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CD155 Expression in Invasive Breast Carcinoma: Association with Immune Tumor Microenvironment

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ABSTRACT

Background & Objective: CD155 is as an immune checkpoint molecule that interacts with various activating and inhibitory receptors on T- lymphocytes and natural killer (NK) cells in tumor microenvironment (TME). NK cells and tumor associated macrophages (TAMs) are major components of the immune TME.

Methods: 85 cases of invasive breast carcinoma (IBC) were evaluated for immunohistochemical expression of CD155, CD56, and CD163.

Results: CD155 was positive in 52.9% of cases, and was significantly associated with larger sized, higher grade, advanced stage tumors, positive lymphovascular invasion (LVI), and aggressive molecular subtypes of IBC. High density of CD56 stained tumor infiltrating NK cells was detected in 30.6% of cases, which was significantly related to larger sized, higher-grade tumors, and aggressive molecular subtypes. High density of stromal TAMs was detected in 55.3% of cases, and was significantly associated with large tumor sizes, higher grade, advanced stage, positive LVI, and aggressive molecular subtypes. CD155 expression was significantly correlated with the densities of NK cells and TAMs in TME.

Conclusion: CD155 expression, high density of tumor infiltrating NK cells, and high density of stromal TAMs contribute to progression of IBC. CD155 can play an important immunoregulatory role in the TME.

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Introduction

Breast cancer (BC) ranks as the second most common diagnosed cancer, and the fourth leading cause of cancer related death worldwide (1). Research on BC has highlighted the complex interplay between cancer cells and the tumor microenvironment (TME) (2). The TME in BC is dynamic, featuring various immune and non-immune cells that interact to regulate tumor progression and anti-tumor immunity (3).

CD155 is a type I transmembrane glycoprotein that belongs to the Nectins family of proteins and is involved in various processes, such as cell adhesion, migration, proliferation, and tumor immune surveillance (4). Although CD155 is expressed at a low level in different normal tissues, its overexpression correlates with poor prognosis in various human malignancies (5). CD155 has attracted considerable attention as an immune checkpoint molecule because of its immunoregulatory functions in the TME (6). Therefore, CD155 may serve as a promising target for immunotherapy to control tumor progression and enhance antitumor immunity.

Natural killer (NK) cells and tumor associated macrophages (TAMs) constitute major components of the TME and are closely related to tumor immunity (7,8). Natural killer cells are highly heterogeneous, and their functions depend on a dynamic balance between activating and inhibitory receptors (9). CD56 is the most important biomarker for distinguishing NK cells from other immune cells in TME (10).

Tumor associated macrophages (TAMs) can differentiate into either M1 or M2 polarized macrophages, which have opposing effects on tumor progression. M2 macrophages produce chemokines and proteolytic enzymes promoting tumor cell proliferation, migration, angiogenesis, and metastasis (11). CD163 could be a highly specific monocyte/macrophage marker for polarized M2 macrophages (12).

This study aimed to investigate the immunohistochemical expression of CD155 in relation to clinicopathological parameters of the studied BC cases. Moreover, we investigated the density of tumor infiltrating NK cells and TAMs in relation to clinicopathological patients' characteristics. The study was extended to investigate the correlation between CD155 expression and the densities of immune cells in TME to explore its role in tumor immune modulation.

Materials and Methods

This retrospective study included 85 cases of invasive breast carcinoma (IBC) retrieved from the archives of Pathology Department, Faculty of Medicine, Tanta University during the period from January 2022 to January 2025. IBC cases with full clinicopathological data and sufficient tissue in paraffin blocks were considered eligible for inclusion in the study. Whereas patients who previously received neoadjuvant chemotherapy, hormonal therapy or radiotherapy were excluded from the study.

Clinicopathological data

All cases were females. Clinical data were obtained from requisition sheets enclosed with the specimens or from the final pathology reports including age, tumor size, laterality, multiplicity hormonal receptors status and molecular subtypes of the tumor.

Histopathological evaluation

The paraffin blocks were serially sectioned (3–5 μm thick sections) and stained with Hematoxylin and eosin, then reviewed to confirm the diagnosis. The routine histopathological examination included assessment of the morphologic appearance of the tumor to identify the histological type, grade, presence of lymphovascular invasion, as well as determining lymph node status and pathological stage of the tumor.

Cases were classified according to the 2019 WHO classification of IBC (13). Nottingham Grading System (NGS) was adopted for grading of cases (14,15). Pathological stage for the studied cases was determined according to 8th edition of TNM staging adopted by the American Joint committee on Cancer (AJCC) (16). Molecular subtypes of the studied cases were determined according to the guidelines of the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) (17).

Immunohistochemical staining

Immunohistochemical staining was performed in Dako Autostainer Link 48 using paraffin embedded sections, cut at 3–5 μm, on positive charged slides using CD155 (rabbit monoclonal antibody, clone ARC59175, Catalog No. A23084, ABclonal Technology, USA), CD56 (ready-to-use monoclonal mouse antibody, clone 123C3, Catalog No. IR628, Dako, USA), and CD163 (rabbit polyclonal antibody, Catalog No. A8383, ABclonal Technology, USA). Deparaffinization and antigen retrieval through Dako PT Link unit along with treatment with peroxidase blocking reagent for 5 min were done before incubation with the primary antibodies for 30 min. Subsequently, slides were incubated with horseradish peroxidase polymer reagent for 20 min and diaminobenzidine chromogen for 10 min. Slides were then counterstained with haematoxylin.

