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Expression of CD44 in Triple Negative Breast Cancer and its Correlation with Prognostic Parameters

Pallavi Punhani[a], Charanjeet Ahluwalia[a], Meetu Agrawal[*a], Preeti Kandwal[a]

[a]*Department of Pathology, VMMC and Safdarjung Hospital, New Delhi, India*

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ABSTRACT

Background: The study aims to evaluate CD44 expression as a cancer stem cell marker in Triple-negative breast cancer (TNBC) and its correlation with prognostic parameters. Evaluation of CD44 immunoexpression in TNBC is vital for understanding tumor aggressiveness and determining its prognostic value.

Methods: In this hospital-based cross-sectional study of 50 cases of primary triple negative breast cancer patients, the tissue sections were subjected to immunohistochemical examination using CD44 antigen marker. The proportion and intensity of CD44 immunostaining were assessed and correlation with prognostic markers such as histological grade, tumor size and nodal status was examined.

Results: CD44 expression was observed in 40% of the total cases with a statistically significant association with histological grade (P= 0.002). Higher CD44 expression was noticed with increasing tumour grade. However, no statistical significance was observed with respect to tumor size and nodal status.

Conclusion: The study suggests that CD44 immunoexpression may serve as a surrogate marker of BCSCs and may hold prognostic value in TNBC patients. However, further studies on larger samples are required to fully understand its role.

INTRODUCTION

Breast cancer became the leading cause of global cancer in 2022, accounting for 23.8% of all cancer cases in women.[1] GLOBOCON statistics reveal an incidence rate of 192020 and a mortality rate of 98337 in India alone.[2] It is a highly heterogeneous disease with distinct biological and clinical behavior and can be classified into subtypes based on histopathology type and molecular profile. Among various breast cancer subtypes, the prevalence of Triple-negative breast cancer (TNBC) has significantly increased from 10% to 43% particularly in India, according to various literature reports, which is much higher as compared to the Western world.[3]

Treatment of TNBC is challenging due to the absence of targeted therapies, necessitating research for new treatment modalities. Newer agents include polymerase inhibitors targeting BRCA mutation carriers and recently, immunotherapy. However, majority of patients have a grim prognosis and still undergo primary ablative surgical procedures.[4]

The 21st century has seen increased research on molecular genetics, epigenetics, and metabolic factors of cancer progression and treatment. In recent decades, evaluation of cancer stem cells has gained attention. Therapeutic approaches only work if all cancer cells are eliminated during anti-tumor therapy.[5] However, cancer stem cells (CSCs) can self-renew and survive even after cytotoxic treatment resulting in metastasis, drug resistance and tumor recurrence. Accumulating evidence has shown the presence of a subpopulation of stem cells in breast cancer patients, particularly those belonging to the TNBC subtype. The presence of breast cancer stem cells (BCSC) is believed to increase aggressiveness and resistance to standard treatments.[6] Several stem cell markers including CD44, CD24, CD133, ALDH1, and ABCG2 have been described in the

***Address for correspondence:**
Dr. Meetu Agrawal, MD,
Department of Pathology, VMMC and Safdarjung Hospital, New Delhi, India
Email: magrawal.sjh@gmail.com

literature, but their exact role in breast cancer remains unclear and controversial.[7]

CD44, one of the most studied cancer stem cell markers, has been extensively investigated in breast carcinoma but the existing data has been largely conflicting. Numerous studies have revealed its role in promoting carcinogenesis and regulating EMT, tumor invasion, therapy resistance and overall survival.[8-11] On the contrary, some studies have failed to show a correlation between CD44 and other prognostic factors.[12]

The purpose of the present study was to evaluate CD44 expression as a surrogate marker for BCSCs in primary TNBC patients and examine its association with established prognostic parameters such as histological grade, tumor size and nodal status. Published studies have failed to reach a consensus on the prognostic role of CD44, particularly in the TNBC subtype. Moreover, there is a paucity of literature for such studies on Indian patients. Evaluation of CD44 immunoexpression in TNBC is vital for understanding tumor aggressiveness and determining its prognostic value.

METHODS

A hospital-based cross-sectional study was conducted in the Department of Pathology, VMMC and Safdarjung Hospital, New Delhi. The participants were selected using simple random sampling method wherein every triple negative breast cancer case diagnosed from July 2023 to November 2023 had an equal and fair chance of being included in the research. This study was approved by the hospital's Ethics Review Committee. Written informed consent was obtained from all participants following a detailed description of the purpose of the study.

Sample Size

As per the study done by Collina *et al.*[13], CD44 expression was detected in 143/160 breast cancer samples, i.e., 89.3 % of the specimens.

