)	6 (12)	0.150	0.699
	Negative (29)	18 (36)	11 (22)		
Ki67	Positive (46)	30 (60)	16 (32)	0.024	0.878
	Negative (4)	3 (6)	1 (2)		
Molecular subtypes	Luminal A (3)	1 (2)	2 (4)	7.502	0.112
	Luminal B (7)	2 (4)	5 (10)		
	Her2 positive (21)	15 (30)	6 (12)		
	TNBC				
	BLBC (9)	7 (14)	2 (4)		
	NCBC (10)	8 (16)	2 (4)		

Table 2: Calretinin expression and clinico–pathological parameters of breast carcinoma cases
TNBC= triple negative breast carcinoma cases, BLBC=basal like subtype, NCBC=non–classified subtype.

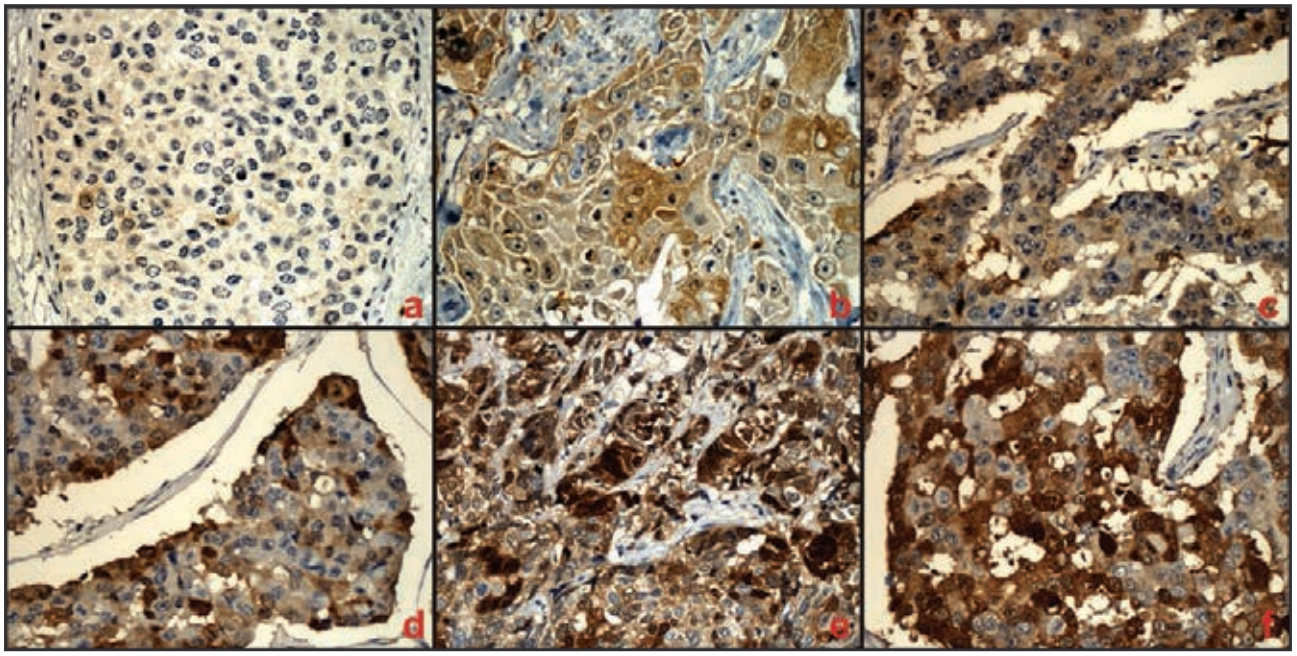


Figure 1: a,b) Photomicrograph showing Cyclin D1 staining score = 1x1=1 (IHC,400X)
c,d) Cyclin D1 staining score of 2x2=4 (IHC,400X)
e,f) Photomicrograph showing Cyclin D1 staining score = 9 (IHC,400X)

Discussion

Calretinin was first identified in the central nervous system. Later, it was recognized in a wide variety of non–neural cells, both neoplastic and non–neoplastic. In the oncologic field calretinin is most commonly used as part of a panel to differentiate between pleural mesothelioma and pulmonary adenocarcinoma.[5] While in most cases highly sensitive and specific for mesothelial origin, calretinin positivity has been reported in carcinomas arising in a myriad of other tissues including ovary, testis, adrenal cortex, colon, breast, sino–nasal tract, thymus, skin and even soft tissue.[8,11,12] To date only a few studies have documented calretinin expression in BC and their association with other well established prognostic factors.

