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Original Research Article

Is CD 44 really a marker of breast cancer metastasis or is nefarious in its nature

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ABSTRACT

Aims and Objectives: To study the expression of immunomarker CD 44 and evaluate its diagnostic and prognostic significance and its correlation with clinicopathological variables in Breast Carcinoma.
Materials and Methods: 50 diagnosed cases of breast carcinoma, presenting clinically with breast lumps were processed routinely for histopathological diagnosis of breast cancer and immunoexpression of CD 44 was performed. The immunoexpression of CD44 was detected mainly at the membrane of tumour cells and the scoring was performed.
Results: 217 (98.2%) were females and 4(1.8%) males. Most common subtype involved was invasive carcinoma (NST) in 205(92.8%) cases. Out of 29 cases of grade 2 tumor, 07 (14.0%) showed 1+ score, 10 (20.0 %) showed 2+ score and 12 (24.0%) cases showed 3+ immunoexpression. Out of 25 cases of T2 (2-5 cm) size, 07(14.0%) showed 1+ score, 09(18.0%) case each showed 2+ score and 3+ immunoexpression. Out of 26 cases of stage III, 04(8.0%) showed 1+ score, 09(18.0%) showed 2+ score and 13(26.0%) cases showed 3+ immunoexpression. Out of 05 cases of N3, 02(4.0%) showed 2+ score and 03(6.0%) showed 3+ immunoexpression. Out of 21 cases of basal cell type, 03(6.0%) showed 1+ score, 07(14.0 %) showed 2+ score and 11(22.0%) cases showed 3+ immunoexpression. Out of 11 (50.0%) cases with weak to moderate expression of CD44, 7(31.8%) cases were stable and alive while 4(18.2%) died due to distant metastasis to various sites.
Conclusions: CD 44 is associated with disease progression, recurrence, advanced metastasis and reduced disease free survival and can be used in future to predict early diagnosis of advanced disease.

1. Introduction

CD44 has been the subject of extensive research for more than 3 decades because of its role in breast cancer, in addition to many physiological processes, but interestingly, conflicting data implicate CD44 in both tumor suppression and tumor promotion.[1,2] CD44 has been shown to promote pro-tumorigenic signaling and advance the metastatic cascade. On the other hand, CD44 has been shown to suppress growth and metastasis. Histopathological studies of human breast cancer have correlated CD44 expression with both favorable and unfavorable clinical outcomes.[2,3] In recent years, CD44 has garnered significant attention because of its utility as a stem cell marker and has surfaced as a potential therapeutic target, necessitating a greater understanding of CD44 in breast cancer.[1]

CD44 isoforms are up-regulated in breast carcinomas.[2] In fact, the presence of a high level of various CD44 isoform (particularly CD44s (the standard form), CD44v3, and CD44v10) expression is emerging as an important metastatic tumor marker in a number of carcinomas and is also implicated in the unfavorable prognosis for a variety of cancers. Carcinomas expressing high levels of CD44 isoforms are more malignant than those carcinomas with a low level of CD44 isoform expression.[3] The level of CD44v3 isoform expression often increases as the histologic grade of each of the breast tumors progresses. In fact, there

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is a direct correlation between CD44v3 isoform expression and increased histologic grade of the malignancy.[2,3]

In breast tumor cells, CD44v3 is also closely associated with matrix metalloproteinases, MMP-9, in the plasma membrane. Therefore, it is likely that the close interaction between CD44v3 and the active form of MMP-9 in the invadopodia structure of breast tumor cells may be required for the degradation of extracellular matrix during breast tumor cell invasion and metastasis.[2,3]

2. Materials and Methods

This prospective study was conducted on 50 diagnosed cases of breast carcinoma, presenting clinically with breast lumps over a period of two years from 2018 to 2020. All 50 specimens were processed routinely for histopathological diagnosis of breast cancer and immunoexpression of CD 44 was performed. Proper written consent was obtained from all the patients. Ethical clearance from the institutional ethical committee was obtained for the present study. Histopathologically diagnosed cases of Breast Carcinoma were included in the study while patient refusing consent, having benign disorders of breast and previous history of another type of cancer are excluded from the study. Exact number of age and sex matched controls was taken along with the case group and the two groups were compared statistically.

