Original Article

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Pathology Section

Expression of Programmed Death Ligand-1 in Head and Neck Squamous Cell Carcinoma: A Cross-sectional Study

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ABSTRACT

Introduction: Head and Neck Squamous Cell Carcinoma (HNSCC) is among the most prevalent malignancies worldwide, with poor survival outcomes despite advances in multimodal therapy. Tumour immune evasion through the Programmed Death-1/Programmed Death Ligand-1 (PD-L1) PDL-1/PD-L1 immune checkpoint pathway has emerged as a crucial mechanism in HNSCC progression. PD-L1 expression, detectable by Immunohistochemistry (IHC), is a promising predictive and prognostic biomarker, especially when evaluated alongside histological grading systems such as Anneroth's multifactorial grading.

Aim: To evaluate PD-L1 expression in HNSCC using IHC and associate it with Anneroth's histological grading.

Materials and Methods: This cross-sectional study conducted at Pt. B.D. Sharma Postgraduate Institute of Medical Sciences, Rohtak over a one-year period from 1st December 2023 to 31st December 2024 included 60 histologically confirmed cases of HNSCC. Histopathological diagnosis was established on routine Haematoxylin and Eosin (H&E) stain. Tumours were classified and graded according to WHO criteria and Anneroth's multifactorial grading system. PD-L1 expression was assessed using IHC and quantified by the Combined Positive Score (CPS). The status of PDL-1 was assessed and association with various clinicopathological prognostic parameters including age, gender, histologic type, histologic grade, Anneroth`s grading parameters and CPS score. The collected data were analysed with the help of Statistical Package for Social Sciences (SPSS) version 24.0. All the data enlisted in the investigation proforma (name, age, gender, clinical diagnosis and history) were collected. Cases were compared to controls. Association was evaluated using Chi-square test. The p-value less than 0.05 were accepted as statistically significant.

Results: Age of the patients ranged from 31-90 years with a median age of 58.0 years. The majority of cases, 21 (35.0%) were in the age group of 51-60 years. 47 (78.3%) cases were male and 13 (21.7%) cases were female. A 13 (21.7%) cases were well-differentiated, 37 (61.7%) cases were moderately differentiated and 10 (16.7%) cases were poorly differentiated SCC. In Anneroth's multifactorial grading system, majority of cases i.e., 37 (61.7%) assigned grade 2, 12 (20.0%) cases were assigned grade 1, 10 (16.7%) cases assigned grade 3 and one (1.7%) cases assigned grade 4. PD-L1 positivity was observed in 45 (75%) cases, with 26 (43.3%) cases showing low expression (CPS 1-20) and 19 (31.7%) cases showing high expression (CPS ≥20). PD-L1 expression was significantly associated with World Health Organisation (WHO) histological grading, with the highest prevalence among moderately differentiated tumours (p-value=0.037). Similarly, PD-L1 expression positively correlated with higher Anneroth's grades (p-value=0.020). No significant association was found between PD-L1 expression and age (p-value=0.079) or presenting complaints (p-value=0.764).

Conclusion: PD-L1 expression in HNSCC is significantly associated with both WHO and Anneroth's histological grades, highlighting its role in tumour aggressiveness and immune evasion. Incorporating PD-L1 profiling alongside detailed histopathological grading provides valuable prognostic information and may guide patient selection for immune checkpoint inhibitor therapy.

Keywords: Anneroth's grading, Immunohistochemistry, Prognostic biomarker

INTRODUCTION

The HNSCC is a biologically diverse malignancy that arises from the mucosal epithelium of the oral cavity, pharynx, and larynx. It remains one of the most prevalent cancers globally, accounting for approximately 600,000 new cases annually, with a substantial burden in developing countries due to delayed diagnosis and limited access to specialised care [1]. Despite advancements in surgery, radiotherapy, and chemotherapy, survival outcomes for advanced-stage HNSCC remain dismal, necessitating a deeper understanding of tumour immunobiology to inform novel therapeutic approaches.

One of the most promising areas of investigation in oncology is tumour immune evasion, particularly through the PD-1)/PD-L1 immune checkpoint pathway. PD-L1, expressed on tumour cells and tumour-infiltrating immune cells, binds to PD-1 receptors on cytotoxic T lymphocytes, leading to T-cell inactivation and apoptosis. This interaction facilitates immune escape and contributes to tumour progression [2]. In HNSCC, where immune infiltration is heterogeneous, PD-L1 has emerged as a biomarker of immune resistance, as well as a therapeutic target [3].

Recent studies have shown that PD-L1 expression is not uniform across HNSCC subtypes, and varies depending on tumour site, HPV status, and histological grade [4]. Moreover, clinical trials such as KEYNOTE-048 have demonstrated that anti-PD-1 therapy (e.g., pembrolizumab) yields survival benefits, especially in patients with high PD-L1 expression [5]. PD-L1 is most commonly evaluated using IHC, and its expression is quantified using two main scoring systems: Tumour Proportion Score (TPS) and CPS. CPS includes both tumour cells and immune cells (lymphocytes and macrophages) showing PD-L1 expression, making it a more comprehensive marker. This has made PD-L1

not only a biologically meaningful molecule but also a clinically actionable biomarker [5].