Applying the formula to calculate sample size for qualitative variables according to prevalence- $1.96^2xpq/d^2$

Where, p= prevalence (from previous studies)

q=1-p

d= marginal error (10%, <0.2 of prevalence), hence d = 0.1x0.89= 0.09

Sample Size n= 3.84x0.89x0.11/0.09x0.09

n= 47

By using the above formula, the required sample size for the study was 47 participants. Thus, a total of 50 TNBC cases diagnosed on core needle biopsy or mastectomy specimens from July 2023 to November 2023 were enrolled in the study.

Patient information was collected from the histopathology requisition forms which were paper-based.

Inclusion criteria

Histopathologically diagnosed cases of invasive breast cancer with TNBC subtype received in the Department of Pathology, VMMC and Safdarjung hospital were included in the study.

Exclusion criteria

Non-invasive cancer, including in situ cases, Metastatic lesions, sarcomas and ER+, PR+ or Her-2 Neu positive cases were excluded from the study.

Histological parameters were determined from H&E stained slides. Clinicopathological characteristics were evaluated for each tumor, including the patient's age at diagnosis, tumor laterality, tumor subtype and histological grade using Modified Bloom-Richardson's grading system.[14] pTNM stage was assessed in all the breast cancer surgery specimens wherein T is tumor size, N is nodal status and M is metastasis.[15]

Immunohistochemical Evaluation

Immunohistochemistry (IHC) was performed for the assessment of ER, PR, Her2neu and Ki67. Only the samples negative for ER, PR, Her2neu, i.e., TNBC subtype, were included in this study. CD44 IHC was performed using mouse monoclonal antibody (BC8, Biocare Clone).

Paraffin blocks of tumor sections were cut on poly-L-lysin-coated slides, which was followed by deparaffinization. The sections were subjected to descending concentrations of alcohol for hydration. Then, 3% Hydrogen peroxide was added, followed by antigen retrieval using pressure cooker heating technique. Primary Mouse monoclonal antibody was applied for approximately 45 minutes to 1 hour, followed by secondary antibody for 45 minutes. The slides were washed using tris buffer after every step. Chromogen-DAB was used to highlight the antibody expression and hematoxylin was used as a counterstain.

Immunohistochemistry Interpretation

The most representative areas were selected for IHC assessment by two pathologists, independently under a light microscope. CD44 expression in tumor cells was evaluated by considering the tumor percentage and intensity of immunopositivity in the cell membrane under low and high power (100x and 400x). There is no standardized scoring system for CD44 assessment; thus, we schematized our scoring system as follows:

Percentage of Positive Tumor cells	Intensity	Score
1. <10%	None/Weak	0 (Negative)
2. 11-25%	Moderate/Strong	1+ (Low Positive)
3. 25-50%	Moderate/Strong	2+ (Intermediate Positive)
4. >50%	Moderate/Strong	3+ (High Positive)

Each specimen was evaluated using the mentioned scoring system and subcategorised into negative (score=0), low positive (1+), intermediate positive (2+) and high positive (3+).

CD44 expression and scores were then correlated with histological grade, T and N stage wherever applicable.

Statistical Analysis

The presentation of the categorical variables was done in the form of numbers and percentages. Quantitative data was presented as means±SD and as median with 25th and 75th percentiles (interquartile range). The association between CD44 expression and prognostic parameters such as tumor grade, T stage and N stage which were qualitative was analysed using Fisher's exact test as at least one cell had an expected value of less than 5. Spearman rank correlation coefficient was used for analyzing the correlation of grade with CD44 score. Univariable logistic regression was used to find out significant risk factors for positive CD44. For statistical correlation, P-value of less than 0.05 was considered significant. Due to lack of a statistically significant association in univariable regression analysis, multivariable regression model was not performed. The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0.

RESULTS

Clinicopathological Characteristics of TNBC Patients

The study included fifty cases of TNBC, including 31 core needle biopsy specimens, 17 mastectomy specimens, and one of the WLE and BCS specimens. The age of the patients ranged from 32 to 74 years with a mean of 49.4 years (SD ± 10.4).