Routine Hematoxylin and Eosin staining and CD 44 antibody was applied on the sections. The immunoexpression of CD44 was detected mainly at the membrane of tumour cells and the scoring will be considered as follows: Negative: 0-10% of positive tumour cells; 1+: 11-25% of positive tumour cells; 2+: 26-50% of positive tumour cells and 3+:>50% of positive tumour cells. Tonsil was taken as the positive control for CD 44 and malignant breast tissue without applying primary antibody as the negative control. All data was tabulated and analysed and appropriate statistical tests (chi square test, Pearson chi square test and unpaired t-test) were applied using computer program SPSS version 25.0 wherever necessary and p value of <0.05 was considered statistically significant.

3. Observations

Majority of the patients were females, 217(98.2%) and males constituted lesser number of cases, 4 (1.8%). Majority of the patients were postmenopausal females, 147(66.5%) as compared to 74(33.5%) premenopausal females. Breast lump was the most common symptom seen in 143(64.7%) cases, followed by lymphadenopathy in 75(33.9%) cases. Ulceration and fungating mass was present in 25 (11.3%) cases and pain and nipple retraction in 38(17.2%) and 34 (15.4%) cases Left sided breast was most commonly involved in 132(59.7%) cases as compared to the right sided breast in 89 (40.3%) cases. Majority of the cases had upper outer quadrant involved in 123(55.7%) cases followed by central in 40 (18.1%) cases and lower inner quadrant in 33(14.9%) cases.

Most common subtype involved was invasive carcinoma (NST) in 205 (92.8%) cases with cords and nests of malignant ductal cells infiltrating the stroma with marked cytologic atypia (Figure 1) followed by 03(1.4%) of paget's disease and metaplastic carcinoma with interlacing bundles of atypical spindle cells admixed with pleomorphic ductal cells.

Out of 205 cases of Invasive Carcinoma NST, most common tumor histological grade seen was grade 2 (moderately differentiated carcinoma) in 102(49.9%) cases, followed by grade 3 (poorly differentiated) in 61(29.9%) cases and grade 1 (well differentiated carcinoma) in 41(20.2%) cases.

Out of 205 cases of Invasive Carcinoma NST, 89 cases were selected for the study whose tumor characteristics were assessed. Among 89 cases, majority of the tumors were of 2-5 cm (T2) in size, 33(37.1%) cases followed by T4 size in 25(28.1%) of the cases. Majority of the cases, 31(34.8%) showed no lymph nodes or 1-3 lymph nodes involvement followed by 4-9 lymph nodes involvement in 18(20.2%) cases. Distant metastasis was absent in all the 89(100%) cases at the time of presentation. Majority of the cases were in stage III disease, 54(60.7%) cases, followed by 28(31.5%) cases in stage II disease.

Out of 221 cases, hormonal immunohistochemistry was applied only on 125 cases. Among 125 cases, majority comprised of triple negative, 50(40.0%) cases followed by 38(30.4%) cases of ER & PR positive and Her2-neu negative tumors. Table 1.

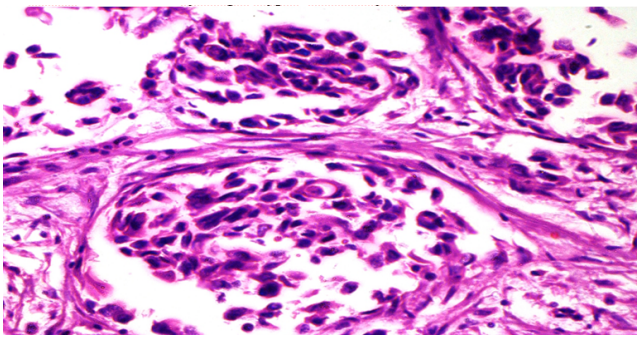

Fig. 1: Invasive carcinoma (NST) showing cords and nests of malignant ductal cells infiltrating the stroma with marked cytologic atypia.Hematoxylin and Eosin x 40X

Immunohistochemical staining of CD44 antibody was performed on 50 cases of Breast carcinoma. Out of 09 cases of grade 1 tumor, 02(4.0%) showed 1+ score, 05 (10.0%) cases showed 2+ score and 02(4.0%) cases showed 3+ immunoexpression. Out of 29 cases of grade 2 tumor, 07(14.0%) showed 1+ score, 10(20.0 %) showed 2+ score and 12(24.0%) cases showed 3+ immunoexpression. Out