Interpretation of CD155 immunostaining

CD155 immunoreactivity was evaluated in the membrane of the tumor cells. Five randomly chosen fields were assessed. An immunoreactivity score (IRS) was used with values from 0 to 12, calculated as follows; IRS = staining intensity × percentage of positive tumor cells. The intensity of staining was scored as follows: 0; negative staining, 1; weak staining, 2; moderate staining and 3; strong staining. The percentage of positive tumor cells was scored as follows: 0; no staining of cells, 1; < 25%, 2; 25–50%, 3; 50–75% and 4; > 75%. An IRS of ≥2 was considered positive, while IRS of < 2 was considered negative CD155 immunostaining (18).

Interpretation of CD56 immunostaining

CD56 immunostaining was assessed as membranous and/ or cytoplasmic expression in tumor-infiltrating NK cells. CD56 immunoreactivity was evaluated by counting the number of positive cells in tumor stroma. CD56 + cells were counted in 10 randomly selected high-power fields (HPF) (x400) using the plug-in "cell counter" in image analysis software Fiji (ImageJ bundled with plugins) (http://fiji.sc). Cases were then divided into negative/ low density group (≤5 CD56 stained cells in 10 HPFs) and high-density group (> 5 CD56 stained cells in 10 high HPFs) (19).

Interpretation of CD163 immunostaining

CD163 immunostaining was assessed as membranous or cytoplasmic immunostaining in macrophages within tumor stroma (20). For each case, three hot spots with highest infiltration by CD163 positive macrophages were selected for counting TAMs. Only cells with monocytoid, macrophage –like morphology were counted. Photographs of the selected areas in a high-power field (x400) were captured, and TAMs were counted in tumor stroma using the plug-in "cell counter" in image analysis software Fiji (http://fiji.sc). The mean value of TAMs was used as a representative for the density of TAMs in each case (21). The median value of TAMs of all cases was applied as cut off point to divide cases into negative/low and high TAMs density groups (22).

Statistical analysis

Tabulated results were statistically analysed using SPSS v26 (IBM©, Chicago, IL, USA). Data were presented as mean ± SD for numerical variables and frequencies for categorical ones. Analysing the relations between CD155 expression, the density of tumor infiltrating NK cells, and the density of TAMs with clinicopathological variables was carried out using chi-square ($\chi 2$). Monte-Carlo test was used when appropriate. Student t-test was used to assess difference between groups in numerical data. Correlation between CD155 expression and density of TAMs and tumor infiltrating NK cells was evaluated using Pearson's correlation coefficient. P value < 0.05 was considered statistically significant.

Results

Clinicopathological results.

The current study included 85 cases of IBC; the clinicopathological features are demonstrated in (Table 1).

Immunohistochemical results.

CD155 expression in the studied IBC cases.

CD155 positive expression was detected as membranous staining in tumor cells in 45 cases (52.9%) of the studied cases (Fig. 1). CD155 immunohistochemical expression was significantly associated with larger tumor size (p= 0.001), higher tumor grade (p= 0.001), presence of LVI (p <0.001), presence of nodal metastasis (p <0.001), advanced tumor stage (p <0.001) and aggressive molecular subtypes (p= 0.018). The relation of CD155 immunohistochemical expression to clinicopathological parameters are summarized in (Table 2).

Table 1. Clinicopathological data of the studied invasive breast carcinoma cases

	Total N (%)
Age (years)	
Mean ± SD	55.37 ± 12.24
Range	30-80
< 50	28 (27.1)
≥ 50	57 (72.9)
Tumor size (cm)	
≤ 2cm	16 (18.8)
>2cm - ≤5cm	51 (60)
>5cm	18 (21.2)
Histopathological types	
IBC NST	46 (54.1)
Lobular carcinoma	16 (18.8)
Tubular carcinoma	2 (2.3)
Cribriform carcinoma	1 (1.2)
Mucinous carcinoma	5 (5.9)
Metaplastic carcinoma	6 (7.1)
Mixed IBC NST and lobular carcinoma	5 (5.9)
Invasive papillary carcinoma	4 (4.7)
Pathological grade	
Grade 1	7 (8.2)
Grade 2	48 (56.5)
Grade 3	30 (35.3)
Lymphovascular invasion	
Present	59 (69.4)
Absent	26 (30.6)
Lymph node status	
N0	35 (41.2)
N1	12 (14.1)
N2	22 (25.9)
N3	16 (18.8)
Pathological stage	
Stage I	12 (14.1)
Stage II	30 (35.3)
Stage III	43 (50.6)
Molecular subtypes	
Luminal A	30 (35.3)
Luminal B	15 (17.6)
HER2-enriched	17 (20)
TNBC	23 (27.1)

SD; standard deviation, IBC NST; invasive breast carcinoma/ no special type, N; lymph node status, TNBC; triple negative breast cancer

CD56 expression in tumor infiltrating NK cells in the studied IBC cases

CD56 immunostaining was assessed as membranous and/or cytoplasmic immunostaining in tumor infiltrating natural killer cells (Fig. 2). Twenty-six cases (30.6%) exhibited high density of CD56 tumor-infiltrating NK cells, while 59 cases (69.4%) had negative/low density. The density of CD56 tumor infiltrating NK cells was significantly associated with larger tumor size (p= 0.004), higher tumor grades (p= 0.025), and aggressive molecular subtypes of invasive breast carcinoma (p= 0.040).