Table 1. Summary of Patients' Clinicopathological features

Patient characteristics	N (%)	Mean ± SD	Median (25th-75th percentile)	Range
Age (years)				
<=45 years	24 (48.00%)	49.4 ± 10.4	46.5(40-59)	32-75
>45 years	26 (52.00%)			
Laterality				
Bilateral	1 (2.00%)			
Left	23 (46.00%)			
Right	26 (52.00%)			
Type of tissue				
WLE	1 (2.00%)			
BCS	1 (2.00%)			
CNB	31 (62.00%)			
MRM	17 (34.00%)			
Grade				
Grade 1	3 (6.00%)			
Grade 2	24 (48.00%)			
Grade 3	23 (46.00%)			
T stage				
Low stage	12 (63.16%)			
High stage	7 (36.84%)			
N stage				
Negative nodal stage	12 (63.16%)			
Positive nodal stage	7 (36.84%)			
CD44				
Negative	30 (60.00%)			
Positive	20 (40.00%)			
CD44 score				
0	30 (60.00%)			
1+	7 (14.00%)			
2+	6 (12.00%)			
3+	7 (14.00%)			

Tumors involved the right breast in 26 (52%) cases, 23 (46%) involved the left side and one was bilateral. Majority of the cases were grade 2 tumors (24 cases, 48%), followed by grade 3 (23 cases, 46%), and 3 (6%) were grade 1. Cases belonging to higher tumor grades were predominant perhaps because of their triple negative status (47/50).

pTNM staging could be assessed in 19 of the total 50 specimens. Tumor sizes less than 2 cms (T1) and 2 to 5 cms (T2) were considered as low T stage and comprised 12 (63.16%) of the cases. Also, 7 cases (36.84%) belonged to higher T stage, i.e., T3/T4 category. Lymph node involvement was found in 7 (36.84%) of the patients, whereas 12 (63.16%) had a negative nodal stage.

Clinicopathological features are summarised in Table 1.

CD44 Expression in Triple-negative breast cancer (Figure 1)

CD44 positive expression was observed in 20 (40%) of the total 50 cases.

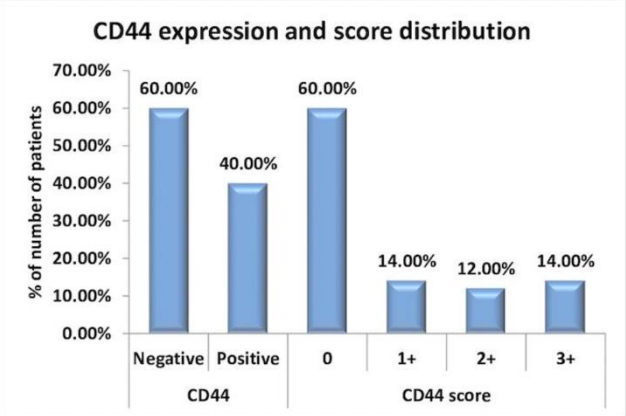

Figure 1. Bar graph displaying percentages of CD44 positive and negative cases and score distribution in triple negative breast cancer. (n=50)

Also, 13 samples (26%) showed intermediate (score 2+) to high (score 3+) expression for CD44. In 7 samples (14%), low expression (score 1+) was observed. The remaining 30 cases (60%) showed a negative expression (score 0). (Figure 2a-2d and 3a-3d).

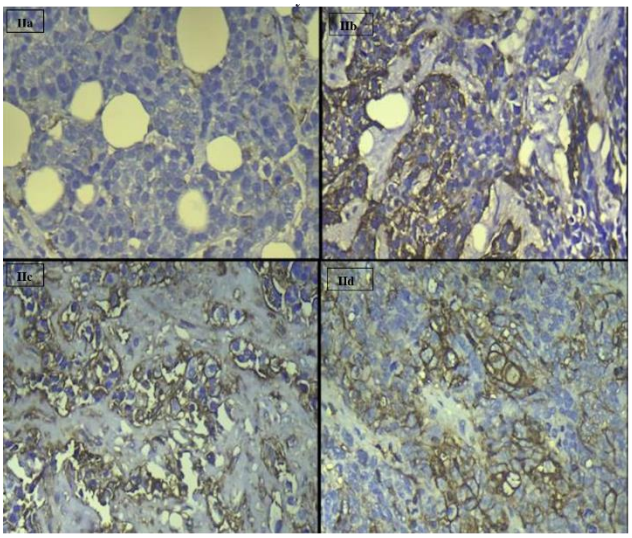

Figure 2. CD44 immunohistochemistry in breast cancer (400x). 2a-Score 0 (Negative), 2b-Score 1+: Tumor cells with CD44 expression in 11-25% of cells (Low positivity), 2c-2d-Score 2+: Tumor cells with CD44 expression in 26-50% of cells (Intermediate/Moderate positivity)

Association of CD44 with Histological grade

The study found a significant association between positive CD44 expression and histological grade (P value using Fisher's exact test=0.002, Table 2).