Table 1: Immunohistochemical profile of hormonal markers (ER, PR, HER2/neu)

Immunohistochemical category	No. of positive cases	Percentage
Luminal A (ER+, PR+, HER2neu-)	38	30.4
Luminal B (ER+, PR+, HER2neu+)	09	7.2
Basal Cell Like (ER-, PR-, HER2neu-)	50	40.0
HER2 Overexpression (ER-, PR-, HER2neu+)	28	22.4
Total	125	100.0

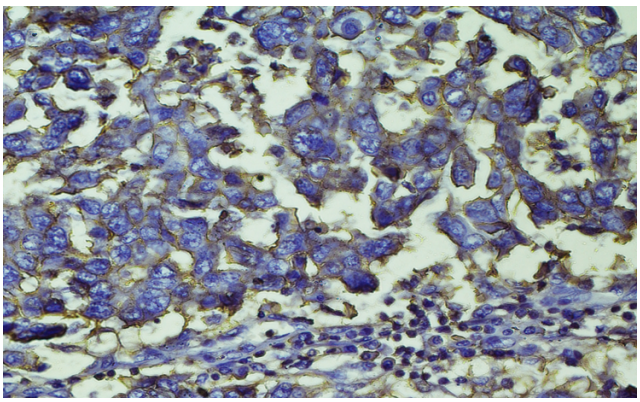

Fig. 2: Tumor cells in stage III disease showed strong complete membranous positivity: Score 3+. IHC CD 44x40X

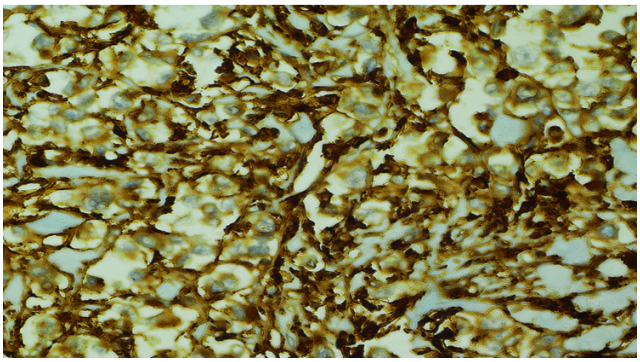

Fig. 3: Grade 3 tumor cells showed strong complete membranous positivity: Score 3+. IHC CD 44x40X

of 12 cases of grade 3 tumor, 02 (4.0%) showed 1+ score, 03(6.0 %) showed 2+ score and 07(14.0%) cases showed 3+ immunoexpression (Figure 2). The statistical correlation between tumor grade and CD44 immunoexpression was found to be insignificant (p=0.52).Table 2

Out of 03 cases of T1 (<2 cm) size, 01 (2.0%) case each showed 1+ score, 2+ score and 3+ immunoexpression. Out of 25 cases of T2 (2-5 cm) size, 07 (14.0%) showed 1+ score, 09 (18.0 %) case each showed 2+ score and 3+ immunoexpression. Out of 13 cases of T3 (>5 cm) size, 02 (4.0%) showed 1+ score, 06(12.0 %) showed 2+ score and 05 (10.0%) cases showed 3+ immunoexpression. Out of 09 cases of T4 size, 01(2.0%) showed 1+ score, 02(4.0%) showed 2+ score and 06(12.0%) showed 3+ immunoexpression. The statistical correlation between tumor size and CD44 immunoexpression was found to be insignificant (p=0.70).