The relation of CD56 expression in tumor infiltrating NK cells to clinicopathological parameters are summarized in (Table 3).

CD163 expression in stromal TAMs in the studied IBC cases

CD163 immunostaining was assessed as membranous or cytoplasmic immunostaining in macrophages within tumor stroma (Fig. 3). Forty-seven cases (55.3%) had high density of CD163 stromal TAMs while 38 cases (44.7%) showed negative/low density. The density of CD163 stromal TAMs was significantly associated with larger tumor size (p= 0.016), higher tumor grades (p= 0.003), advanced tumor stages (p <0.001), the presence of LVI (p <0.001), presence of nodal metastasis (p <0.001) and aggressive molecular subtypes (p =0.003).

The relation of CD163 expression in TAMs to clinicopathological parameters are summarized in (Table 4).

Correlation between CD155 expression in tumor cells and density of CD56 stained tumor infiltrating NK cells, and CD163 stained TAMs in tumor stroma.

A statistically significant moderate positive correlation was detected between CD155 expression and CD56 tumor infiltrating NK cells density (r= 0.535; P < 0.001). In addition, a statistically significant strong positive correlation was detected between CD155 expression and CD163 TAMs density (r= 0.652; P <0.001) as illustrated (Fig. 4.).

Table 2. Relation between CD155 expression and the clinicopathological parameters of the studied invasive breast carcinoma cases.

	Total	CD155 expression		P value
		Negative N=40 (%)	Positive N=45 (%)	
Age (years)				
Mean ± SD		53.12 ± 12.18	57.02 ± 12.68	0.135
<50	28	14 (50)	14 (50)	0.703
≥50	57	26 (45.6)	31 (54.4)	
Tumor size (cm)				
≤ 2cm	16	13 (81.3)	3 (18.7)	0.001*
>2cm - ≤5cm	51	24 (47.1)	27 (52.9)	
>5cm	18	3 (16.7)	15 (83.3)	
Histological types				
IBC NST	46	22 (47.8)	24 (52.2)	0.439
Lobular carcinoma	16	9 (56.3)	7 (43.7)	
Tubular carcinoma	2	2 (100)	0 (0)	
Cribriform carcinoma	1	1 (100)	0 (0)	
Mucinous carcinoma	5	2 (40)	3 (60)	
Metaplastic carcinoma	6	1 (16.7)	5 (83.3)	
Mixed IBC NST and lobular carcinoma	5	2 (40)	3 (60)	
Invasive papillary carcinoma	4	1 (25)	3 (75)	
Pathological grade				
Grade 1	7	7 (100)	0 (0)	0.001*
Grade 2	48	24 (50)	24 (50)	
Grade 3	30	9 (30)	21 (70)	
Lymphovascular invasion				
Present	59	19 (32.2)	40 (67.8)	<0.001*
Absent	26	21 (80.8)	5 (19.2)	

	Total	CD155 expression		P value
		Negative N=40 (%)	Positive N=45 (%)	
Lymph node status				
N0	35	27 (77.1)	8 (22.9)	<0.001*
N1	12	3 (25)	9 (75)	
N2	22	6 (27.3)	16 (72.7)	
N3	16	4 (25)	12 (75)	
Pathological staging				
Stage I	12	11 (91.7)	1 (8.3)	<0.001*
Stage II	30	18 (60)	12 (40)	
Stage III	43	11 (25.6)	32 (74.4)	
Molecular subtypes				
Luminal A	30	20 (66.7)	10 (33.3)	0.018*
Luminal B	15	8 (53.3)	7 (46.7)	
HER2-enriched	17	4 (23.5)	13 (76.5)	
TNBC	23	8 (34.8)	15 (65.2)	

*Significant p value, SD; standard deviation, IBC NST; invasive breast carcinoma/ no special type, N; lymph node status, TNBC; triple negative breast cancer

Table 3. Relation between the density of CD56 tumor infiltrating NK cells and the clinicopathological parameters of the invasive breast carcinoma cases studied.