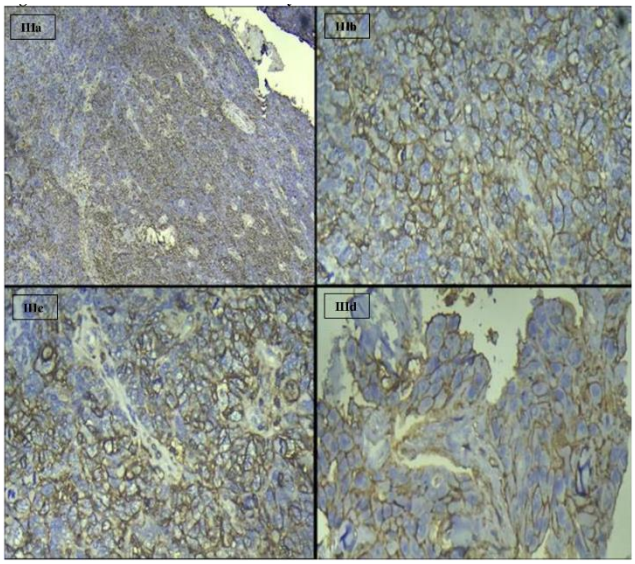

Figure 3. Score 3+ (High/Strong positivity): Tumor cells with strong CD44 expression in >50% of cells. 3a- Low magnification (100x). 3b-3d- High magnification (400x)

Table 2. Association of CD44 expression with histological grade.

CD44	Grade 1(n=3)	Grade 2(n=24)	Grade 3(n=23)	Total	Low Grade (1)	High Grade (2&3)	P-value
Negative	3 (10%)	19 (63.34%)	8 (26.67%)	30 (100%)	3 (10%)	27 (90%)	
Positive	0 (0%)	5 (25%)	15 (75%)	20 (100%)	0 (0%)	20 (100%)	0.002*
Total	3	24	23	50			

* Fisher's exact test

Stronger CD44 expression was observed with increasing tumor grade. Of the total 20 cases with positive CD44 expression, majority (15, 75%) were grade 3 tumors followed by grade 2 (5, 25%), whereas

none of the grade 1 (0%) cases showed positivity for CD44. On applying univariable logistic regression model, the study failed to show a significant correlation between CD44 expression and tumor grade (P-value using Fisher's exact test >0.05, Table 4).

The distribution of CD44 scores showed a similar pattern across different tumor grades. For cases with score 1+ i.e., low positive, the proportions were 0, 2 (28.5%), and 5 (71.5%) for cases at grades 1,2 and 3,respectively. Similarly, in cases with score 2+, the proportions were 0, 2 (33.34%), and 4 (66.67%), respectively. Lastly, for cases exhibiting strong positivity i.e., score 3+, the highest number of cases belonged to Grade 3, i.e., 6 (85.71%), followed by Grade 2, 1 (14.28%). The P-value associated with this distribution was marginally significant (P=0.052 using Fisher's exact test, Table 3).

Table 3. Association of CD44 score and distribution with histological grade.

CD44 score	Grade 1(n=3)	Grade 2(n=24)	Grade 3(n=23)	Total	Low Grade (1)	High Grade (2&3)	P value
0	3 (10%)	19 (63.34%)	8 (26.67%)	30 (100%)	3 (10%)	27(90%)	
1+	0 (0%)	2 (28.5%)	5 (71.5%)	7 (100%)	0 (0%)	7 (100%)	
2+	0 (0%)	2 (33.34%)	4 (66.67%)	6 (100%)	0 (0%)	6 (100%)	0.052*
3+	0 (0%)	1 (14.28%)	6 (85.71%)	7 (100%)	0 (0%)	7 (100%)	
Total	3	24	23	50			

* Fisher's exact test

A stronger expression both in intensity and tumor percentage was noticed in the worst histological grade. Using the Spearman rank correlation coefficient, a moderately positive correlation was observed between CD44 score and increasing tumor grade (Correlation coefficient of 0.485, P-value= 0.0004).

Expression of CD44 in Mastectomy specimens

CD44 positivity was observed in 10/19 (52.63%) of the mastectomy specimens. Majority of the positive cases (5 cases, 50%) showed an intermediate immunoreactivity score (2+), followed by score 1+ 4 (40%). One case stained high for CD44 with the score 3+.

CD44 was additionally correlated with tumor size and lymph node spread in these cases.

Association of CD44 immunoexpression with T stage

No statistical significance was observed between CD44 immunoexpression and tumor stage (P-value using Fisher's exact test =0.592). Logistic regression test was applied and no significance was observed between CD44 expression and T stage (P-value=0.494, Table 4) Ten out of the 19 surgery specimens showed a positive CD44 expression, with an equal number of cases belonging to lower T1/T2 stage and high T3/T4 stage.

