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Original Article

Clinicopathological correlation and expression of PD-L1 in Cervical Carcinoma: An Immunohistochemical study

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ABSTRACT

Background: Cervical cancer is the fourth most common cancer in women globally and the second leading cause of cancer deaths in India. Risk factors include HPV infection, smoking, long-term oral contraceptive use, early pregnancy, nulliparity, and multiple sexual partners. Programmed cell death-1/ programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors may improve outcomes in recurrent, persistent, or metastatic cervical cancer. This study aimed to determine the various histological types of cervical carcinoma, determine PD-L1 expression, correlate it with PDL1-positive TILs, and provide insight into clinicopathological parameters such as age, stage, etc.

Materials and methods: This prospective cross-sectional study (July 2022–June 2023) analyzed 50 histopathologically confirmed cervical carcinoma cases at a tertiary care institute in India. The tumors were classified, graded, and subjected to PD-L1 immunohistochemistry.

Results: Squamous cell carcinoma was the most common type, followed by adenocarcinoma. PD-L1 positivity was observed in 36% of cases, predominantly in squamous cell carcinoma (39.1%). Expression increased with tumor grade and stage ($p = 0.046$), while tumor-infiltrating lymphocytes decreased in poorly differentiated tumors, indicating reduced immune response.

The study highlights the significance of PD-L1 expression in cervical carcinoma and suggests routine immunohistochemical testing to identify patients eligible for targeted therapy, facilitating personalized treatment approaches.

Conclusions: The study highlights the significance of PD-L1 expression in cervical carcinoma and suggests routine immunohistochemical testing to identify patients eligible for targeted therapy, facilitating personalized treatment approaches.

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INTRODUCTION

Worldwide, Cervical cancer is the fourth most common cancer in women globally with around 660,000 new cases and around 350,000 deaths in 2022. In the same year, about 94% of the 350,000 deaths caused by cervical cancer occurred in low and middle-income countries.[1] HPV, smoking, having multiple full-term pregnancies, long-term use of oral contraceptives, young primigravida, nullipara, and women with multiple sexual partners increase the risk of cervical cancer. Squamous cell carcinomas account for about 80% of cancers of the uterine cervix, and the majority of the remainder are adenocarcinomas.[2] Due to the

lack of absolute sensitivity and specificity of the various prognostic biomarkers such as tumor size, stage, and lymph node status, it has become alarmingly required to discern feasible and novel prognostic markers to predict survival outcomes and for patient-specific management of cervical carcinoma patients.[3] PD-L1 is expressed on a variety of cell types including placenta, vascular endothelium, pancreatic islet cells, mesenchymal stem cells as well as on immune cells such as B cells, T cells, dendritic cells, macrophages and mast cells.[4] Programmed cell death-ligand 1 (PD-L1) is a trans-membrane protein that is considered to be a co-inhibitory factor of the immune response (suppression of T-cell activation), it can combine with Programmed cell death-1 (PD-1) to reduce the proliferation of PD-1 positive cells, inhibit their cytokine secretion and induce apoptosis. Since CD8+ T cells are vital in eliminating cancer cells, their inhibition interferes with cancer eradication and permits its immune escape.[5]

The present study was carried out in an attempt to determine the PD-L1 positivity status of cervical carcinoma patients and interpret its correlation with the stage and grade of tumor. For patients with recurrent, persistent, metastatic cervical cancer: Programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors might be a novel choice to improve the clinical outcome of these patients.

MATERIALS AND METHODS

This was a cross-sectional study conducted from 1st July 2022 to 30th June 2023 including 50 histopathologically proven cases of cervical carcinoma in hysterectomy specimens received in the Department of Pathology in a tertiary care institute, Amritsar, Punjab, India. Ethical clearance was taken from the institution's Ethical Committee. A semi structured proforma was created in which hospital numbers and biopsy numbers were noted, and relevant demographic profiles like age, clinical findings, gross and histopathological findings along with clinical staging were collected from the data available in the department.

Inclusion criteria: Only those cases that were reported as malignant and had adequate tissue for testing were included in the study.

These lesions were classified and graded according to World Health Organization 2016 guidelines and further subjected to immunostaining for PD-L1 expression. The cervical tissue was formalin-fixed, paraffin-embedded, and then stained with hematoxylin and eosin for histopathological typing and grading. All these cases were then subjected to immunohistochemistry for PD-L1 expression using rabbit monoclonal antibody by BIOCARE MEDICAL. Positive controls and negative controls were run for every batch. All the slides were reviewed by at least three pathologists and final interpretations were made.

