Zagazig University Medical Journal
www.zumj.journals.ekb.eg

DOI 10.21608/zumj.2019.15879.1421 General Surgery

ORIGINAL ARTICLE

Immunohistochemical expression of programmed death-ligand 1 (PD-L1) in invasive duct Carcinoma of the breast of no special type and correlation with patients' clinicopathological parameters

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ABSTRACT

Background: Breast cancer is still the most significant cancer-causing mortality among females around the world. Invasive duct carcinoma of no special type is the most prevalent type of breast cancer. So it is essential to search for novel and promising markers detected by immunohistochemistry helping in the prognosis of cancer breast.

Aim of the study: To evaluate programmed death-ligand 1 (PD-L1) immunohistochemical expression in invasive ductal carcinoma of the breast of no special type (IDC NST) and to analyze the correlation between PD-L1 expression and clinicopathological parameters of cases.

Materials and Methods: A cross-sectional study was conducted on eighty patients diagnosed with IDC NST enrolled in this study during the period from January 2017 to May 2019 at Zagazig University Hospitals. All lesions were submitted for immunohistochemical analysis using PD-L1 antibody (rabbit monoclonal antibody clone CAL 10), and PD-L1 expression was assessed. Results were correlated with clinicopathological parameters. The resulted data were statistically analyzed.

Results: PD-L 1 expression was detected by immunohistochemistry in 30% (24/80) of breast cancer cases. PD-L1 expression was significantly correlated with well-perceived parameters of poor prognosis, including youthful patient age, high tumor grade, Estrogen and progesterone receptors negative status, necrosis and lymphovascular invasion ($p< 0.001$, $= 0.004$, <0.001, < 0.001, < 0.001 respectively).

Conclusions: Expression of PD-L1 in breast cancer by immunohistochemistry correlates with poor clinicopathologic parameters. PD-L1 may have a valuable prognostic role in breast carcinoma, especially in triple negative subtype.

Key Words: Invasive duct carcinoma, NST, breast, Immunohistochemistry, PD-L1.

INTRODUCTION

Breast cancer is the commonest widely recognized cancer influencing females around the world. Breast, lung, and colorectal cancers have the most common tumors incidence in women, which all represent one-half of all new diagnoses, breast cancer alone records for 30% (268,600 cases) of all new cancer cases in women [1]. Breast cancer is representing 38.8% of all female cancer cases in Egypt [2].

PD-L1 is an immune checkpoint regulatory molecule, several investigations have recently revealed that PD-L1 expression in many cancer types may have an integral and basic function in the interaction between tumor cells and host immune response which may prevent resistance to tumors by immune system [3].

Various previous studies recognized PD-L1 expression by immunohistochemistry in many solid tumors such as breast, ovarian, renal, pancreatic, and colorectal and lung cancers

which were associated with poor prognosis [4, 5, 6, 7, and 3].

As of late, the improvement of immunotherapy through the immune checkpoint blockage prompts immune reactions in several cancers which are unmanageable by standard treatments such as malignant melanoma or lung adenocarcinoma [8].

It was considered that breast cancers are less immunogenic contrasted with other tumor types [9], however, many studies declared that PD-L1 expression is observed in 20% of triple negative breast cancers [10].

Anti-PD-L1 monoclonal antibodies therapies have been tried in breast cancer, especially in the triple negative subtype which is an aggressive subtype with no hormonal targeted therapy, with promising outcomes reported when conveyed as monotherapy or in blend with traditional treatments [11].

MATERIALS AND METHODS

-Patients and tissue specimens

Eighty patients with IDC (NST) were enrolled in this study, during the period from January 2017 to May 2019 at general surgery and pathology departments in Zagazig University. The diagnosis of breast cancer was achieved through clinical examination followed by mammography, ultrasonography and eventually core biopsy. Specimens taken were 50 mastectomy specimens (modified radical mastectomy and breast conservation) and 30 were core biopsies. Clinico-pathological data including tumor size, site, and lymph nodes were collected by the general surgeon. Breast cancer clinical staging are based on (T, N, and M categorization) through a combination of clinical examination, ultrasound, and mammogram. Evaluation of Estrogen receptor (ER) expression, Progesterone receptor (PR) expression, and HER2-neu expression was done. Nuclear positive ER and PR expressions were considered if the stain is strong and present in more than 1% of tumor cell nuclei and Her2-neu was considered positive if the stain is circumferential, complete, intense and membranous in more than 10% of tumor cells.