Out of 20 cases of Nx, 03(6.0%) showed 1+ score, 09(18.0%) cases showed 2+ score and 08(16.0%) cases showed 3+ immunoexpression. Out of 14 cases of N1, 04 (8.0 %) showed 2+ score and 05(10.0%) cases each showed 1+ and 3+ immunoexpression. Out of 11 cases of N2, 03 (6.0%) each showed 1+ score and 2+ score and 05(10.0%) cases showed 3+ immunoexpression. Out of 05 cases of N3, 02(4.0%) showed 2+ score and 03(6.0%) showed 3+ immunoexpression. The statistical correlation between lymph node status and CD44 immunoexpression was found to be insignificant (p=0.62).Table 3

Out of 03 cases of stage I, 01(2.0%) case each showed 1+ score, 2+ score and 3+ immunoexpression. Out of 21 cases of stage II, 06(12.0%) showed 1+ score, 08(16.0%) showed 2+ score and 07(14.0%) cases showed 3+ immunoexpression. Out of 26 cases of stage III, 04(8.0%) showed 1+ score, 09(18.0%) showed 2+ score and 13(26.0%) cases showed 3+ immunoexpression (Figure 3). The statistical correlation between tumor stage and CD44 immunoexpression was found to be insignificant (p=0.87).Table 4

Out of 12 cases of luminal type A, 04 (8.0%) cases each showed 1+ score, 2+ score and 3+ immunoexpression. Out of 09 cases of luminal type B, 03 (6.0%) showed 1+ score, 04 (8.0 %) showed 2+ score and 02(4.0%) cases showed 3+ immunoexpression. Out of 21 cases of basal cell type, 03 (6.0%) showed 1+ score, 07(14.0%) showed 2+ score and 11(22.0%) cases showed 3+ immunoexpression. Out of 08 cases of HER2 overexpression, 01(2.0%) showed 1+ score, 03(6.0%) showed 2+ score and 04(8.0%) cases showed 3+ immunoexpression. The statistical correlation between hormonal markers and CD44 immunoexpression was found to be insignificant (p=0.66).Table 5

Out of 50 patients, 22 patients were followed at an interval of 3 months, 6 months, 9 months and 12 months with complete clinicoradiological study and routine laboratory investigations performed. Out of 22 patients, 2(9.1%) patients died before 3 months due to metastasis. At 3 months follow up, 20 (90.9%) patients were alive. At 6 months follow up, 2(9.1%) patients died and 18(81.8%) were alive. At 9 months follow up, 3(13.6%) patients died and 15(68.2%) were alive. At 12 months follow up, 1(4.5%) patient died and 14(63.6%) were alive.

Table 2: Immunoexpression of CD44 in relation to Grade of Tumor

Grade of tumor	No. of cases	CD44 Immunoexpression (Score)				p value
		0	1+	2+	3+	
		No. of cases (Percentage)				
1	09	-	02(4.0)	05(10.0)	02(4.0)	
2	29	-	07(14.0)	10(20.0)	12(24.0)	**0.52**
3	12	-	0 (4.0)	03(6.0)	07(14.0)	
Total	50	-	11(22.0)	18(36.0)	21(42.0)	

Table 3: Immunoexpression of CD44 in relation to Lymph node status

No. of lymph nodes involved	No. of cases	CD44 Immunoexpression (Score)				p value
		0	1+	2+	3+	
		No. of cases (Percentage)				
Nx	20	-	03(6.0)	09(18.0)	08(16.0)	
N1	14	-	05(10.0)	04(8.0)	05(10.0)	**0.62**
N2	11	-	03(6.0)	03(6.0)	05(10.0)	
N3	05	-	-	02(4.0)	03(6.0)	
Total	50	-	11(22.0)	18(36.0)	21(42.0)	

Table 4: Immunoexpression of CD44 in relation to Stage of tumor

Stage of tumor	No. of cases	Cd44 Immunoexpression (Score)				P value
		0	1+	2+	3+	
		No. of cases (Percentage)				
I	03	-	01(2.0)	01(2.0)	01(2.0)	
II	21	-	06(12.0)	08(16.0)	07(14.0)	**0.87**
III	26	-	04(8.0)	09(18.0)	13(26.0)	
IV	-	-	-	-	-	
Total	50	-	11(22.0)	18(36.0)	21(42.0)	

Table 5: Immunoexpression of CD44 in relation to ER, PR and HER-2neu expression

Hormonal IHC	No. of cases	CD44 Immunoexpression (Score)				p value
		0	1+	2+	3+	
		No. of cases (Percentage)				
Luminal A ER+,PR+,HER2/neu-	12	-	04(8.0)	04(8.0)	04(8.0)	
Luminal B ER+,PR+,HER2/neu+	09	-	03(6.0)	04(8.0)	02(4.0)	**0.66**
Basal Cell Like ER-,PR-,HER2/neu_	21	-	03(6.0)	07(14.0)	11(22.0)	
HER2 Overexpression ER-,PR-,HER2/neu+	08	-	01(2.0)	03(6.0)	04(8.0)	
Total	50	-	11(22.0)	18(36.0)	21(42.0)	