Tumor Proportion Score (TPS) was assessed, and the percentage was utilized for various correlations. The staining intensity was categorized as mild, moderate, or strong and reported according to standard immunohistochemical guidelines.

Table 1: PD-L1 scoring algorithm for cervical carcinoma[6]

Tumor cell staining assessment	PD-L1 expression
Histologic evidence of cell surface membrane or cytoplasmic staining in 5% or more cells.	Positive
Histologic evidence of cell surface membrane or cytoplasmic staining in <5% of cells.	Negative

RESULTS

Out of the 50 cases, 46 were SCC (92%) and 4 were Adenocarcinoma (8%). 28 (56%) cases were premenopausal whereas 22(44%) cases were postmenopausal.

Most of the cases were in the 41-60 yrs age group comprising a total of 32 cases (64%). Among these 32 cases, 13 cases (40.6%) were PD-L1 positive as shown in Table 2.

Table 2: Correlation PD-L1 positivity with age

Age (years)	Total number of cases	Number of positive cases	Percentage (%) of PD-L1 positive cases
30	1	0	0%
31-40	8	2	25%
41-50	19	8	42.1%
51-60	13	5	38.5%
61-70	7	2	28.6%
>70	2	1	50%

Among 46 SCC cases, 18 (39.1%) cases were positive for PD-L1 expression while none of the Adenocarcinoma cases showed PD-L1 expression (p-value=0.11-not significant).

The PD-L1 positivity was found to be highest in poorly differentiated SCC (46.7%) followed by well differentiated (40%) and moderately differentiated (34.6%) SCC cases (p-value = 0.74-not significant) as mentioned in Table 3.

Table 3: PD-L1 positive cases as per the grades of Squamous Cell Carcinoma.

Differentiation of tumor (SCC)	Number of cases	Positive cases	Percentage (%)
Well-Differentiated	5	2	40%
Moderately Differentiated	26	9	34.6%
Poorly Differentiated	15	7	46.7%

72.2% of the positive cases showed diffuse expression (i.e. throughout the tumor) with only 27.5% of cases showing marginal expression (i.e. between the tumor and stromal interface).

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In 18 PD-L1 positive SCC cases, the maximum number of cases showed a percentage of cells positive in the range of 11-50%.

Out of the 18 SCC cases that were positive with PD-L1, 03 (16.7%) cases showed mild intensity, 05 (27.7%) cases showed moderate intensity, and 10 (55.5%) cases showed strong intensity. (fig.1) Thus, the maximum number of cases showed strong staining intensity as mentioned in Table 4.

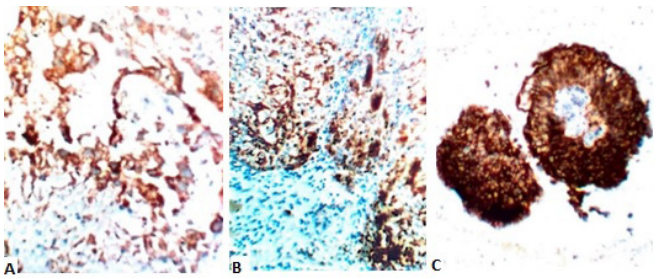

Figure 1: *Microphotograph showing PD-L1 positivity: (A) Mild membranous intensity; (B) Moderate membranous intensity; (C) Diffuse strong membranous intensity. [Immunohistochemistry; x100]*

Table 4: Correlation of percentage PD- L1 positive tumor cells and staining intensity, with tumor differentiation in squamous cell carcinoma.

Differentiation (SCC)	Percentage (%) of PD-L1 positive tumor cells			Intensity		
	5-10%	11-25%	26-50%	mild	moderate	strong
Well-differentiated	1	0	1	0	1	1
Moderately differentiated	1	4	4	2	2	4
Poorly differentiated	0	4	3	1	3	4

Tumor-infiltrating lymphocytes (TILs) were positive in 11 cervical carcinoma cases, among which 36.4% were associated with PD-L1 positivity. A high percentage of moderately differentiated tumors i.e. 33.3% showed PD-L1positive TILs, followed by 20% cases of well-differentiated tumors. However, no statistical correlation was found (p-value = 0.44) as shown in Table 5 and Table 6.