Table 4. Univariate logistic regression to evaluate significant risk factors for positive CD44 expression.

Variable	Beta coefficient	Standard error	P-value	Odds ratio	Odds ratio Lower bound (95%)	Odds ratio Upper bound (95%)
Grade						
Grade 1				1.000		
Grade 2	0.662	1.802	0.714	1.938	0.057	66.308
Grade 3	2.523	1.788	0.158	12.470	0.375	414.499
T stage						
Low stage				1.000		
High stage	0.789	1.154	0.494	2.201	0.229	21.126
N stage						
Negative nodal stage				1.000		
Positive nodal stage	-0.606	1.220	0.620	0.546	0.050	5.964

On performing univariate regression, none of the variables were found to be significant risk factors for positive CD44 expression (P-value>0.05).

Association of CD44 immunoexpression with N stage

The association between CD44 immuno-expression and nodal status did not show any statistical significance (P-value using Fisher's exact test= 1). Logistic regression analysis failed to show an association between CD44 positivity and N stage (P-value= 0.620, Table 4). Majority of nodal negative

cases (8 cases, 70%) displayed positive CD44 expression, compared to 2 (30%) cases of positive nodal involvement.

DISCUSSION

Breast cancer treatment options have not yielded desirable outcomes for TNBC patients, necessitating the exploration of new prognostic parameters and therapeutic targets.[16] Recent studies on cancer stem cells (CSCs) have explored their unique properties, with CD44 being a key marker associated with increased cancer growth and chemotherapy resistance.[17,18] However, results have been contradictory due to variable methodology, lack of standardized quantification systems and diverse isoforms of CD44 in stem cells.

In the present study, CD44 expression was observed in 20 (40%) of the total 50 cases. A substantial number (13 cases, 26%) of positive cases showed a higher CD44 score with a moderate to strong expression. Our results were comparable to research conducted by Almasi *et al.*, Liu *et al.* and Chekhun *et al.*[10,19,20] Collina *et al*. found a higher percentage of CD44 expression (89.37%) in TNBC. Such high positivity may be due to the absence of a lower tumor percentage limit for positive cases.[13]

A statistically significant association was observed between CD44 immunoexpression and histological grade (P-value<0.05). Higher histological grades showed an elevated CD44 expression. Moreover, a comparison of CD44 score distribution showed a moderately positive correlation with increased tumor grade using the Spearman Rank correlation coefficient test. However, P-value associated with this distribution was marginally significant with a P-value of 0.052. Our findings were in concordance with a study done by McFarlane *et al.*[21] who observed an association between the overexpression of CD44 and increasing tumor grade. Similarly, a meta-analysis carried out by Xu *et al*. demonstrated a positive link between CD44 expression and clinical features including histological grade and basal subtype, leading to significantly worse overall survival (hazard ratio =1.27; 95% CI: 1.04–1.55).[22]

In our study, CD44 expression and score distribution failed to show a significant correlation with tumor size and nodal spread. Our findings were parallel to observations made by Jang *et al.*[12] However, they did not find any correlation between CD44 overexpression and tumor grade, which was contrary to our findings. Conversely, the systematic review done by Shadbad *et al.* concluded that CD44+CD24-/low expression is linked to advanced tumor stage, size, grade, metastasis, and lymphatic involvement in TNBC patients.[23] Another study by Zou *et al.* on 51 TNBC patients reported similar findings suggesting the role of CD44 and CD24 as independent prognostic markers for patients with TNBC.[24] CD44 expression did not correlate with tumor size or nodal status in our study, as majority of the cases were diagnosed early and belonged to lower tumor stage, i.e., T1/T2 and N0. A univariate regression analysis was also performed and none of the variables were found to be significant risk factors for positive CD44 expression (P-value>.05).

CONCLUSION

CD44, a key breast cancer stem cell marker, has demonstrated a significant association with several prognostic factors in triple negative breast cancer. [25,26] However, studies have reported controversial results. Our study recorded a positive expression of CD44 in 40% of TNBC samples with a statistically significant association with increased histological grade. No correlation was found between CD44 expression and tumor size or lymph node status. The study concludes that CD44 may be treated as a surrogate marker for BCSCs and may hold prognostic value in TNBC patients. Our research is one of the few in India to examine such an association. Further studies are required to verify these results using a larger sample size.

ETHICAL CONSIDERATIONS

This study was approved by the hospital's Ethics Review Committee. Written informed consent was obtained from all participants following a detailed description of the purpose of the study.

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CONFLICT OF INTEREST

The authors declare no confilict of interest for this article.

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