	Total	CD56 positive tumor infiltrating NK cells/10 HPF		P value
		Negative/low density N=59 (%)	High density N=26 (%)	
Age (years)				
Mean ± SD		53.69 ± 11.97	58.58 ± 13.32	0.098
<50	28	20 (71.4)	8 (28.6)	0.777
≥50	57	39 (68.4)	18 (31.6)	
Tumor size (cm)				
≤2cm	16	14 (87.5)	2 (12.5)	0.004*
2-5 cm	51	38 (74.5)	13 (25.5)	
>5 cm	18	7 (38.9)	11 (61.1)	
Histopathological types				
IBC NST	46	31 (67.4)	15 (32.6)	0.134
Lobular carcinoma	16	15 (93.8)	1 (6.2)	
Tubular carcinoma	2	2 (100)	0 (0)	
Cribriform carcinoma	1	1 (100)	0 (0)	
Mucinous carcinoma	5	3 (60)	2 (40)	
Metaplastic carcinoma	6	2 (33.3)	4 (66.7)	
Mixed IBC NST and lobular carcinoma	5	3 (60)	2 (40)	
Invasive papillary carcinoma	4	2 (50)	2 (50)	
Pathological grade				
Grade 1	7	7 (100)	0 (0)	0.025*
Grade 2	48	36 (75)	12 (25)	
Grade 3	30	16 (53.3)	14 (46.7)	

	Total	CD56 positive tumor infiltrating NK cells/10 HPF		P value
		Negative/low density N=59 (%)	High density N=26 (%)	
Lymphovascular invasion				
Present	59	42 (71.2)	17 (28.8)	0.593
Absent	26	17 (65.4)	9 (34.6)	
Lymph node status				
N0	35	27 (77.1)	8 (22.9)	0.095
N1	12	5 (41.7)	7 (58.3)	
N2	22	17 (77.3)	5 (22.7)	
N3	16	10 (62.5)	6 (37.5)	
Pathological stage				
Stage I	12	10 (83.3)	2 (16.7)	0.177
Stage II	30	23 (76.7)	7 (23.3)	
Stage III	43	26 (60.5)	17 (39.5)	
Molecular subtypes				
Luminal A	30	26 (86.7)	4 (13.3)	0.040*
Luminal B	15	11 (73.3)	4 (26.7)	
HER2 enriched	17	9 (52.9)	8 (47.1)	
TNBC	23	13 (56.5)	10 (43.5)	

*Significant p value, SD; standard deviation, IBC NST; invasive breast carcinoma/ no special type, N; lymph node status, TNBC; triple negative breast cancer

Table 4. Relation between the density of 163 positive stromal TAMs and the clinicopathological parameters of the studied invasive breast carcinoma cases.

	Total	CD163 positive stromal TAMs/ HPF		P value
		Negative/low density N=38 (%)	High density N=47 (%)	
Age (years)				
Mean ± SD		53.55 ± 12.34	56.51 ± 12.65	0.282
<50	28	13 (46.4)	15 (53.6)	0.823
≥50	57	25 (43.9)	32 (56.1)	
Tumor size (cm)				
≤2cm	16	12 (75)	4 (25)	0.016*
2-5 cm	51	21 (41.2)	30 (58.8)	
>5 cm	18	5 (27.8)	13 (72.2)	
Histopathological types				
IBC NST	46	19 (41.3)	27 (58.2)	0.229
Lobular carcinoma	16	10 (62.5)	6 (37.5)	
Tubular carcinoma	2	2 (100)	0 (0)	
Cribriform carcinoma	1	1 (100)	0 (0)	
Mucinous carcinoma	6	1 (20)	4 (80)	
Metaplastic carcinoma	6	1 (16.7)	5 (83.3)	
Mixed IBC NST and lobular carcinoma	5	2 (40)	3 (60)	
Invasive papillary carcinoma	4	2 (50)	2 (50)	

	Total	CD163 positive stromal TAMs/ HPF		
		Negative/low density N=38 (%)	High density N=47 (%)	P value
Pathological grade				
Grade 1	7	6 (85.7)	1 (14.3)	0.003*
Grade 2	48	25 (52.1)	23 (47. 9)	
Grade 3	30	7 (23.3)	23 (76.7)	
Lymphovascular invasion				
Present	59	17 (28.8)	42 (71.2)	<0.001*
Absent	26	21 (80.8)	5 (19.2)	
Lymph node status				
N0	35	26 (74.3)	9 (25.7)	<0.001*
N1	12	4 (33.3)	8 (66.7)	
N2	22	5 (22.7)	17 (77.3)	
N3	16	3 (18.7)	13 (81.3)	
Pathological stage				
Stage I	12	10 (83.3)	2 (16.7)	<0.001*
Stage II	30	18 (60)	12 (40)	
Stage III	43	10 (23.3)	33 (76.7)	
Molecular subtypes				
Luminal A	30	21 (70)	9 (30)	0.003*
Luminal B	15	6 (40)	9 (60)	
HER2 enriched	17	3 (17.6)	14 (82.4)	
TNBC	23	8 (34.8)	15 (65.2)	

*Significant p value, SD; standard deviation, IBC NST; invasive breast carcinoma/ no special type, N; lymph node status, TNBC; triple negative breast cancer