Table 5: Cases with PD-L1 positive Tumor Infiltrating Lymphocytes (TILs); p-value=0.44

PD-L1 status of TIL	Number of cases	TIL in PD-L1 positive tumors	Percentage (%)
POSITIVE	11	4	36.4%
NEGATIVE	39	14	35.9%

Table 6 showing correlation of PD-L1 positive Tumor Infiltrating Lymphocyte (TIL) with tumor differentiation (SCC)

Differentiation (SCC)	Total number of cases	TIL present	PD-L1 positive TILs	Percentage (%)
Well Differentiated	05	05	1	20.0%
Moderately Differentiated	26	24	8	33.3%
Poorly Differentiated	15	12	2	16.7%

Table 7: Correlation of stage of tumor with PD-L1 positivity (p-value: <0.001)

Stage	Total no. Of cases	PD-L1 positive cases	Tumor differentiation		
			Well-differentiated	Moderately differentiated	Poorly differentiated
1A	3	0	2	1	0
1B	38	9(23.6%)	3	25	10
2A	6	6(100%)	0	3	3
2B	1	1(100%)	0	0	1
3	2	2(100%)	0	1	1
4	0	0	0	0	0

On correlating the percentage positivity of PD-L1 with the stage of the tumor, it was observed that as the stage of the tumor increased, the percentage positivity increased with maximum positivity seen in stages 2 and 3.

Also, correlating the stage of tumor with differentiation, it was significant with the p-value of 0.046.

DISCUSSION

Cervical Carcinoma is a major cause of cancer related mortality in women.[7] Two Human papillomavirus (HPV) genotypes (16 and 18) are responsible for nearly 50% of high-grade cervical pre-cancers. For the early detection and treatment of cervical cancer, various screening methods have been introduced that mainly target the main pathological cause i.e. HPV infection. However, due to the rising incidence of CC, various other predictive markers have also been introduced to curb its pathogenesis, amongst which one major factor is tumor immune surveillance. Various IHC markers used in the diagnosis of CC include: p53, Ki67, p16, p63, Carcinoembryonic antigen, Nuclear factor kappa-beta, Cyclin D1, E-Cadherin, Caspase inhibitor of apoptosis protein and PD-L1.[8] Although tumor cells express numerous antigens, tumor eludes T-cell responses and host immunity through checkpoint inhibitors of the immune system, such as programmed death-1 (PD-1), programmed cell death-ligand-1 (PD-L1)/ programmed cell death-ligand-2 (PD-L2), cytotoxic T lymphocyte antigen 4 (CTLA-4), T-cell immunoglobulin mucin 3 (TIM3), 2B4, the B and T lymphocyte attenuator (BTLA), and lymphocyte-activation gene 3 (LAG3).[9-11] The expression of PD-L1 is noted on

the surface of the cervical tumor cells, antigen-presenting cells (APCs), and tumor-infiltrating lymphocytes (TILs), while the PD-1 cells were mostly recognized as T cells in the stroma of cervical cancers.[4] Multiple studies have provided insight into the independent role of the PD-1/PD-L1 pathway in cancerous cell proliferation and growth in cervical carcinoma.[12]

In this study, 28 (56%) cases were premenopausal whereas 22 (44%) cases were postmenopausal. A similar distribution was also observed in the study by Son SM et al. wherein 68.5% of the CC were found in premenopausal women (<55 years), compared to 31.4% in post-menopausal women (>55 years).[13]

Studies done by Franceschi et al., Emeka K Enwere et al., and Cora Ngelange et al. on 205, 120, and 356 cases respectively, also concluded SCC to be the most common histopathological type accounting for 94%, 88%, and 91% of the total cases respectively.[14-16]

The CC cases were subjected to differentiation amongst which, moderately differentiated tumors were the highest constituting 60% of the total, followed by poorly differentiated comprising 30%, and well-differentiated tumors accounting only for 10% of the cases. Studies conducted by Sandhu JK et al. and Shruthi PS et al. also demonstrated that moderately differentiated tumors constituted the majority of cases, comprising 82% and 54.7% of the total cases, respectively.[17,18] Similarly, a study done by Vasilescu F found that only 11.53% of the cases were of well-differentiated tumors in comparison to moderately and poorly differentiated tumors comprising 30.76% and 34.61% of all the cases respectively.[19]

Cervical Carcinoma staging is based on the results of a physical exam, imaging scans, and biopsies. It is assigned as Stage 1 (1A and 1B), 2 (2A and 2B), 3 (3A, 3B and 3C) and 4 (4A and 4B). In the present study, the maximum cases were of 1B and 2A comprising 88% of the total CC cases. It was observed that, as the stage of the disease increased, the tumor grade increased (p-value = 0.046). A similar study was done by Hopkins MP et al. who concluded that as the stage of the disease progressed, the tumor grade increased and it was associated with a poorer survival rate.[20]

Various authors have observed that tumor PD-L1 over-expression confers poor prognosis for the patient thus making therapeutic interventions on this immunomodulatory axis beneficial for the patient. Thus it is important to screen tumors for PD-L1 expression for finding patients who may benefit from the therapy.