Molecular classification of patients was as follow: 20 luminal A, 20 luminal B, 20 triple negative and 20 HER2-neu enriched types. After revision of H&E slides, the tumors were graded according to the Nottingham system for grading [12].

-Inclusion criteria

1- Female patients diagnosed with IDC of the breast (NST).
2- Collected accurate and complete Patient's clinicopathological data regarding: patient age, size of the tumor, histological grade, clinical stage, lymph node metastasis, Estrogen receptor expression, Progesterone receptor expression, HER2-neu expression, Ki-67 index

-Exclusion criteria

1. Other breast cancer special types.
2. Lobular carcinoma of the breast.
3. Patients who have other malignancies.

-Immunohistochemistry of PD-L1

Serial sections from the blocks were submitted for immunohistochemical staining with PD-L1. Sections 5 µm thick were cut, mounted on positively charged slides, the slides were deparaffinized and gradually rehydrated. Antigen retrieval was performed using Dako target retrieval solution (pH 6.0) boiled in a microwave. The sections were incubated overnight with the primary antibodies of PD-L1. Slides were incubated for 10 minutes in 0.3 % hydrogen peroxide to block endogenous peroxidase activity conjugated with a rabbit monoclonal antibody to PD-L1 (PD-L1Rb, isotope IgG, Clone CAL10 1:100 dilution, Biocare medical 4040 corporation, pike lane, concord, USA, catalogue number 94520) and visualized using Diaminobenzidine (DAB) chromogen solution. Finally, sections were counterstained with Mayer's hematoxylin and then rinsed in running tap water and phosphate-buffered saline.

(PBS). Universal kit designated to detect specific antigens in formalin fixed, paraffin embedded blocks (FFPE) using modified labeled Avidin-Biotin technique. Positive control (tonsil) and negative controls were used.

-Interpretation and evaluation of immunostaining

PD-L1 was considered positive when tumor cells with partial or complete cell membrane staining or cytoplasmic staining. PD-L1 positivity will be defined as >1% of positive

tumor cells [13, 14]. While scoring the percent of tumor cell positivity for PD-L1 staining intensity were ignored, the results were divided into three groups: zero staining were considered negative, 1-49% staining were considered low positive, 50-100%% staining were considered high positive [15, 16].

-Ethical Considerations

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Institutional Review Board (IRB) of the faculty of Medicine Zagazig University affirmed the study protocol (No. 3498) [17].

Statistical analysis and data management

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA. P-value < 0.05 was considered statistically significant (S).

RESULTS

The cases were distributed in the age group of 35□80 years, With the mean age was 55.3 years, 49/80 (61.3%) cases were grade 3, 29/80 (36.3%) cases were grade 2, 70/80 (87.5%) of cases showed lymph node metastasis, an associated intraductal component was seen in 28 cases (35%), evidence of lymphovascular invasion was detected in 45 cases (56.3%) and necrosis was noted in 27 cases (33.7%).

Immunohistochemical expression of PD-L1 in tumor cells among the studied patients (N=80).

The current study showed that the expression of PD-L1 was detected in 24/80 (30%) of the tumor cells, either membranous expression **(Figure 1 & Figure 2)** or cytoplasmic expression **(Figure 3),** with 9 (11.3%) cases showed low positive PD-L1 stain, and 15 (18.8%) cases showed high positive PD-L1 stain, while negative PD-L1 stain was observed in 35 cases (**Figure 4),** as shown in **Table 1.**

