Section: Pathology

Original Research Article

IMMUNOHISTOCHEMICAL EXPRESSION OF PROGRAMMED CELL DEATH LIGAND 1 (PD-L1) IN CERVICAL CARCINOMA

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Abstract

Background: The study aimed to evaluate the expression of Programmed Death-Ligand 1 (PD-L1) in cervical carcinoma. **Materials and Methods:** This institution-based descriptive study with a cross-sectional design was conducted at the Department of Pathology, B.R.D. Medical College, Gorakhpur, U.P., from May 2023 to April 2024. The study included cervical biopsies from patients with cervical carcinoma. Histopathological examination and immunohistochemical expression of PD-L1 were analyzed using specific antibodies. **Result:** The study included 100 cervical carcinoma cases, with 85% showing PD-L1 expression. Most cases were non-keratinizing moderately differentiated squamous cell carcinoma (82%). PD-L1 expression varied significantly, with 30% of tumors exhibiting >50% expression. Tumor infiltrating lymphocytes (TILs) were present in varying degrees, with 41% in the 1-10% range. PDL-1 expression, also CPS and their extent was high in poorly differentiated cervical SCC, followed by moderately differentiated and well differentiated cervical SCC. **Conclusion:** The high prevalence of PD-L1 expression in cervical carcinoma suggests its potential role in immune evasion and as a therapeutic target for PD-L1 inhibitors. Further research is needed to explore the relationship between PD-L1 expression and tumor aggressiveness to improve prognostic assessments and personalized treatment strategies.

INTRODUCTION

The role of immune checkpoint inhibitors has been explored in several malignancies, including uterine cervical cancer,[1] due to their ability to interfere with the body's defense mechanisms against cancer, but this role has been scarcely studied in the progression from squamous intraepithelial lesions (SILs) to squamous cell carcinoma (SCC).[2] Programmed cell death protein-1 (PD-1) and its ligand programmed death-ligand 1 (PD-L1) are coinhibitory regulators that suppress proliferation and cytokine production by CD8+ T lymphocytic cells, preventing tumor surveillance and destruction by immune cells.[3,4]

Cancer of the uterine cervix is the third most common gynecologic cancer in the United States, with approximately 13,000 new cases and 4120 cancer deaths estimated to occur in 2016.[5] Persistent human papillomavirus (HPV) infection, particularly with HPV16, HPV18, and other high risk types, plays a key role in the development of cervical cancer. While screening measures for cervical dysplasia have decreased the incidence of cervical cancer in the United States, cervical cancer remains a major world health problem for women.[6,7]

Depending on the disease stage, treatment for cervical cancer may involve a combination of hysterectomy, pelvic lymph node dissection, and chemoradiation. Targeted therapies using small molecules or monoclonal antibodies are largely still in clinical trial stages.[7] PD-1 is an immune suppressive molecule in the B7-CD28 family that regulates T-cell activation.[8] PD-L1 is a transmembrane protein that can be expressed on tumor cells in the cancerous microenvironment.[9] PD-L1 has been hypothesized to bind its receptor PD-1 on T-cells to downregulate anti-tumor T-cell activity and facilitate immune evasion.[10] Expression of PD-L1 has also been found to be associated with worse survival in solid tumors, including esophageal,

gastric, colorectal cancers, and pulmonary adenocarcinoma.[11,12]

The study aimed to evaluate the expression of Programmed Death-Ligand 1 (PD-L1) in cervical carcinoma.

MATERIALS AND METHODS

The study was conducted at the Department of Pathology, B.R.D. Medical College, Gorakhpur, UP for 12 months from May 2023 to April 2024.

The study population consisted of small cervical biopsies of malignant lesions in uterine cervix received in the department of Pathology from the Gynecology department in Nehru Chikitsalaya, Gorakhpur, UP during over the study period.

Inclusion Criteria

- All patients with cervical carcinoma

Exclusion Criteria

- Autolysed sample.
- Inadequate sample.
- Ill fixed specimen.
- Any previous chemotherapy/ radiotherapy received

Data Collection Technique: After informed and written consent had been obtained, the histopathological examination and immunohistochemical expression of PD-L1 on the specimens of the uterine cervix received in the department were analyzed. Tissues preserved in the pathology department of B.R.D. Medical College were also utilized for the study.