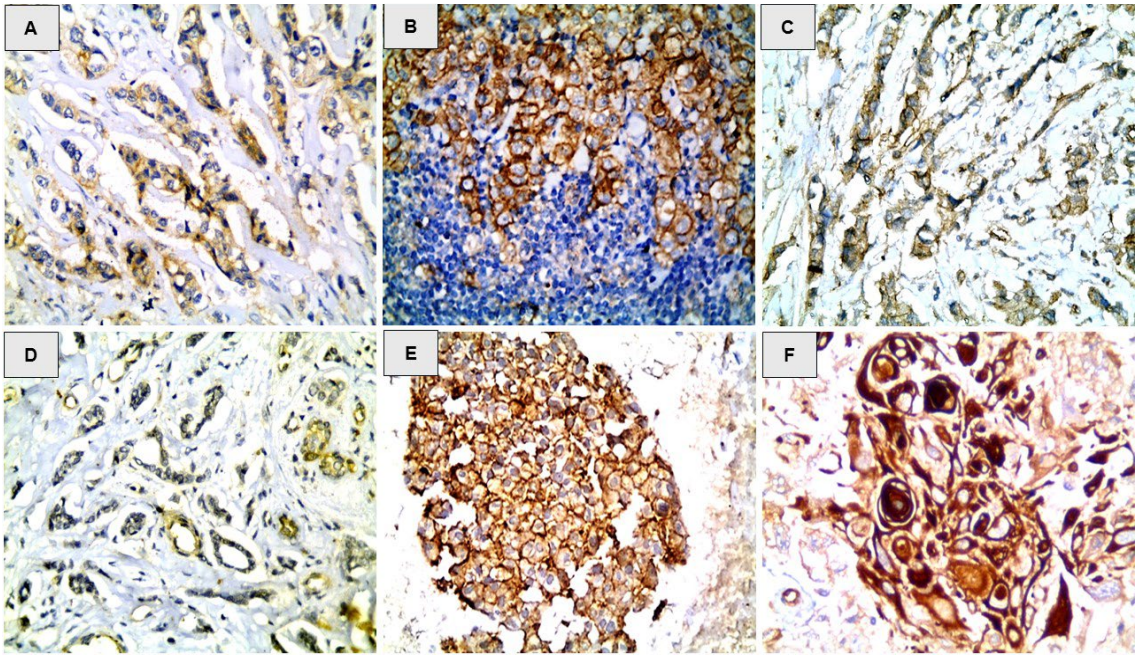

Fig. 1. CD155 expression in IBC (x400). (A) Positive expression (IRS=6) in IBC-NST, grade 2. (B) Positive expression (IRS=12) in IBC (medullary pattern), grade 3 (C) Positive expression (IRS=8) in pleomorphic lobular carcinoma, grade 3. (D) Negative expression (IRS=1) in tubular carcinoma, grade 1. (E) Positive expression (IRS=12) in mucinous carcinoma, grade 2. (F) positive expression (IRS=12) in metaplastic carcinoma, grade 3. IBC-NST; invasive breast carcinoma of no special type, IRS; immunoreactivity score

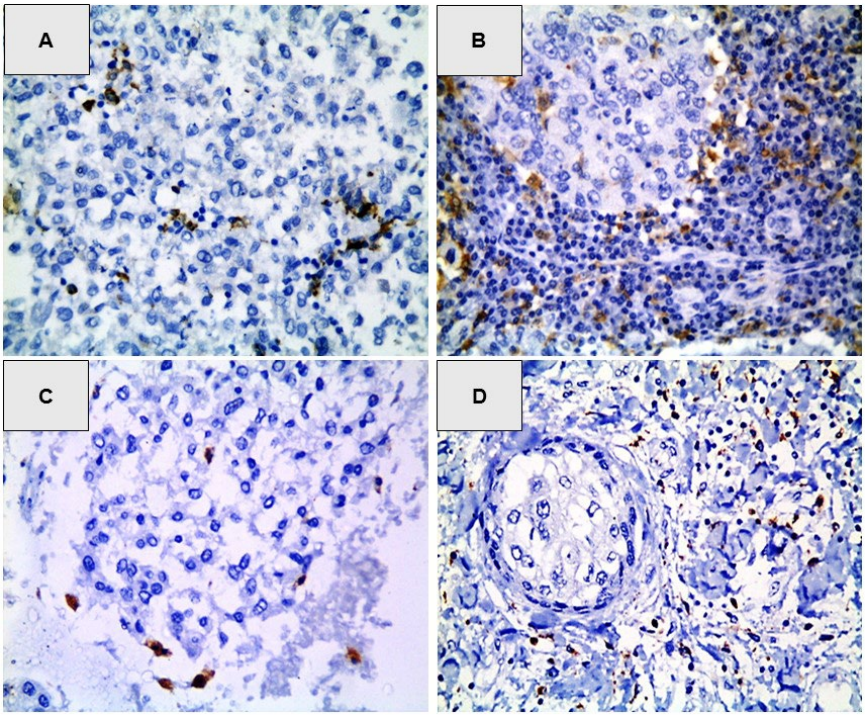

Fig. 2. CD56 expression in tumor infiltrating NK cells in IBC (x400). (A) High density in IBC-NST, grade 3. (B) High density in IBC (medullary pattern), grade 3. (C) Low density in mucinous carcinoma, grade 2. (D) High density in metaplastic carcinoma, grade 3. IBC-NST; invasive breast carcinoma of no special type, NK; natural killer

