

Assessment of PDL-1 expression in Triple-negative breast cancer via immunohistochemistry

Maria Khan, Raazia Mahmood, Maria Tasneem Khattak, Ayesha Safdar, Ayesha Sajjad, Iqbal Muhammad

ABSTRACT

Objective: To assess the frequency of PDL-1 positivity in triple-negative breast carcinoma (TNBC) and correlate it with the clinicopathological parameters.

Study Design and Setting: Cross-sectional study conducted at Histopathology Department of Rehman Medical Institute, Peshawar.

Methodology: The study period was from September 2023 to October 2024. Biopsy specimen of 41 female patients diagnosed with TNBC were received in the Histopathology department. Specimens underwent eosin/hematoxylin staining and immunohistochemistry analysis. Demographic and histopathological parameters were recorded and analyzed using SPSS version 23.

Results: Mean age was 54.58(6.14) years, and the most common type of TNBC was invasive breast carcinoma of no special type in 23(56.1%). Out of 41 specimens, we observed that stage N2 and stage T3 were the most prevalent as observed in 18(43.9%) and 19(46.3%) specimens respectively. Frequency of PDL-1 positivity was observed in 16(39.02%) with a trend towards higher PDL-1 positivity observed in invasive ductal carcinoma of no special type and tumors exhibiting size of >20mm. Lymphovascular invasion was seen in 17 (41.46%) out of which 09 (56.3%) were PDL-1 positive. Tumor-infiltrating lymphocytes of the moderate category were significantly associated with PDL-1 positivity with a p-value of 0.024.

Conclusion: PDL-1 expression is observed in a substantial number (39.02%) of TNBC patients. Our research concludes an important association between PDL-1 expression and tumor-infiltrating lymphocytes in TNBC which enlightens new avenues for immunotherapy. This association may have profound implications in the future for prompt diagnosis and targeted treatment.

Keywords: Breast carcinoma, Lymphocytes, Triple-negative breast neoplasms

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INTRODUCTION

Breast cancer is one of the evolving pathologies with an increase of around 5% yearly leading to an increased burden on healthcare system. Prevalence of triple-negative breast carcinoma (TNBC) is around 15% with a recorded 5-year survival of 8% to 16%. Expression of different receptors is a hallmark of various types of breast cancers. However, TNBC is a distinct type of breast cancer that does not express receptors like estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (Her2). Breast cancer is sub classified into four molecular types based on genetic profiling. The four subtypes are Luminal Type A and Type B, Her 2- Enriched subtype and Triple Negative breast cancer (TNBC). Each subtype has its own well established morphological, genetic and prognostic characteristics. Immunohistochemical markers for Estrogen receptor ER, Progesterone receptor PR and Human Epidermal Growth Factor Receptor 2, i.e. Her2 are employed as substitute for determining the class of breast cancer and the use of these markers have been well established in clinical practice. These markers also stratify the breast cancer patients for viable therapeutic options based on presence or absence

of each marker. These treatments include Anti endocrine therapy and Anti- Her 2 agents for the Luminal category and Her2 enriched breast cancers respectively. Triple Negative Breast Cancer is characterized by the immunohistochemical absence of ER, PR and Her2 receptors. Genetically, the TNBC is characterized by a basal like profile, with a signature resembling the normally found basal myoepithelial cells of the breast ductal elements. They are shown to express high levels of Cytokeratin 5/6. The histological spectrum of TNBC is varied and includes Invasive mammary carcinoma of no special type, medullary carcinoma, metaplastic carcinoma and also some low grade tumors of salivary gland phenotype that occur in the breast namely, adenoid cystic carcinoma and secretory carcinoma. The tumors of salivary gland phenotype are distinct from the basal like tumors and carry their own signature molecular profiles. Due to a distinct nature of TNBC and the increased ability of cancerous cells to mutate, the prognosis of TNBC is not very predictable. Based on immunohistochemical analysis, breast cancers are divided into certain types of which TNBC belongs to the basal type which is due to a mutation of the breast cancer gene (BRCA) 1 gene. Due to the intrinsic nature of TNBC with absent expression of ER, PR, and HER2, treatment options against the cancerous cells are limited and conventional therapies for breast cancer that target the said receptors become ineffectual. Furthermore, natural outcome of this cancer type is dismal and is characterized by aggressive course, with increased chance of recurrences and less than ideal response to chemotherapy. Therefore, early detection of TNBC may be helpful for timely intervention. Diagnostic advancements in the field of medical science have enabled healthcare workers to use radiographic modalities or immunohistochemistry for detecting cancers. Radiographic investigations of cancers have the risk of radiation and may result in false positive or false negative results. Immunohistochemistry (IHC) is a more promising technique that helps in analyzing the histological characteristics of the tumors and detection of tumor markers which may help in prognostication of the cancerous cells.