All the patients completed chemotherapeutic cycles and received radiotherapy except 2 cases who died few days after surgical intervention. Out of 22 patients, 10 (45.5%) patients were stable with no new complaints, 2 (9.0%) patients had recurrence after completing 8 cycles of chemotherapy and 10 (45.5%) patients had shown distant metastasis. Out of 10(45.5%) patients with distant metastasis, 8 (36.4%) died and 2(9.1%) were alive, however in poor clinical state. Out of 11(50.0%) cases with strong immunoexpression of CD44, 5(22.7%) cases had distant metastasis to various organs like spine, kidney, liver, lungs and buccal mucosa and succumbed to death except one with metastasis to the lungs, 2 (9.1%) cases had local recurrence and 4(18.2%) cases were alive and healthy. Out of 11(50.0%) cases with weak to moderate expression of CD44, 7(31.8%) cases were stable and alive while 4(18.2%) died due to distant metastasis to various sites.

Out of 14(63.6%) cases of stage III tumor, 6(27.3%) patients died of distant metastasis, 2(9.1%) had recurrence while 6(27.2%) were alive and in good health. Out of 7(31.8%) cases of stage II tumors, 2(9.1%) died of distant metastasis while 5(22.7%) were alive. A single case (4.7%) of stage stage I tumor was alive and disease free.

4. Discussion

Development and advances in screening as well as accurate treatment modalities have led to significant decrease in mortality and morbidity in patients of breast cancer and

thereby increased overall survival.[4]

In our study majority of the cases occured in their fifth decade of life (30.8%) followed by 4^{th} decade (27.1%). Vijaya et al in 2020 noted that maximum number of cases were in the age category of 41-60 years (57.8%) followed by >60 years (23.4%).[5] In India breast cancer peaks during 45 to 50 years of age.[6] Gedam et al in 2018 showed that most of the patients were in the age group of 41-50 years (40%) followed by 31-40 years (33.3%).[7]

In our study majority of the patients (98.2%) were females compared to 1.8% males. Vijaya et al in 2020 in 2013 found more preponderance in females (99.8%).[5] In general, male breast cancer incidence trends were variable and a minority of countries showed increasing incidence while female incidence rates showed an increasing trend in a majority of countries.[7]

Majority of the females in our study were postmenopausal (66.5%) as compared to premenopausal females (33.5%). Zuo et al 2018 studied that premenopausal patients accounted for 44.5% and postmenopausal patients accounted for 55.5%.[8] According to study done by Unlu et al in 2017, premenopausal females (54.9%) patients were more than postmenopausal (45.1%) but the risk was greater in postmenopausal females.[9]

In our study, breast lump was the most common symptom seen in 143(64.7%) cases, followed by lymphadenopathy in 75(33.9%) cases. Patients presenting with fungating mass are very rare.[10]

In our study left side (59.7%) of the breast was more commonly involved as compared to the right (40.3%) side. Alotaibi et al in 2018 found that left side (49.8%) was more commonly involved than right side (47.7%) in breast cancer patients.[11] Cheng et al in 2018 observed that left sided breast cancer was approximately 5% more than the right breast.[12] Uyisenga et al in 2020 observed bilateral breast cancer in some patients.[13]

Majority of the cases of breast carcinoma in our study had upper outer quadrant (55.7%) involvement followed by central (18.1%) cases, lower inner quadrant (14.9%), lower outer quadrant (8.6%) and upper inner quadrant (2.7%). Vijaya et al in 2020 observed upper outer quadrant (54.6%) was the most common tumour location followed by upper inner quadrant (21.8%), lower inner quadrant (17.1%), central quadrant (6.2%) and lower outer quadrant (3.1).[5]