Figure 1

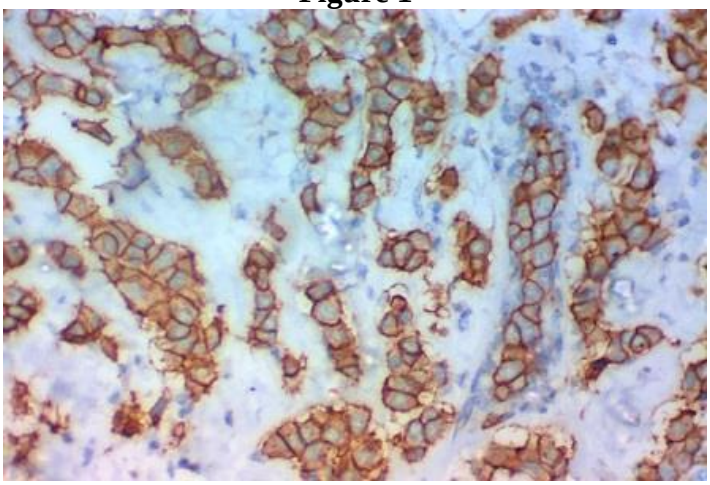

Figure 2

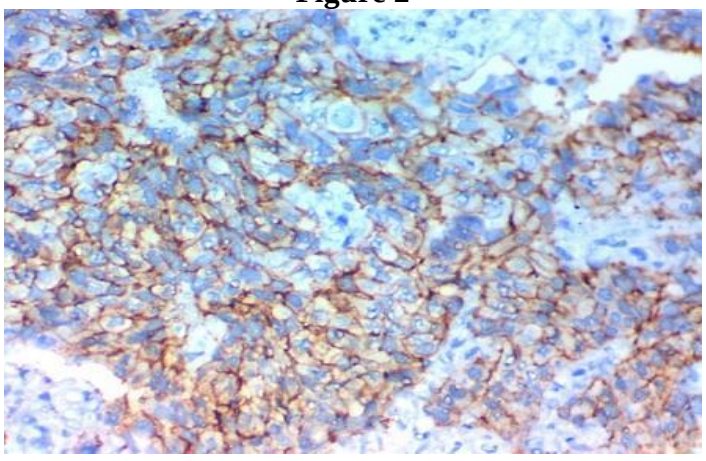

Figure 3

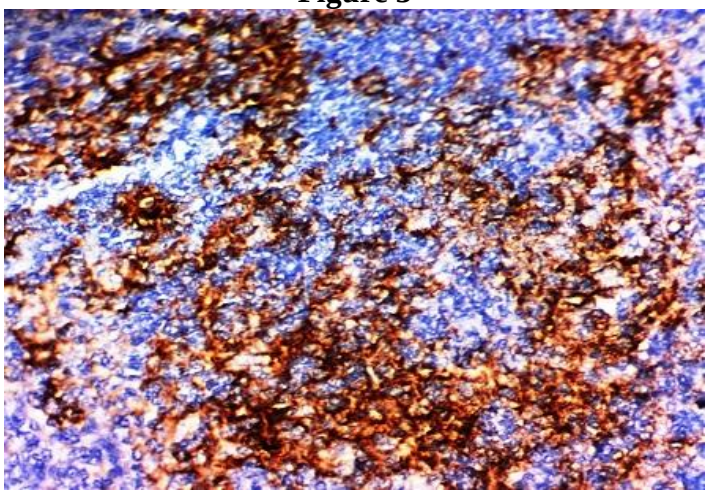

Figure 4

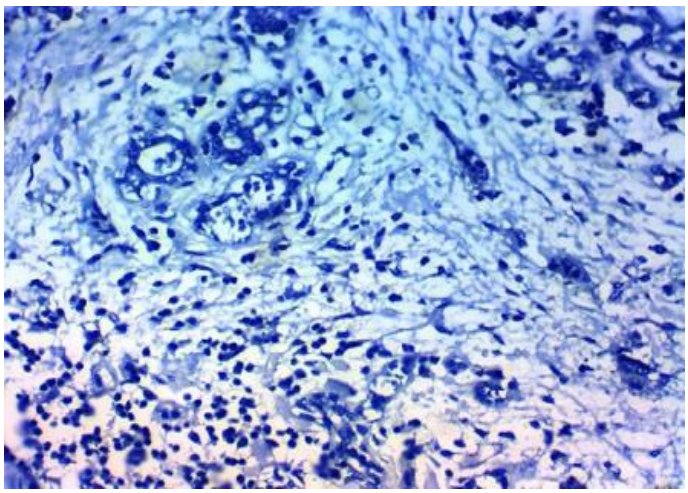

Table 1: Immunohistochemical expression of PD-L1 in tumor cells among the studied patients (N=80).

PD-L1 Immunohistochemical expression	All studied patients (N=80)	
	No.	%
Negative	56	70%
Low positive	9	11.3%
High positive	15	18.8%

Association between PD-L1 immunohistochemical expression in tumor cells and clinicopathological parameters of the studied patients (N=80).