The available treatment options include cisplatin based chemotherapy amongst others, but the prognosis and outcome has remained dismal for TNBC patients. Immense breast cancer research has become focused on exploring more treatment options that can improve survival. In the world of oncology, a lot of interest has been established in the niche of Immunotherapy. It essentially involves the enhancement of body's own immune system to overcome and destroy the cancer cells. Programmed death ligand 1 (PDL1) is a protein expressed in cancerous cells that binds to programmed death protein PD1 and protects the cancerous cells from the destruction by T-cells. The discovery of the interaction between PDL1 and PD1 leading to antitumor activity has led to evolutionary immunotherapies that aim to inhibit these interactions. T lymphocytes are a key arm

of our immune system that is directly involved in anti-tumor activity. PD1 is protein receptor that is expressed on the cell membrane of T lymphocytes. This receptor allows the T lymphocytes to recognize and participate in the destruction of cancer cells. In contrast, Programmed Death Ligand 1, PDL-1, is a protein expressed on tumor cells that binds the PD1 on T cells, essentially blocking its effects of anti-tumor activity. Thus, the cancer cells can bypass this immune checkpoint and escape recognition and destruction by the immune system. Tumors have been shown to harness this pathway and overexpress PDL-1 on their cell surfaces to escape the immune system. This tumor-Immune system interaction pathway has led to the discovery and development of Immunotherapy agents that target PDL-1 called Immune Checkpoint Inhibitors. These Anti-PDL-1 agents block the PDL-1 receptors on the tumors cells, allowing the T cells to recognized and destroy the cancer. A considerable number of studies have been underway to determine the PDL-1 expression in various tumors in order to determine their suitability for Immunotherapy, especially the tumors that haven't performed well under current available treatment regimes. Determining the PDL-1 status of tumor cells has been an object of many studies. PDL-1 Immunohistochemical marker has emerged as a proven surrogate to determine its expression. Several studies have been conducted to evaluate the expression of growth factors in TNBC. However, there exists a gap in research when assessing the relation of PDL1 expression and its association with clinicopathological parameters in TNBC. This research aims to assess PDL1 expression in TNBC and its association with clinicopathological parameters. In the future, our research may prove helpful in predicting if the patients with TNBC will likely benefit from PDL1-directed immunotherapies. Research on PDL1 in TNBC may pave the way to further research for combination immunotherapies, progression of disease, and recurrence of disease.

METHODOLOGY

After obtaining approval from the local ethical committee of hospital, the cross-sectional study was conducted at Rehman Medical Institute, Peshawar under ERC # RMI-REC/Ethical Approvals/CPSP Synopsis/43 dated 06 Sep 2024 from 10 September 2023 through 10 October 2024.

Using a World Health Organization (WHO) sample size calculator a sample size of n=41 was calculated with an estimated prevalence of 12% TNBC when the power of study was 95% with a 10% level of significance. Sampling was conducted using non-probability convenient technique.

An informed consent was obtained from the participants and biopsy specimens of female patients of any age diagnosed with triple-negative breast carcinoma were included in the trial. Histotypes of TNBC included invasive ductal carcinoma, medullary carcinoma and metaplastic carcinoma. This distinction was made to uniformize the differences in

prognosis of various histological subtypes of TNBC such as those of salivary gland phenotype. Patients were excluded if male, inadequate biopsy specimen or diagnosed with low-grade TNBC.