Scoring

Programmed Death- Ligand 1 (PD-L1)

Expression of PD-L1 in the tumor was quantified manually and classified as positive when staining (PD-L1: membranous) was present in ≥1% of tumor cells. Staining extent was further characterized in the following subcategories: 1–5%, 6–10%, 11–25%, 26–50%and >50%. The 1% threshold for positivity was selected based on data demonstrating clinical response to PD-L1 inhibition. Immune microenvironment staining was scored positive, when ≥1% of peritumoral and intratumoral immune cells showed reactivity. It was subdivided as 1–10%, 11–25%, 26–50% and >50%.

Combined positive score (CPS):[13,14]

The combined positive score was determined manually and was based on the equation described previously for gastric and gastroesophageal junction cancers.

CPS = [(number of PD-L1-positive tumor cells and mononuclear inflammatory cells)/(total number of tumor cells)]. In the CPS system, immune cell scoring is based on PD-L1-positive lymphocytes and macrophages (‘mononuclear inflammatory cells’) identified in association with a tumoral immune response. This includes both intratumoral immune cells and peritumoral immune stromal cells, but not immune cells in stroma distant from the tumor.15

Control of IHC

PDL 1

Positive Control: Tonsil

Negative control: Normal cervical tissue and benign cases.

Interpretation of IHC

Positive: Any membranous staining within the tumor cells

Negative: Complete absence of membranous staining within the tumor cells with concurrent internal control positive.

Ethical Consideration

The Institutional Ethics Committee of study institute reviewed and approved the project before it was carried out. All of the participants were informed in their own language about the study and their rights for participation. They were informed about the participant’s role and rights, to clarify that their participation was voluntary, the information was treated confidentially, and they could withdraw from the study at any time. After the collection of data, the data was cleaned, anonymised and stored in a password protected spreadsheet for data analysis.

Data Analysis

The collected data were checked for consistency, completeness and entered into Microsoft Excel (MS-EXCEL, Microsoft Corp.) data sheet. Analyzed with the statistical program Statistical Package for the Social Sciences (IBM SPSS, version 22). Data were organized and presented using the principles of descriptive and inferential statistics. The data were categorized and expressed in proportions. A statistician help was taken. Where analytical statistics were performed, a p-value of <0.05 was considered to be statistically significant for the purpose of the study.

RESULTS

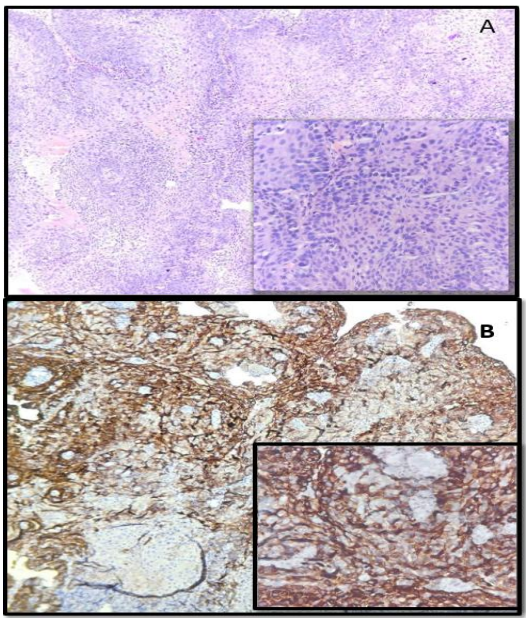

Figure 1: Squamous Cell Carcinoma ofthe cervix (A) H&E image, 10X, Inset; 40x, with the presence of PD-L1 expression in tumor cells and PD-L1 in TILs (B) 10X, Inset;40x