In our study, most common subtype involved was invasive carcinoma (NST) in 205(92.8%) cases with cords and nests of malignant ductal cells infiltrating the stroma with marked cytologic atypia followed by metaplastic, paget's and lobular carcinomas. On histopathological assessment done by Vijaya et al in 2020, majority of the patients had invasive carcinoma (89.1%) followed by lobular carcinoma (10.9%).[5] Among invasive carcinomas, majority comprised of no special type (20.3%). Liao et al in 2018 showed that invasive carcinoma (NST) accounted for 91.6% of patients followed by metaplastic carcinoma, mixed lobular-ductal carcinoma and lobular carcinoma.[14] Uyisenga et al in 2020 concluded that invasive ductal carcinoma accounted for the majority of the patients (81.9%) followed by invasive lobular carcinoma (8.7%).[13] Leon et al in 2018 and Kim et al in 2020 found 70.0% and 86.0% of invasive carcinoma (NST) cases in their study respectively.[15,16]

In present study, out of 205 cases of Invasive Carcinoma NST, most common tumor histological grade seen was grade 2 (moderately differentiated carcinoma) in 102(49.9%) cases followed by grade 3 (poorly differentiated) in 61(29.9%) cases and grade 1 (well differentiated carcinoma) in 41(20.2%) cases. Unlu et al in 2017 and Oddo et al in 2018 showed grade 2 was the most common histologic grade (49.0% & 45.3%) followed by grade 3(35.1% & 42.1% respectively).[9,17]

In this study, out of 205 cases of Invasive Carcinoma NST, 89 cases were assessed for tumor characteristics. Among 89 cases, majority of the tumors were of 2-5 cm (T2) in size, 33(37.1%) cases followed by T4 size in 25(28.1%) of the cases. Unlu et al in 2017 had similar findings with majority of T2 (46.7%) size followed by T1 (31.6%) size.[9] Leon et al in 2018 had majority of T1 (51.1%) size cases followed by T2 (43.5%) size. Chen et al in 2017 observed 70.5% T1 cases which were more than T2 cases.[15]

In the present study, 34.8% showed no lymph nodes or 1-3 lymph nodes involvement followed by 4-9 lymph nodes involvement in 20.2% cases. In study done by Leon et al in 2018, 64.6% cases did not show lymph node involvement followed by 1-3 lymph nodes (21.5%) involved.[15] Uyisinga et al showed lymph node invasion in 70.6% of patients as compared with 29.4% node negative tumors. N0 consisted of 308 patients (58.3%), the N1 consisted of 164 (31.1%) patients, the N2 consisted of 35 (6.6 %) patients, and the N3 consisted of 2 (4.0%) patients.[13]

In our study, 27.0% of the cases were in stage IIIB disease cases followed by stage IIIA in 23.6%, stage IIIC in 10.1%, stage IIB in 22.5%, stage IIA in 9.0%, stage IA in 5.6% and IB in 2.2% cases. Vijaya et al in 2020 found 53.1% cases of IIIA and 25% in IIIC followed by IIIB in 9.3%, IIA in 4.6%, IIB in 4.6% and IB in 3.1% cases.[5] Uyisenga et al in 2020 concluded that tumor stage III was the most common stage accounting for 62.5% followed by stage II in 24.8% cases.[13]

In this study, hormonal immunohistochemistry was applied only on 125 cases. Among 125 cases, 40% were triple negative cases followed by 30.4% of luminal A, 22.4% of Her2 overexpression and 7.2% of luminal B cases. Uyisenga et al in 2020 observed that 37.7% hormonal receptor negative tumors were most predominant as compared with other hormonal receptor tumors.[13]

Although higher expression of CD44 was seen in grade 2 than grade 3, but it is not found to be statistically

significant (p value=0.52). Chen et al in 2020 observed no significant correlation between grade of tumor and CD 44 expression.[18] However, Qiu et al in 2016 and Louhichi et al in 2018 found a significant association between tumor grade and CD44 expression which are contradictory to the present findings.[19,20]

In this study, no significant correlation was seen between CD44 expression and tumor size (p value=0.70). Different sizes of tumor showed variable immunoexpression ranging from weak to moderate to strong. Study done by Chen et al in 2020 showed concordant results between CD44 expression and tumor size.[18] However, Louhichi et al in 2018 also reported no relationship between tumor size and CD44 expression.[20]