Studies conducted by various authors in different regions on PD-L1 expression by CC showed the expression ranging from 19-88%.[6,15,21-23] This varied percentage of expression may be due to the different sample sizes and geographical variations in these studies as shown in Table 8.

Table 8: Research studies on PD-L1 positivity in cervical carcinoma.

Year	Researcher	Total no. of cases	Percentage of PD-L1 positive tumor
2009	Karim et al21	115	19%
2016	Heeren et al6	252	54%
2017	Reddy et al22	93	34.4%
2017	Enwere et al15	120	88%
2018	Min Feng et al23	219	32.4%

In the present study, PD-L1 positive results were seen in 36% of the total cases, which is similar to the observation made by Reddy OL et al. with PD-L1 expression seen in 34.4% of all the cases. In the current study, on correlating the PD-L1 expression with the histopathological type, its expression was found to be highest in the squamous cell carcinoma type comprising 39.1%, which was similar to the findings of Reddy OL et al., who reported PD-L1 positivity in 37.8% of all squamous cell carcinoma cases.[22]

Also, it was observed that the percentage of PD-L1 positivity was the highest in the poorly differentiated type comprising 46.7%, 34.6% in the moderately differentiated tumors, and 40% positivity was noted in well-differentiated tumors.

A similar study was done by Chen Z et al. in which 50% of cases were of the poorly differentiated grade.[24] From the above observation of the highest expression in poorly differentiated tumors, an inference can be made that PD-L1 is a poor prognostic marker.

In the current study, a correlation was also noted between the tumor differentiation and the intensity of staining and it was found that as the tumor progressed to a poorer grade, the intensity of staining increased. Reddy OL et al also evaluated the staining intensity for PD-L1 but could not find any correlation between the grade and intensity.[22]

Activated T cells bind to PD-L1 on the tumor epithelial cells sending negative immunoregulatory signals to the T cells thus resulting in evasion of tumor surveillance. TILs are also considered an independent prognostic factor. Meng et al. stated that TILs were found at the tumor invasive front, suggesting a defect of T cell infiltration which was possibly due to PD-L1 over-expression by the tumor.[25]

In the current study, 36.4% of cases of PD-L1 positive tumors were associated with infiltration by mononuclear cells. On correlating the PD-L1 positive TILs with the grade of cervical carcinoma it was found that 33.3% of the moderately differentiated tumors and only 16% of the poorly differentiated tumors showed infiltration, which correlates with the research findings of TILs being associated with better prognosis.

In the present study, it was noted that PD-L1 positivity increased as the tumor progressed to a higher stage with

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100% of the stage 2 cases staining positive for PD-L1 (p-value <0.001). Similar observations were made by Meng Y et al. who reported 90% of the stage 2 to 4 cases staining positive with PD-L1.[25] Thus correlating with the finding of the present study- PD-L1 expression is associated with higher stage of tumor.

PD-L1 expression in the tumor cells is taken as a bad prognosis but most of the studies have found that it does not have a direct effect on the overall survival of the patient. But, on the other side it has been supported that in SCC cervix, patients with diffuse PD-L1 expression as compared to those with marginal PD-L1 expression; the disease-free and specific survival were significantly poorer. It has been seen that PD-L1 expression increased with increasing stage as it is not exhibited in benign cervical tissue. Thus, the cases showing PD-L1 expression may benefit from targeted therapy.

Emeka K Enwere et al conducted a study on the expression of PD-L1 and the presence of CD8-positive T cells in pre-treatment specimens of locally advanced cervical cancer and concluded that PD-L1 is expressed in the vast majority of locally advanced cervical cancer specimens and has attracted considerable interest as both a predictive and prognostic marker. [15]

The presence of tumor-infiltrating lymphocytes is generally considered a good prognostic factor in many cancer types, however, these cells are often ineffective due to the immunosuppressive environment deployed by the tumor. [26-28]

CONCLUSIONS

This study highlights the significance of PD-L1 expression in cervical carcinoma and its correlation with increasing tumor grade and stage, suggesting a potential role of PD-L1 as a marker of tumor aggressiveness.

A strong correlation between PD-L1 expression and tumor-infiltrating lymphocytes (TILs) was noted, indicating an immunosuppressive microenvironment. Given the increasing evidence of the role of PD-L1 in immune evasion, the study reinforces the potential of PD-1/PD-L1 inhibitors as a promising therapeutic option for recurrent, persistent, and metastatic cervical carcinoma. Future research with larger sample sizes and long-term survival data is required to further validate the prognostic and predictive value of PD-L1 expression in cervical carcinoma patients.

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