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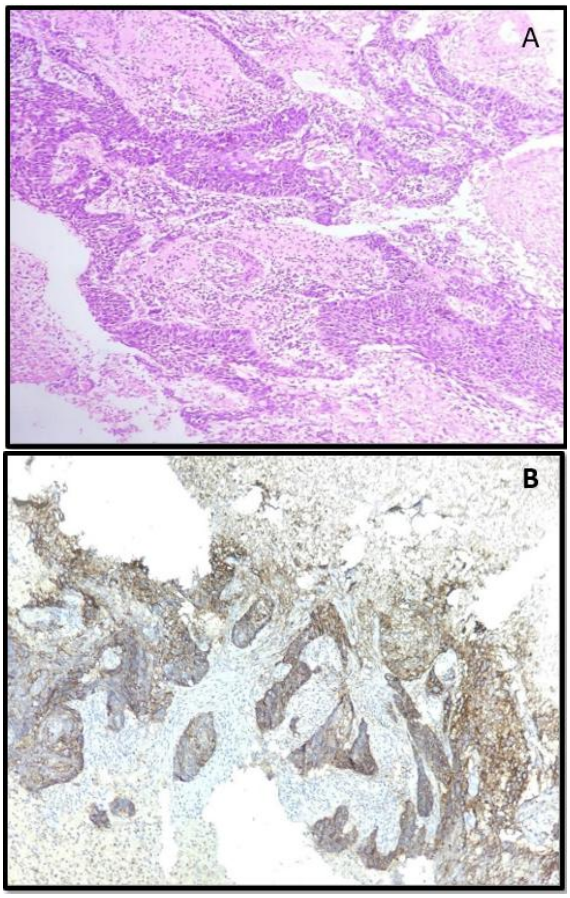

Figure 2: A case of Poorly differentiated Squamous cell carcinoma of cervix (A) H&E image with the presence of PD-L1 expression in tumor cells and PD-L1 in TILs (B): 10X

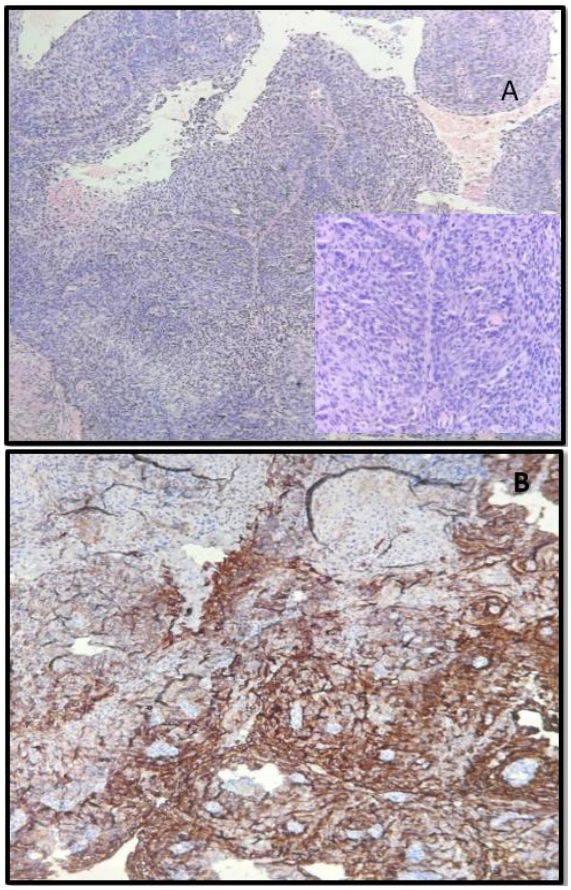

Figure 3: A case of Moderately differentiated Squamous Cell Carcinoma ofthe cervix (A) H&E , with the presence of PD-L1 expression in tumor cells and PD-L1 in TILs (B):10X

Table 1: Patient data.