No significant association was seen on comparing node negative and node positive breast cancer cases with the CD44 expression (p value=0.62). Our findings were concordant with the observations made by Chen et al in 2020 and Louhichi et al in 2018.[18,20] However, studies done by Qiu et al in 2016 showed discordant results in relation to cases presenting with nodal metastasis and those without nodal metastasis, with reference to expression of CD44.[19]

In our study in TNM stage I disease, weak to strong immunoexpression was present equally in all the cases while in tumors in patients having TNM stage II and III disease showed a spectrum of expression from moderate to strong. Hence, no significant correlation could be obtained between tumor stage and CD44 expression (p value=0.87). Concordant results were seen in studies done by Jang et al in 2016.[21] However, Chen et al in 2020 showed positive association between tumor stage and CD44 immunoexpression.[18]

In our study, no significant correlation was found between CD44 immunoexpression and hormonal markers (p value=0.66) but high intensity staining was seen with basal cell like subtype followed by Her2-neu over expressive tumors. Our findings were concordant with Chen et al in 2020 who reported no significant correlation of hormonal receptors with CD44 expression.[18] In study done by Jang et al in 2016, the expression of CD44 was significantly correlated with HER2-negative status, a finding discordant with our study.[21] Diaz et al in 2005 noted an inverse relationship between anti-CD44 positivity and HER-2neu overexpression and a significant correlation between anti-CD44s staining and ER positivity.[22]

In our study, none of the clinicopathological parameters correlated with CD44 immunoexpression but a deregulation in the CD44 expression pattern was seen in malignant tumors. The immunoexpression of CD44 was high in cases with lymph node metastasis but did not correlate significantly (p value=0.62). Horiguchi et al in 2010 observed a higher expression of CD44 is significantly associated with a smaller tumor size, lack of axillary lymph node involvement and lower stages of breast cancer.[23]

In our study, we found that immunoexpression of CD44 was moderate to strong in cases where disease progression was seen in the form of recurrence, distant metastasis and cancer related deaths. In our study, out of 11 cases with strong immunoexpression of CD44, 5 cases had distant metastasis to various organs like spine, kidney, liver, lungs and buccal mucosa which resulted in death of the patients except one with metastasis to lungs, 2 cases had recurrence at the same site as the previous tumor and 4 cases were alive with no new complaints and were healthy. Cases in which the immunoexpression of CD44 was weak were stable and had disease free survival in our study. Out of 11 cases with weak to moderate expression of CD44, 7 cases were stable with no new complaints while 4 of them died due to distant metastasis to various sites. An association was also seen between immunoexpression of CD44 and disease progression & survival in our study. Mc Farlane et al in 2015 showed correlation of increased CD44 immunoexpression with disease recurrence and reduced disease-free survival in patients with lymph-node positive or large tumors.[24] Abraham et al in 2005 observed that high expression of CD44 may favour distant metastasis but not overall clinical outcome and survival.[25]

In our study, prognosis of patients with strong immunoexpression of CD44 was predominantly poor but good in few patients with strong expression while prognosis was good in patients with weak to moderate expression of CD44 with few patients having bad prognosis. This shows the dual role of the marker CD44 in breast carcinomas. CD44 expression was elevated in basal cell type tumors, some of which had distant metastasis and recurrence with poor prognosis. Xu et al in 2016 concluded that CD44 expression was increased in basal type tumors and high risk of metastasis and relapse was associated with CD44 expression.[26] Nakshatri et al in 2009 observed that CD44 may show favourable prognosis in early non-invasive cancer, and may not function as a marker of tumor-initiating cells at early phase in breast cancer progression.[27] Kim et al in 2020 showed that CD44 expression affected prognosis predominantly in the receptor negative study group and correlated with favourable prognosis.[16]

5. Conclusions

CD 44 has a dual role and shows both tumor suppressive as well as tumor progressive activity in breast carcinomas. CD 44 is associated with disease progression, recurrence, advanced metastasis and reduced disease free survival and can be used in future to predict early diagnosis of advanced disease. The potential of CD 44 as a plasma marker for detecting the presence of breast cancer deserves further evaluation and can be used to predict survival.

6. Conflicts of Interest

All contributing authors declare no conflicts of interest.

7. Source of Funding

None.

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