We included 41 specimens of biopsy-proven TNBC in our study which were assessed by two different classified pathologists for confirmation of diagnosis. Employing the protocol of our laboratory eosin and hematoxylin staining was performed. The size of the tumor, type of tumor, N-stage, T-stage, lymphovascular invasion, and tumor-infiltrating lymphocytes were assessed on the histological exam and recorded. This was followed by application of PDL-1 immunohistochemical marker after Heat Induced epitope retrieval of the antigen. The PDL-1 antibody clone utilized was Rabbit Monoclonal Primary Antibody PDL-1 (28–8) manufactured by Cell Marque. Immunohistochemistry analysis was done using lymph nodes as controls. Employing a combined positive score (CPS) PDL1 expression was assessed. Using the formula of the number of PDL1 staining cells divided by the total number of viable tumor cells multiplied by 100 was used. Tumors exhibiting a CPS score of ≥ 10 were recorded as PDL1 positive while tumors with a CPS score of < 10 were recorded as PDL1 negative. Figure-II shows membranous staining in invasive carcinoma (CPS > 10). A predesigned proforma was used for recording the variables.

We used Statistical Package for Social Sciences (SPSS) version 23 for data analysis. Quantitative variables like age were computed using mean and standard deviation while frequencies and percentages were computed for qualitative variables like metastasis, N-Staging, T stage, lymphovascular invasion, tumor-infiltrating lymphocytes, recurrent Tumors. For analysis of significance, a chi-square test was used for categorical variables and a p-value of $= 0.05$ was taken as significant.

RESULTS

We included 41 female patients in our study with a mean age of 54.58 (6.14) years and the most common type of TNBC was invasive breast carcinoma of no special type in 23 (56.1%). Figure-I shows invasive breast carcinoma of no special type with high grade features. Out of 41 specimens, 18 (43.9%) had N2 stage on immunohistochemistry while a majority of T3 stage was seen in 19 (46.3%) specimens. We observed a low frequency of tumors with metastases in 02 (4.9%) while 03 (7.3%) had recurrent tumors. Demographic and baseline characteristics are shown in Table-1. When CPS > 10 was considered as PDL1 positive the frequency of PDL1 positivity was observed in 16/41 (39.02%). We concluded that invasive ductal carcinoma of no special type and tumors with size > 20 mm exhibited higher PDL1 positivity without establishing a significant

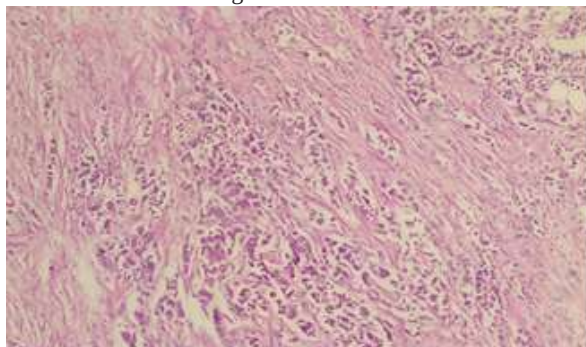
Table-1: Demographic and baseline characteristics (n=41)

Variables		Results
Age in years Mean (S.D)		54.58(6.14)
Tumor size n (%)	<20mm	11 (26.8%)
	>20mm	30 (73.2%)
Type of tumor n(%)	Invasive breast carcinoma no special type	23 (56.1%)
	Invasive carcinoma with medullary features	13 (31.7%)
	Metaplastic carcinoma	05 (12.2%)
Metastasis n (%)	Yes	02 (4.9%)
	No	39 (95.1%)
N-Stage n (%)	N0	03 (7.3%)
	N1	16 (39%)
	N2	18 (43.9%)
	N3	04 (9.8%)
T stage n (%)	T1	02(4.9%)
	T2	16(39%)
	T3	19(46.3%)
	T4	04(9.8%)
Lymphovascular invasion n (%)	Present	17 (41.5%)
	Absent	24 (58.5%)
Tumor-infiltrating lymphocytes n (%)	Low	18 (43.9%)
	Moderate	19 (46.3%)
	Marked	04 (9.8%)
Recurrent tumor n (%)	Yes	03 (7.3%)
	No	38 (92.7%)

Table-2: Clinicopathological characteristic of PDL1 positive and PDL1 negative TNBC (n=41)