Age (years)	Frequency (No of CSCC)	Percentage
30-40	4	4
41-50	26	26
51-60	31	31
61-70	39	39
Diagnosis		
Keratinizing well-differentiated squamous cell carcinoma	6	6
Non-keratinizing moderately differentiated squamous cell carcinoma	82	82
Non-keratinizing poorly differentiated squamous cell carcinoma	12	12
Residence		
Rural	63	63
Urban	37	37
Marital status		
Married	97	97
Unmarried	3	3
Menopausal status		
Yes	85	85
No	15	15
Morphological variant		
Keratinizing	6	6
Non-keratinizing	94	94

The study population comprised individuals aged 30 to 70 years, with the highest representation in the 61-70 age group (39%), followed by the 51-60 age group (31%), the 41-50 age group (26%) and the least representation in the 30-40 age group (4%). The majority of the cases were diagnosed as non-keratinizing moderately differentiated squamous cell carcinoma (82%), followed by non-keratinizing poorly differentiated squamous cell carcinoma (12%) and keratinizing well- differentiated squamous cell

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carcinoma (6%). 63% of the participants belonged to rural families. 97% of the women in the study sample were married, 3 were unmarried. 85% had achieved menopause at the time of presentation. The vast majority of the squamous cell carcinoma cases were non-keratinizing (94%), with only a small fraction being keratinizing (6%).

Table 2: Tumor grade, Expression of PDL-1, P16 in cervical SCC

Tumor grade	Frequency	Percentage
Well-differentiated	6	6
Moderately differentiated	82	82
Poorly differentiated	12	12
PDL-1		
Expressed	85	85
Not expressed	15	15
P16		
Block positive	95	95
Not associated	5	5

Most tumors were moderately differentiated (82%), with poorly differentiated tumors accounting for 12% and well-differentiated tumors making up 6%. A significant majority (95%) of the cases were block positive for P16, while 5% were not associated.

Table 3: Degree of PDL-1 expression in cervical SCC and Tumor infiltrating lymphocytes grading in tumor

Degree of PDL-1 expression in CSCC	Frequency	Percentage
<1%	15	15
1-5%	0	0
6-10%	17	17
11-25%	25	25
26-50%	13	13
>50%	30	30
TILS		
<1%	0	0
1-10%	41	41
11-25%	27	27
25-50%	14	14
>50%	18	18

PD-L1 expression varied widely, with 30% of tumors showing >50% expression, followed by 25% with 11-25% expression, 17% with 6-10% expression, 15% with <1% expression, and 13% with 26-50% expression. The majority of tumors had TILs in the range of 1-10% (41%), followed by 11- 25% (27%), >50% (18%), and 25-50% (14%).

Table 4: Combined positive score grading in patients

CPS	Frequency	Percentage
<1	15	15
1-5	11	11
6-10	6	6
11-25	25	25
26-50	25	25
>50	18	18

CPS grading showed a wide distribution, with 25% of cases each in the 11-25% and 26-50% ranges, 18% in the >50% range, 15% in the <1% range, 11% in the 1-5% range, and 6% in the 6-10% range.

Table 5: Relation between PDL-1 expression and age

Age	PD-L1 expression			p-value
	Present (%)	Absent (%)	Total (%)	
30-40	4 (4.7)	0 (0)	4 (4)	0.287
41-50	21 (24.7)	5 (33.3)	26 (26)	
51-60	29 (34.1)	2 (13.3)	31 (31)	
61-70	31 (36.5)	8 (53.3)	39 (39)	
Total	85 (100)	15 (100)	100 (100)	

PD-L1 expression was present in 85% of cases and absent in 15%. Among those with PD-L1 expression, the highest prevalence was observed in the 61-70 age group (36.5%), followed by 51-60 years (34.1%), 41-50 years (24.7%), and 30-40 years (4.7%). For those without PD-L1 expression, the highest prevalence was in the 61-70 age group (53.3%), followed by 41-50 years (33.3%) and 51-60 years (13.3%).

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Table 6: Relation between PDL-1 expression and morphological variant of SCC

Morphological variant	PD-L1 expression			p-value
	Present (%)	Absent (%)	Total (%)	
Keratinizing	3 (3.5)	3 (20)	6 (6)	0.059
Non keratinizing	82 (96.5)	12 (80)	94 (94)	
Total	85 (100)	15 (100)	100 (100)	

PD-L1 expression in different morphological variants of squamous cell carcinoma (SCC) showed a non-significant trend (p=0.059). PD-L1 was present in 96.5% of non-keratinizing SCCs compared to 3.5% in keratinizing SCCs. Among those absent, 80% were non-keratinizing and 20% keratinizing.