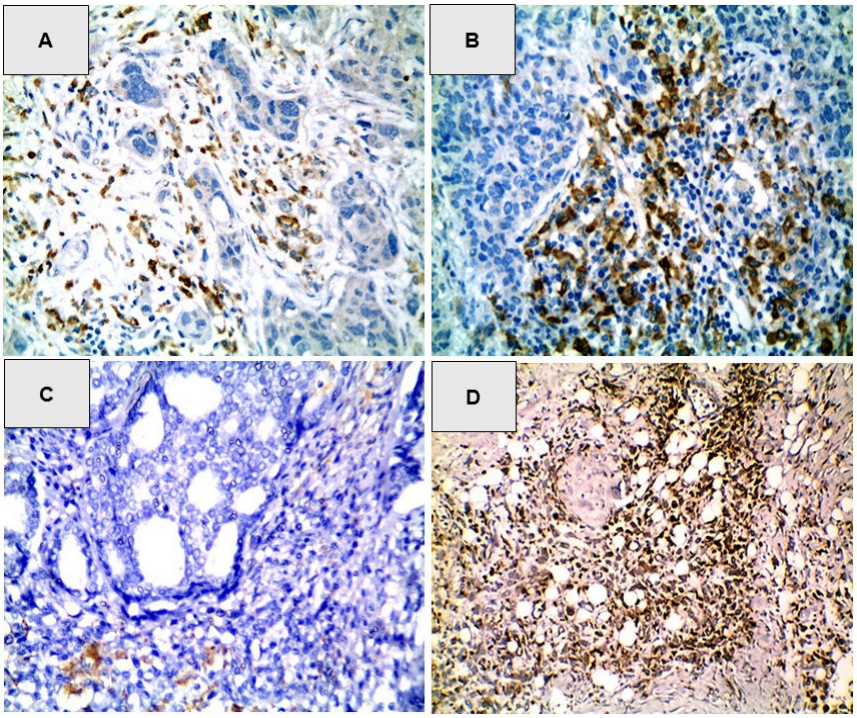

Fig. 3. CD163 expression in stromal TAMs in IBC. (A) High density in IBC-NST, grade 3 (x400). (B) High density in IBC (medullary pattern), grade 3 (x400). (C) Low density in cribriform carcinoma grade 1 (x400). (D) High density in metaplastic carcinoma, grade 3 (x200). IBC-NST; invasive breast carcinoma of no special type, TAMs; tumor associated macrophages

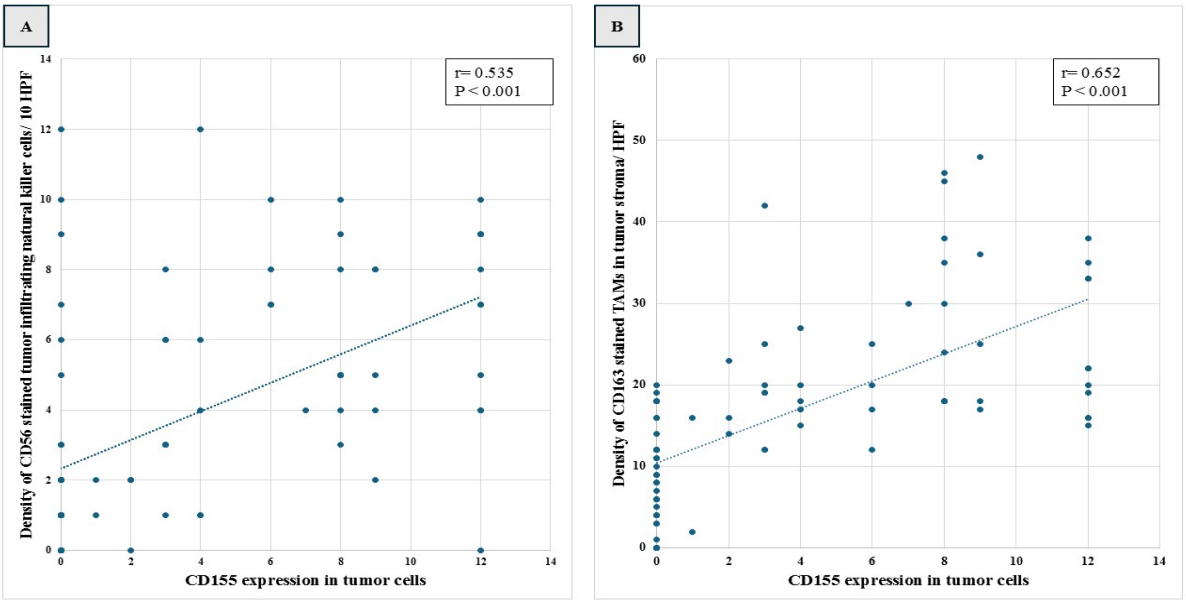

Fig. 4. (A) Correlation between CD155 expression in tumor cells and density of CD56 stained tumor infiltrating natural killer cells. (B) Correlation between CD155 expression in tumor cells and density of CD163 stained TAMs in tumor stroma. NK cells; natural killer cells, TAMs; tumor associated macrophages, HPF; high power field

Discussion

Breast cancer is highly heterogeneous disease with complex and diverse TME (23). Previous research has focused on tumor cells as main target for antitumor therapy. However, the interaction between tumor cells and adjacent stromal or immune cells has gained attention in recent years as therapeutic target to improve patient outcome (24).