Parameters		PDL1 positive (n=16)	PDL1 Negative (n=25)	p-value using chi square test
Tumor size in mm N (%)	<20mm	06 (37.5%)	05 (20%)	0.217
	>20mm	10 (62.5%)	20 (80%)	
Type of tumor n (%)	Invasive breast carcinoma of no special type	11 (68.8%)	12 (48%)	0.390
	Invasive carcinoma with medullary features	04 (25%)	09 (36%)	
	Metaplastic carcinoma	01 (6.3%)	04 (16%)	
Metastasis n (%)	Yes	01 (6.3%)	01 (4%)	0.744
	No	15 (93.8%)	24 (96%)	
n stage n (%)	N0	03 (18.8%)	0	0.136
	N1	05 (31.3%)	11 (44%)	
	N2	06 (37.5%)	12 (48%)	
	N3	02 (12.5%)	02 (8%)	
T stage n (%)	T1	02 (12.5%)	0	0.086
	T2	06 (37.5%)	10 (40%)	
	T3	05 (31.3%)	14 (56%)	
	T4	03 (18.8%)	01 (4%)	
Lymphovascular invasion n (%)	Present	09 (56.3%)	08 (32%)	0.124
	Absent	07 (43.8%)	17 (68%)	
Tumor-infiltrating lymphocytes n (%)	Low	03 (18.8%)	15 (60%)	0.024
	Moderate	10 (62.5%)	09 (36%)	
	Marked	03 (18.8%)	01 (4%)	
Recurrent tumors n (%)	Yes	01 (6.3%)	02 (8%)	0.834
	No	15 (93.8%)	23 (92%)	

Figure-I: Invasive breast carcinoma of no special type with high grade features

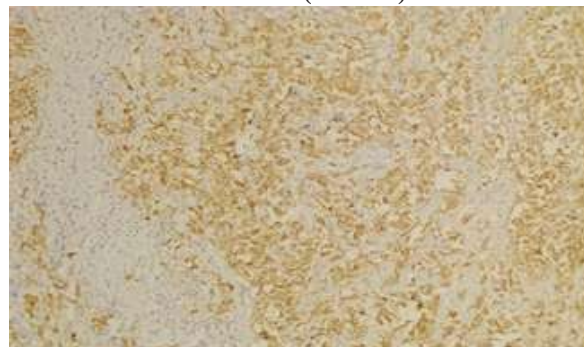


association. Tumors exhibiting N2 stage represented the majority of the specimens 18/ 42 (42.86%) of which 12/18(48%) were PDL1 negative. Tumors with T3 stage on histological exam were observed in 19 (46.3%) specimens (p-0.086). Lymphovascular invasion was seen in 17 (41.46%) out of which 09 (56.3%) were PDL1 positive (p-0.124). Tumor-infiltrating lymphocytes of the moderate category were observed in 17(46.34%) specimens out of which 10 (62.5%) were PDL1 positive with a p-value of 0.024. The association of PDL-1 and clinico-pathological variables is shown in Table-2.

DISCUSSION

The cross-sectional study was conducted to assess PDL1

Figure-II: PDL-1 IHC showing membranous staining in invasive carcinoma (CPS >10)



expression in TNBC and its association with clinicopathological parameters. We concluded that the mean age of patients diagnosed with TNBC was 54.58 (6.14) years and the most common type of TNBC was invasive ductal carcinoma of no special type in 23(56.1%). A similar cross-sectional study revealed that the median age of patients with TNBC was 47 (28-65) years. In comparison to our study, in which the PDL1 positivity was seen in 16 (39%) specimens, another study concluded that the frequency of PDL1 positivity was 29%.⁸ In a similar study the mean age of patients with TNBC was found to be 53.23 (8.21) years which was close to the mean age observed in our study. We observed that PDL1 positivity was higher in frequency 10

(62.5%) for tumors with a size greater than 20 mm as compared to 06 (37.5%) tumors with a size less than 20mm however it did not reach a significant level. A similar study done by Dođukan R *et al* revealed that the mean size of TNBC tumor was 4.2(3.3cm) and the most common type of TNBC was invasive breast carcinoma of no special type observed in 42 (68.9%) of the patients with TNBC. Association of PDL1 positivity and clinico-pathological parameters revealed that there was no significant relationship between PDL1 positivity and the N-stage of the tumor. Most of the tumors were found to have N2 stage on immunohistochemistry observed in 18 out of 41(43.9%) biopsy specimens. Similarly, no significant association was observed between the T-stage of the tumor and PDL1 positivity. Similar results in concordance with our findings were observed by Al-Jussani who found no significant association between PDL1 and clinicopathological variables. Our results showed only 2 out of 41 (4.8%) tumors having evidence of metastasis without any significant association with PDL1 positivity. However, in contrast another cross-sectional study revealed that PDL1 positivity was higher in breast tumors with evidence of metastasis as compared to non-metastatic breast tumors. This may imply that in breast tumors not specifically TNBC metastasis may be predicted by PDL1 overexpression. We observed that lymphovascular invasion was seen in 17 (41.5%) specimens with 09 (56.3%) PDL1 positive and 08 (32%) PDL1 negative tumors (p=0.124). A similar study revealed that the frequency of lymphovascular invasion observed in TNBC was 74.2% without any significant association with PDL1 positivity.