In this study calretinin expression was seen in 66% (33/50) of cases which is higher limit of the range (53% to 68%) documented in literature. Here we considered calretinin positivity when tumor cells expressed nuclear positivity with or without cytoplasmic expression with scores other than zero. [8] Calretinin expression was statistically significantly associated with absent ER and PR expression in this study. This finding supported the observation that high calretinin expressing tumors were more frequently hormone receptor negative as documented in studies in the literature.[4,5,8] Maximum HER2/neu expressing tumors in this study exhibited calretinin positivity (15/21,71.43%) though statistically insignificant. This was in line with previous studies where statistically significant positive correlation was observed between calretinin expression and HER2/neu expression. [4,5,8]

A recent study has observed that Ki67 values above 10%–14% define a high–risk group in BC patients making these patients successful candidates for neoadjuvant therapy. Considering 14% cut off, maximum cases showing calretinin expression exhibited statistically insignificant Ki67 immunopositivity in this study. A study by Farrag et al demonstrated statistically significant association between higher calretinin expression and higher Ki67 indices. [8]

Calretinin expression was statistically significantly associated with higher grade (Grade III;26/50,52%) in this study as reported by studies in literature. LVI provides a strong predictor of outcome in patients with invasive BC. In this study, maximum BC cases showing LVI expressed statistically insignificant calretinin expression in contrast to study done by Farrag et al where no association was found between LVI and calretinin expression.[8] Maximum cases expressing calretinin belonged to BC cases with positive lymph node status though statistically insignificant. No significant association was found between high level of calretinin expression and lymph node status in a study by Taliano et al. [4] Maximum cases expressing calretinin belonged to higher stage (StageII+Stage III=31/50;62%) as documented in literature however not statistically significant.[8]

Molecular classification in this study showed maximum of HER 2neu positive cases (21/50; 42%) followed by Triple negative BC (19/50, 38%) which includes 9 cases of BLBC and 10 cases of NCBC. Luminal B and luminal A constituted 7 (14%) and 3 (6%) cases respectively. Most studies in Indian literature document fewer Her2/neu positive cases as against our study. Our hospital is a charitable one and caters to the rural population. Due to low socioeconomic status of these patients, BC cases are usually diagnosed in advanced stages. Our patients had tumors with high stage and grade, accounting for the higher percentage of HER2/neu positive and triple negative BC. Also including unequivocal cases (+2) as positive in our study could be the reason for the high percentage.[13]

Different molecular subtypes of BC show varied calretinin expression. 80% (10/20) of NCBC, 77.78% (7/9) of BLBC and 71.43% (15/21) of Her2 positive cases expressed calretinin in this study followed by 50% (1/2) of luminal A and 28.57% (2/7) of luminal B cases. Most studies document high calretinin expression in BLBC when compared with other molecular subtypes.[4,8]

Calretinin expression was seen in 68.57% (24/35) of invasive BC no special type (IBC NST), 87.50% of metaplastic (7 cases) and both medullary (100%, 2 cases) cases. Mucinous (1 case) carcinoma, IBC NST + lobular (1 case) and invasive cribriform carcinoma (1 case) were negative for calretinin expression. This can be explained by the fact that medullary and metaplastic carcinoma subtypes are frequently triple negative and express frequently basal like phenotype.[14,15] In this study both medullary carcinomas expressed basal like phenotype. Only one case of metaplastic carcinoma expressed basal like phenotype and the rest cases were unclassifiable. In contrast, mucinous, invasive lobular and cribriform carcinoma subtypes are usually low grade and express hormone receptors more frequently and only very rarely express basal markers. [8,12]

The authors foresee these findings to introduce calretinin as having a fascinating potential as a new therapeutic target for BC in Indian setting. However, more data generated by molecular studies needs to be documented to elucidate the matter further.

Conclusion

In BC cases, calretinin expression was significantly associated with higher tumor grade, absence of ER and PR expression and statistically insignificantly associated with LVI, positive lymph node status, higher stage, Ki67 positivity and HER2/neu positivity. In TNBC and BLBC cases, calretinin expression was statistically insignificantly associated with higher tumor grade and stage, positive lymph node status, presence of lymphovascular invasion and Ki67 positivity. Thus, increased calretinin expression was associated with mostly well–established poor prognostic factors. Thus, calretinin can be used as a prognostic marker and should be included in routine IHC workup of BC cases as it could aid in development of appropriate targeted therapy.

Limitations:

TMA technique was used for calretinin, ER, PR, Her2 and Ki67. Whole sections were not used for their IHC evaluation. However, utmost care was taken to sample the most representative area from the original whole section blocks for TMA. HER2/neu was assessed only by IHC. Evaluation by FISH was not available, especially for the equivocal cases with HER2 expression 2+. Follow–up time for the patients was limited.

Funding and Conflict of Interest:

We have not received any funding. I hereby declare that there is no conflict of interest.

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