CD155 has attracted attention as an immune checkpoint molecule that can initiate either stimulatory or inhibitory tumor immune response (25). Therapies focusing on antibodies that target checkpoints molecules have significantly improved outcomes for different malignant tumors, including breast cancer (26,27).

In the current study, CD155 positive expression was significantly related to larger tumor size. These results are in concordance with Yong et al. (8). In contrast, a study by Yoshikawa et al. (28) revealed lack of a significant relation between CD155 positive expression and tumor size in TNBC. Moreover, CD155 positive expression was significantly higher in poorly differentiated studied IBC cases. This is in line with other studies (19,29,30).

The association between CD155 expression with higher tumor grades can be explained by cooperation between CD155-mediated signals and growth factors derived signals to regulate tumor cell proliferation and differentiation (31). CD155 synergizes with platelet derived growth factor (PDGF) potentiating the Ras-Raf-MEK-ERK signalling pathway to promote cell proliferation (32).

Moreover, the present study revealed a statistically significant relation between CD155 expression and the presence of LVI. Similar findings were observed by Shibel & Abd Elmaogod (30); however, their results didn't reach a significant level. This may be explained by CD155 ability to facilitate angiogenesis through interaction with vascular endothelial growth factor (VEGF) receptor directly or indirectly via controlling the interaction of VEGF receptors with other molecules, including integrin, mediating VEGF-induced angiogenesis (33).

In agreement with Yong et al. (8), the present study revealed a significant relation between CD155 expression and LN involvement. CD155 was negative in most cases lacking nodal metastasis (N0). In contrast, Triki et al. (19), and Shibel & Abd Elmaogod (30) revealed a lack of a significant relation between CD155 expression and nodal metastasis. Moreover, CD155 positive expression significantly increased with advancing tumor stages of the studied cases. Similar results were obtained by Yong et al. (8) and Shibel & Abd Elmaogod (30), but their results were statistically insignificant. CD155 up-regulation can be considered as an advantage for tumor growth as it represents a pro-oncogenic molecule favouring proliferative signals and tumor growth along with cancer cell invasion and metastasis (4,5).

In good consistency with its association with poor prognostic parameters, the present study revealed a statistically significant relation between CD155 expression and aggressive molecular subtypes of IBC. Similar to these results, Li et al. (29), and Zheng et al. (18) reported higher expression of CD155 in TNBC molecular subtype of their studied cases. However, Triki et al. (19) didn't reveal a significant difference in CD155 expression among different molecular subtypes of IBC. The higher CD155 expression in non- luminal

cases suggests that such poor prognosis cases could benefit from CD155 targeted therapy.

Natural killer (NK) cells constitute a major component of the TME and are closely related to tumor immunity (9). In the present study, 30.6% of cases expressed high density of CD56 tumor-infiltrating NK cells. These results are close to other studies (19,30,34).

The present study revealed a statistically significant relation between the density of CD56 tumor infiltrating NK cells and tumor size, which is in agreement with results obtained by others (19,30,34,35); however, their results didn't reach a statistical significance. Moreover, high density of tumor infiltrating NK cells was significantly more predominant in poorly differentiated compared to well differentiated tumors. Similar findings were demonstrated by others (19,30,34,35).

Interestingly, although NK cells have potent killing abilities against transformed cells, the TME can inhibit NK cell function via production of soluble modulators such as transforming growth factor (TGF)-β, and prostaglandin E2 (PGE2). Moreover, the low nutrient levels, and hypoxic conditions negatively regulate maturation, proliferation, activation, and effector function of NK cells (36). Consequently, NK cells undergo functional exhaustion and become dysfunctional with limited release of effector cytokines and decreased ability to kill malignant cells contributing to tumor growth, progression and loss of differentiation (37). Dealing with the distribution of tumor infiltrating NK cells in different molecular subtypes, the current work demonstrated that high NK cells density was significantly more observed in TNBC and Her2/neu enriched breast cancer, compared to luminal tumors. These findings are consistent with other studies (19,30,34).

Tumor associated macrophages (TAMs) constitute critical component of the TME that play an essential role in tumor immunity (38). High density of CD163+ stromal TAMs was detected in 55.3% of the studied cases in this work. This is close to the results obtained by other studies (39,40).

In the current work, high density of CD163+ stromal TAMs was significantly associated with larger tumor size and higher tumor grade. These results are in line with other studies (40-44). In contrast, Sousa et al. (39) and Jeong et al. (21) didn't detect a significant relation between CD163+ stromal TAMs density and tumor size.

The previous findings can be supported by the complex interplay between tumor cells and TAMs. High-grade tumors produce higher levels of monocyte colony stimulating factor, interleukin 10 (IL-10), and TGF-β, which results in recruiting high number of M2 macrophages in TME (39). In turn, TAMs secrete different cytokines and growth factors that provide mitogenic signals to malignant cells contributing to high proliferation and dedifferentiation of tumor cells (45, 46).