Immunohistochemistry of 41 specimens revealed that moderate levels of tumor-infiltrating lymphocytes (TILs) represented most tumors i.e. 19 out of 41 specimens out of which 10 (62.5%) were PDL1 positive with a p-value of 0.024. Tumor infiltrating lymphocytes imply the body's protective response. They comprise of a varied population of immune cells, predominantly including Lymphocytes, which infiltrate the stroma associated with tumor or the tumor cells directly. TILs can be regarded as an indicator of host immune surveillance and its ability to mount an immune response against the tumor. Observations have been made about tumors which show abundant immune cell infiltration may be more immunogenic and as a result may be more amenable to Immunotherapeutic agents. In many studies, higher levels of tumor infiltrating lymphocytes in Triple negative breast cancer has been associated with better clinical outcomes including better overall survival. It has also been proven as an independent factor in regard to prognostication. The relationship between tumor infiltrating lymphocytes and PDL-1 is complex and multi – directional. The lymphocytes in tumor microenvironment release various cytokines including Interferon Gamma to enhance the anti-tumor activity. These cytokines in turn cause a reactionary enhanced expression of PDL-1 by the tumor cells in order

to evade that destructive immune activity and build immune resistance. Conversely, tumors with intrinsically high expression of PDL-1 receptors inherently sustain greater levels of tumor immune cells, giving rise to a immune – inflamed phenotype. This intricate interplay between TILs, Tumor microenvironment and PDL-1 on tumor cells helps explain why tumors with high PDL-1 expression have increased density of TILs and this Immune – hot environment of the tumor can be the ideal target for various Anti-immune therapeutic agents including Anti-PDL-1 agents. We could not continue to assess the overall survival. However, a similar study on TNBC revealed that the presence of infiltrating lymphocytes in the tumor was significantly correlated with improved overall survival in patients with TNBC. TILs signified the host protective environment against the tumor and tumors exhibiting high TILs resulted in significantly higher disease-free survival and overall survival. In another research when TILs were categorized into low and high, the percentage of TNBC exhibiting low TIL count was 78.01% as compared to 21.9% of tumors exhibiting higher numbers of TILs. Expression of PDL1 with TIL was significantly correlated with a p-value of < 0.001.

We could not record and follow up the patients for a longer period of time to assess the prognosis and response to treatment in our patients. With a relatively small sample size and participants included from a single hospital may lead to unreliable prediction about TNBC in people of different regions. Since we have not recorded the mortality, therefore a general statement about the survival rate in different age groups was not possible. Additionally, PDL-1 expression is known to be heterogeneous within a tumor and tissue sampling may not be entirely representative of tumor microenvironment. These limitations emphasize the necessity of developing standardized protocols and further studies should be underway utilizing complementary molecular techniques for a more accurate assessment of the role of PDL-1 and its interaction with tumor microenvironment.

In the arena of breast carcinoma, tumor-infiltrating lymphocytes and PDL-1 play a significant role in the prognostication of the tumor. It can be used as an indicator to guide immunotherapies. Previous research indicates that assessment of PDL-1 and TILs altogether may be beneficial in identifying tumor-rich environments. Novel therapies are emerging that may help target immune checkpoints and TILs plays a crucial role in immunity against the tumor. Hence our study reveals a significant association between TILs and PDL-1-positivity which may lead to delineating the treatment protocol of TNBC, leading to better outcomes in the future.

CONCLUSION

PDL-1 expression is observed in a substantial number (39.02%) of TNBC patients. Our research concludes an important association between PDL-1 expression and tumor-

infiltrating lymphocytes in TNBC which enlightens new avenues for immunotherapy. This association may have profound implications in the future for prompt diagnosis and targeted treatment.

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Ayesha Safdar: Analysis

Ayesha Sajjad: Literature Review

Iqbal Muhammad: Conception, final approval

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