The current study showed highly significant association was found between PD-L1 expression in tumor cells and poor clinicopathological parameters of breast cancer as young age less than 50 years, lymphovascular invasion, necrosis, and negative ER\PR status (p_{all}<0.001), also showed significant correlation with high grade (p<0.05), high Ki 67 index (p<0.05), and clinical stage (p=0.041) with no significant association were found with tumor size, lymph node status, and HER2 status (p_{all}>0.05) as shown in **Table 2.**

Table 2: Association between clinicopathological parameters and immunohistochemical expression of PD-L1 in breast cancer (N=80).

Clinico-pathological parameters		%	PDL1 immunohistochemical expression						Test	p-value
	Number		Negative (N=56)		Low positive (N=9)		High positive (N=15)			
			No.	%	No.	%	No.	%		
Age										
≤50 years	31	38.8%	13	41.9%	6	19.4%	12	38.7%	19.404§	<0.001 (HS)
>50 years	49	61.2%	43	87.8%	3	6.1%	3	6.1%		
Grade										
Grade I	2	2.5%	2	100%	0	0%	0	0%	8.307‡	0.004 (S)
Grade II	29	36.3%	25	86.2%	3	10.3%	1	3.4%		
Grade III	49	61.3%	29	59.2%	6	12.2%	14	28.6%		
Lymphovascular invasion										
Absent	35	43.8%	18	51.4%	3	8.6%	14	40%	18.448§	<0.001 (HS)
Present	45	56.3%	38	84.4%	6	13.3%	1	2.2%		
Intraductal components										
Absent	52	65%	39	75%	7	13.5%	6	11.5%	5.297§	0.071 (NS)
Present	28	35%	17	60.7%	2	7.1%	9	32.1%		
Necrosis										
Absent	53	66.3%	47	88.7%	4	7.5%	2	3.8%	28.527§	<0.001 (HS)
Present	27	33.8%	9	33.3%	5	18.5%	13	48.1%		
Lymph node metastasis										
Negative	10	12.5%	8	80%	0	0%	2	20%	1.459§	0.482 (NS)
Positive	70	87.5%	48	68.6%	9	12.9%	13	18.6%		
Clinical stage										
Stage I	7	8.8%	6	85.7%	0	0%	1	14.3%	4.176‡	0.041 (S)
Stage II	22	27.5%	10	45.5%	1	4.5%	11	50%		
Stage III	51	63.7%	40	78.4%	8	15.7%	3	5.9%		
ER/PR status										
Negative	40	50%	19	47.5%	6	15%	15	37.5%	21.786§	<0.001 (HS)
Positive	40	50%	37	92.5%	3	7.5%	0	0%		
HER2/neu status										
Negative	45	56.2%	27	60%	6	13.3%	12	26.7%	5.304§	0.070 (NS)
Positive	35	43.8%	28	80%	4	11.5%	3	5.7%		
Ki-67 index										
≤20%	23	28.7%	21	91.3%	2	8.7%	0	0%	8.333§	0.016 (S)
>20%	57	71.3%	35	61.4%	7	12.3%	15	26.3%		

Kruskal Wallis H test.
§ Chi-square test.
‡ Chi-square test for trend.
p< 0.05 is significant.
(S): significance.
(H.S): high significance.
(N.S): non significance.

Association between immunohistochemical expression of PD-L1and molecular subtypes of the studied patients (N=80).

In the current study, a highly significant correlation was found between PD-L1 expression and molecular subtypes (p <0.001). PD-L1 expression was observed mainly in hormone negative breast cancer as 15/20 (75%) of triple negative breast cancer cases (TNBC) showed positive PD-L1 expression in their tumor cells as shown in **Table 3.**

Table 3: Association between immunohistochemical expression of PD-L1 and molecular subtypes of breast cancer (N=80).

PDL1 expression	Molecular subtype								Test§	p-value
	Luminal A (N=20)		Luminal B (N=20)		HER2 enriched (N=20)		Triple negative (N=20)			
	No.	%	No.	%	No.	%	No.	%		
Negative	18	90%	20	100 %	13	65%	5	25%	39.260	<0.001 (HS)
Low positive	2	10%	0	0%	4	20%	3	15%		
High positive	0	0%	0	0%	3	15%	12	60%		

§ Chi-square test.
p< 0.05 is significant.
(HS): highly Significant**.**

DISCUSSION

Breast cancer is a heterogeneous disease with various hereditary adjustments that are being implicated in its growth pathogenesis; it varies greatly among different patients [18].