In the present work, high density of TAMs was significantly more detected in cases with LVI and nodal metastasis. These results agree with other studies (40,42,43, 44 ,47). Moreover, Ye et al. (48) reported that high infiltration of CD163+ stromal TAMs was significantly associated with nodal metastasis in TNBC. Contradictory to these results, Sousa et al. (39), Jeong et al. (21) and Omilian et al. (44) revealed no significant relation between density of CD163+ stromal TAMs and lymph node involvement in IBC. Furthermore, the present study revealed that the high density was significantly related to advanced tumor stages. These results agreed with those of Mwafy & El-Guindy (40) and Omilian et al. (44). On the other hand, these findings are inconsistent with those of Ni et al. (49).

The previous findings can be explained by the role of M2 TAMs in induction of angiogenesis and vascular dissemination of the tumor cells through expression and production of VEGF, TGF-β, angiogenesis chemokine (CXCL12), and PDGF (50). Moreover, TAMs enhance tumor invasion through the basement membrane by production or activation of several proteolytic enzymes such as cathepsin B and extracellular matrix metalloproteinase inducer (EMMPRIN) (51). TAMs could also activate endothelial cells and stimulate existing lymphatic endothelial cells proliferation and thus facilitating LN metastasis (52).

In the current work, most of Her2 enriched and TNBC were associated with high density of CD163 positive TAMs. These results are consistent with other studies (40,43,44). Stossi et al. (53) demonstrated that conditioned media from macrophages could stimulate different pathways inside breast cancer cells which was crucial for downregulation of ER expression. Furthermore, You et al. (54) reported that HER2 overexpression in IBC leads to significant increase in the secretion of several cytokines, particularly Chemokine (C-C motif) ligand 2 (CCL2), which further enhance TAMs recruitment and production of pro-inflammatory cytokines from M2 TAMs, thereby promoting tumorigenesis.

As CD155 exhibits a complex immuno-regulatory function on various immune cells within TME, the current work investigated the correlation between CD155 expression on tumor cells and the density of immune cells in the TME. A statistically significant moderate positive correlation (r=0.535) was detected between CD155 expression and the density of CD56 tumor infiltrating NK cells. This finding agreed with Shibel & Abd Elmaogod (30) and Triki et al. (19). Moreover, Liu et al. (55) revealed a moderate positive correlation between CD155 expression and CD56 positive cells in TME in gastric adenocarcinoma.

A study by Chauvin et al. (56) demonstrated that membranous CD155 induces DNAM-1 internalization and degradation, thereby reducing its stimulatory effect

on NK cells and shifting the receptor balance toward inhibitory interactions with T cell immunoreceptors with IG and ITIM domain (TIGIT). Additionally, tumor cells may produce soluble CD155 to inhibit DNAM-1+ NK cells without direct contact (57). Binding of TIGIT to CD155 transduces inhibitory signals that suppress DNAM-1-mediated cytotoxic function. Thus, elevated levels of both CD155 and TIGIT may contribute to an immunosuppressive environment, providing a mechanism for immune evasion (5).

Furthermore, this study revealed a statistically significant strong positive correlation between CD155 expression on tumor cells and the density of CD163 TAMs in TME (r=0.652). This is in line with Yong et al. (8). Moreover, a study by Jin et al. (58) revealed that high serum CD155 level was correlated with increased number of CD163+M2 macrophages in hepatocellular carcinoma. CD155 may influence tumor progression by inhibiting M1 macrophage function and promoting M2 macrophage polarization (55). TIGIT directly interacts with CD155, resulting in reduced M1 macrophage-mediated cytotoxicity and decreased expression of pro-inflammatory genes such as tumor necrosis factor alpha (TNFα), and IL-12 (59). Additionally, cisplatin-resistant lung cancer cells have been shown to promote M2 polarization of TAMs through the Src/CD155/macrophage inhibitory factor, which contributes to cancer progression (60).

Conclusion

CD155 may serve as a poor prognostic indicator in patients with IBC that contributes to tumor progression, invasion, and metastasis. High density of CD56 positive tumor infiltrating NK cells, and CD163 positive stromal TAMs can be considered as poor prognostic parameters in IBC cases. CD155 expression in tumor cells had significant positive correlation with the density of CD56 positive tumor infiltrating NK cells, and CD163 positive stromal TAMs. Therefore, CD155 may play an important immunoregulatory role in the TME.

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Authors' Contributors

AA and FMKh contributed to the selection and diagnosis of cases. In addition, they contributed to writing the manuscript, performing histopathological examination, and assessment of the immunohistochemical results. RO, AA, and KE revised the diagnosis of the cases, interpretations of the markers and manuscript writing. All authors read and approved the final manuscript.

Data Availability

The datasets generated and analyzed during the current study are not publicly available; however, the data can be shared for research and authentication purposes upon reasonable request.

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Ethics Approval

Approval from the research ethics committee, Faculty of Medicine, Tanta University, Egypt with approval code (34846/8/21) was taken antecedent to conducting of the study.

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Conflict of Interest

The authors declared no conflict of interest.

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