Table 7: Relation between PDL-1 expression and tumor grade

Tumor grade	PD-L1 expression			p-value
	Present (%)	Absent (%)	Total (%)	
Moderately differentiated	71 (86.58%)	11 (13.41%)	82 (100)	0.001*
Poorly differentiated	12 (100%)	0 (0%)	12 (100)	
Well- differentiated	2 (33.33%)	4 (66.67%)	6 (100)	
Total	85	15	100 (100)	

A significant relationship was found between PD-L1 expression and tumor grade (p=0.001). Poorly differentiated tumors had the highest PD-L1 expression (100%), followed by Moderately differentiated (86.58%) and well-differentiated (33.33%) tumors.

Table 8: Relation between PDL-1 expression and P16 expression

P16	PD-L1 expression			p-value
	Present (%)	Absent (%)	Total (%)	
Block positive	80 (94.1)	15 (100)	95 (95)	0.335
Not associated	5 (5.9)	0 (0)	5 (5)	
Total	85	15	100 (100)	

Among those with PD-L1 expression, 94.1% were block positive for P16, while 5.9% were not associated. All cases without PD-L1 expression were block positive for P16.

DISCUSSION

Cervical cancer has a high prevalence in India, accounting for a substantial part of the global disease burden.[16] As the second most common cancer among women in India, cervical cancer has a profound impact on the health and well-being of Indian women.[17] High-risk types of human papillomavirus (HPV) infection has been implicated in the causative pathway for cervical cancer.[18] The incidence and prevalence of HPV infection in India are high, contributing to the substantial burden of cervical cancer. According to the Global Cancer Observatory (GLOBOCAN) 2020 data, India has nearly one-fifth of the global burden of cervical cancer, with approximately 123,907 new cases and 77,348 deaths annually.[19] This elevated incidence rate is likely due to a combination of factors such as marrying at a young age, having many children, inadequate genital hygiene, and restricted access to screening and vaccination programs.[20]

The age distribution in this study indicates that cervical carcinoma predominantly affects older women, particularly those aged 51 and above. This finding is consistent with several studies that have demonstrated a higher incidence of cervical cancer in older women. Feng et al,[21] observed that cervical carcinoma was more prevalent among women aged over 50, with a peak incidence in the 60-70 age group. The distribution of cervical carcinoma types in this study shows a predominant occurrence of non-keratinizing moderately differentiated squamous cell carcinoma (82%), followed by non-keratinizing poorly differentiated squamous cell carcinoma (12%) and keratinizing well-differentiated squamous cell carcinoma (6%). This finding aligns with previous research indicating that non- keratinizing squamous cell carcinomas are more common. Yang et al,[22] highlighted that non-keratinizing variant of squamous cell carcinoma, especially those with moderate differentiation, are frequently observed in cervical cancer patients, suggesting a distinct pathophysiological pathway driven by HPV infection.

The distribution of participants' residence in this study indicates that a significant majority, 63%, belonged to rural families, while 37% were from urban areas. This finding aligns with several studies highlighting the higher prevalence of cervical cancer in rural populations. Meng et al,[23] found that cervical cancer incidence was notably higher in rural areas compared to urban settings, primarily due to limited access to healthcare facilities and screening programs in rural regions. The marital status distribution in this study reveals that a vast majority of the participants, 97%, were married, while only 3% were unmarried. This finding is consistent with previous studies indicating that marital status can influence the risk and prevalence of cervical cancer. Saglam et al,[24] observed that married women tend to have a higher risk of developing cervical cancer due to factors such as higher parity and longer duration of

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sexual activity, which increase the likelihood of persistent HPV infection.

The study found that 85% of the participants had achieved menopause at the time of presentation, highlighting the prevalence of cervical carcinoma among postmenopausal women. This observation is consistent with several studies that have shown a higher incidence of cervical cancer in postmenopausal women. Feng et al,[21] reported that the risk of cervical cancer increases with age, particularly after menopause, due to prolonged exposure to oncogenic HPV strains and the gradual weakening of the immune system. The study found that 94% of the squamous cell carcinoma (SCC) cases were non-keratinizing, with only 6% being keratinizing. This predominance of the non-keratinizing morphological variant aligns with typical histopathological observations in cervical carcinoma. Yang et al,[22] reported that non-keratinizing SCC is the most common variant in cervical cancer, often associated with high-risk HPV types and more aggressive disease progression.