To avoid antitumor immunity, tumors utilize numerous mechanisms to keep away from recognition by the host immune system, which is the hallmark for the advancement and progression of cancers [19].

Ongoing investigations have announced that PD-L1 has a fundamental function in malignancy progression through restricting antitumor resistance by immune response via interaction with its receptor (PD-1) [20].

PD-L1 expressed on tumor cells and also in cells responsible for immunity such as T cells and B cells [21]. Expression of PD-L1 in the tumor cells associates immovably with the nearness of tumor-infiltrating lymphocytes to the tumor microenvironment [22, 23].

Clinical trials in many cancers testing the correlation between expression of PD-L1 in tumor cells and immunity with a promising approach for augmenting antitumor immunity [24].

Recently, the advancement in chemotherapy, radiotherapy, and immunotherapy has essentially improved breast cancer outcomes. Focusing on the PD-L1 pathway to upgrade antitumor resistance is under investigation in multiple human cancers. Presently, there are some continuous clinical preliminaries under investigation with monoclonal antibodies counteracting the PD-L1 pathway in breast cancer to enhance antitumor immunity, which is considered a novel idea in the immunotherapy treatment of breast cancer [25, 26].

Previous studies reported that PD-L1 expression present in breast cancer between 15.8% and 30 % [27,28,25,29], these results consistent with the present study results in which expression of PD-L1 was reported in 30% in tumor cells of breast cancer, which confirm that PD-L1 expression in breast cancer is lesser than its expression in other cancer types.

The ongoing study revealed that expression of PD-L1in breast cancer was significantly associated with young the age of patients lesser than 50, high tumor grade, areas of necrosis, negative ER/PR status, and high

proliferative Ki-67. Consistent with our findings the view of **Wimberley et al.** [22] who found that expression of PD-L1 was more common in age below 50, and results obtained by **Ghebeh et al.** [30], who stated that expression of PD-L1 in breast cancer is correlated with high Ki-67. **Muenst et al.** [28] and **Li et al.** [31], also stated the same results which confirm that PD-L1 expression is associated with well-recognized parameters of poor prognosis.

Results of the current study also are in line with results of studies convoyed by **Mittendorf et al**. [10] and **Soliman et al.** [7], who have investigated the expression of PD-L1 in breast cancer and reported its relation with negative estrogen, progesterone receptors, and high grade.

Current study reported that PD-L1 expression show highly significant association with triple negative subtype, these results are near to results observed by **Bellucci et al**. [32] and **Ali et al**. [33], who stated that PD-L1 expression was statistically different between breast cancer molecular subtypes and reported that PD-L1 was detected in higher proportions of triple negative breast cancer.

Our results in addition with the previous studies have augmented the idea that PD-L1 is mainly expressed in triple negative breast cancer subtype, and that stratification of PD-L1 immunohistochemical expression based on hormonal markers negativity, our observations suggested that PD-L1 inhibitors may also benefit a little subset of females with triple negative that express PD-L1 which could promote the better understanding of its role on patients' prognosis and outcome [10].

In contrast the findings of the present study, the results which found by **Lou et al**. [34], who stated that expression of PD-L1 was insignificantly associated with young age of patient , However he observed a significant relation with clinical stage and histologic grade of the tumor which is consistent with findings of the present study.

This discrepancy in findings may be due to many factors such as different cancer types, patient races, sample sizes, different immunohistochemistry protocol methods used, or other factors which may affect the behavior of the tumor, so, additional researches including a larger study number could be needed to confirm our results.

CONCLUSION

This study point to a strong correlation between PD-L1 detection by immunohistochemistry in breast cancer and poor clinicopathologic parameters, which indicated that PD-L1 could be one of valuable prognostic markers in some breast cancer subtypes especially triple negative subtype.

Disclosure of potential conflicts of interest: No conflicts of interest. This study was fully funded by the authors.

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abdelrahman, D., Assaf, M., Rashed, H., ibrahim, D., Ibrahim Abdelhamid mansy, M. Immunohistochemical expression of programmed death-ligand 1 (PD-L1) in invasive duct carcinoma of the breast of no special type and correlation with patients' clinicopathological parameters. *Zagazig University Medical Journal*, 2020; (928-936): -. doi: 10.21608/zumj.2019.15879.1421