The study revealed that 82% of the cervical carcinoma cases were moderately differentiated, 12% were poorly differentiated, and 6% were well-differentiated. Zhang et al,[25] reported that moderately differentiated tumors are frequently observed in cervical carcinoma, indicating an intermediate level of aggressiveness and a potential for progression if not adequately managed. The study observed PD-L1 expression in 85% of the cervical carcinoma cases, indicating a high prevalence of this biomarker in the tumor samples. This finding is consistent with several studies that have demonstrated the common upregulation of PD-L1 in cervical carcinoma. Song et al,[26] found that high PD-L1 expression is frequently associated with cervical cancer, contributing to immune evasion mechanisms and tumor progression. The distribution of PD-L1 expression levels in this study showed considerable variability, with 30% of tumors exhibiting >50% expression, 25% with 11-25% expression, 17% with 6-10% expression, 15% with <1% expression, and 13% with 26-50% expression. Yang et al,[22] found similar variability in PD-L1 expression levels, noting that higher PD-L1 expression was associated with more aggressive tumor behavior and poorer prognosis. The combined positive score (CPS) grading in this study showed a wide distribution, with 25% of cases each in the 11-25% and 26-50% ranges, 18% in the >50% range, 15% in the <1% range, 11% in the 1-5% range, and 6% in the 6-10% range. This diversity in CPS scores reflects varying levels of PD-L1 expression and immune cell infiltration, which could significantly influence the prognostic and therapeutic outcomes for patients with cervical carcinoma. Meng et al,[23] found that higher CPS scores were associated with poorer prognosis and increased tumor aggressiveness, as high PD-L1 expression and immune cell infiltration can contribute to tumor immune evasion and progression.

The study investigated the relationship between PD-L1 expression and age among 100 participants, revealing no significant correlation (p=0.287). PD-L1 expression was observed in 85% of cases, predominantly in the 61-70 age group (36.5%), followed by 51-60 years (34.1%), 41-50 years (24.7%), and 30-40 years (4.7%). Among those without PD-L1 expression, the highest prevalence was in the 61-70 age group (53.3%), followed by 41-50 years (33.3%) and 51-60 years (13.3%). This finding aligns with Rivera-colon et al[27] found PD-L1 expression in 95% of CINs and 80% of cervical cancers, emphasizing its role regardless of age. The study assessed the relationship between PD-L1 expression and morphological variants of squamous cell carcinoma (SCC) in 100 participants, revealing a non-significant trend (p=0.059). PD-L1 was present in 96.5% of non-keratinizing SCCs, compared to 3.5% in keratinizing SCCs. Among those absent, 80% were non-keratinizing, and 20% were keratinizing. This indicates a higher prevalence of PD-L1 expression in non-keratinizing SCCs, suggesting a trend that may warrant further investigation. This aligns with findings by Meng et al23 who observed PD-L1 expression in 95% of CINs and 80% of cervical cancers, with higher levels in non-keratinizing types.

The study investigated the relationship between PD-L1 expression and P16 expression in 100 participants. PD-L1 expression was not significantly associated with P16 expression (p=0.335). Among those with PD-L1 expression, 94.1% were block positive for P16, while 5.9% were not associated. All cases without PD-L1 expression were block positive for P16, indicating a high prevalence of PD-L1 expression in P16 block positive cases. This suggests a potential overlap in the biological pathways of PD-L1 and P16 in cervical carcinoma. These findings are consistent with previous studies. Yang et al[22] reported a correlation between increased PD-L1 expression and HPV positivity, which often involves P16 expression, highlighting the potential interaction between these markers.

CONCLUSION

The high prevalence of PD-L1 expression in cervical carcinoma suggests its potential role in immune evasion and as a therapeutic target for PD-L1 inhibitors. Further research is needed to explore the relationship between PD-L1 expression and tumor aggressiveness to improve prognostic assessments and personalized treatment strategies.

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