From a histopathological standpoint, the aggressiveness of HNSCC has long been evaluated using grading systems. While the WHO classification (WHO Classification of Head and Neck Tumours, 2022) broadly categorises tumours into well, moderately, and poorly differentiated forms, this system does not fully capture the biological nuances of tumour behaviour [6]. To address this, Anneroth's G et al., proposed a more detailed histologic grading system based on six parameters: degree of keratinisation, nuclear polymorphism, number of mitotic figures, mode of invasion, depth of invasion, and lymphoplasmacytic response [7].

Each of these parameters reflects a distinct aspect of tumour biology. High nuclear pleomorphism and increased mitotic activity indicate genomic instability, whereas diffuse invasion patterns and reduced host immune response suggest aggressive local spread. These features, when combined, enable stratification of tumours into grades I, II, and III, corresponding to low, intermediate, and high malignant potential, respectively [8]. The study was conducted to assess the association between histological indicators of aggressiveness with PD-L1 expression, providing insights into how tumour differentiation and immune checkpoint expression co-evolve.

Previous studies have suggested that poorly differentiated tumours or those with higher Anneroth's grades are more likely to express PD-L1, possibly due to greater mutational burden, hypoxia-induced signaling, and interferon-γ pathway activation, all of which upregulate PD-L1 transcription [9,10]. However, findings remain inconsistent across different populations and tumour sites, highlighting the need for locoregional studies that combine histological analysis with IHC.

The present study was undertaken to evaluate PD-L1 expression in HNSCC using IHC and associate it with Anneroth's histological grading. The goal is to assess whether PD-L1 can serve not only as a predictive marker for immunotherapy but also as an indicator of tumour histological gical aggressiveness, thus bridging morphological pathology with immune-oncology.Hence, the study aimed to determine the expression of PD-L1 in. HNSCC using IHC and to associate its expression with clinical parameters and histopathological grades as per WHO and Anneroth's grading systems.

MATERIALS AND METHODS

This was a cross-sectional study conducted in the Department of Pathology at Pt. B.D. Sharma Postgraduate Institute of Medical Sciences, Rohtak over a one-year period from 1st December 2023 to 31st December 2024. The study was approved by the Institutional Ethics Committee with IEC No. BREC/23/TH-Pathology/12. Informed written consent was obtained from all patients whose samples were included in the study.

Sample size calculation: The study sample was estimated using the formula

$4PQ/L^2$ (Where P- Prevalence of PD-L1 in HNSCC, L- Allowable error; P = 14% and L= 20% of P). Based on sample size calculation, a minimum of 60 cases were included in the study [11].

Inclusion and Exclusion criteria: The study included 60 histologically confirmed excision biopsy cases of HNSCC. Only primary tumours from the head and neck region with definitive histological evidence of squamous cell carcinoma were considered. Non squamous cell carcinomas of the head and neck, inadequate or necrotic biopsies, cases lacking complete clinical data or with prior treatment affecting tissue morphology were excluded from the study.

Study Procedure

Specimens were fixed in 10% neutral buffered formalin for 12-24 hours. Gross examination of the tissues was followed by representative sectioning and processing using standard paraffin-embedding techniques. These sections were stained with Haematoxylin and Eosin (H&E) for routine histopathological examination. Tumours were classified according to the WHO classification and further graded using Anneroth's multifactorial grading system as shown in [Table/Fig-1], which evaluates six parameters: Degree of keratinisation, Nuclear pleomorphism, Number of mitoses per high-power field, Pattern of invasion, Stage of invasion and Lymphoplasmacytic infiltrate [6]. Each parameter was scored from 1 to 4.

Tumour grade	Cumulative score using Anneroth's multifactorial grading system
I (Well-differentiated)	5-10
II (Moderately differentiated)	11-15
III (Poorly differentiated)	16-20
IV (Undifferentiated)	>20

[Table/Fig-1]: Anneroth's multifactorial grading system using CPS score [5].

Immunohistochemical analysis was performed on 3-4 µm thick sections taken from formalin-fixed, paraffin-embedded blocks. The primary antibody used was anti–PD-L1 (Clone 22C3, Dako), which is FDA-approved for clinical PD-L1 assessment. PD-L1 expression was evaluated in both tumour cells (TCs) and immune cells (ICs) using the CPS: CPS = (Number of PD-L1positive tumour cells + immune cells)/(Total number of viable tumour cells) × 100.

Evaluation criteria

Tumour cells: Only membranous staining (partial or complete) was considered positive.

Immune cells: Staining of mononuclear inflammatory cells (lymphocytes and macrophages) in tumour nests or stroma.

Minimum of 100 viable tumour cells were required for CPS calculation.

Necrotic areas and staining artifacts were excluded from scoring.

All slides were independently reviewed by two pathologists, and discrepancies were resolved by consensus.

Demographic details such as age, gender, chief complaints, and tumour site were recorded.

Histopathological features including tumour grade and Anneroth's parameters such as degree of keratinisation, nuclear polymorphism, number of mitotic figures, mode of invasion, depth of invasion and lymphoplasmacytic response were documented.

IHC results for PD-L1 expression were recorded as per CPS categories as shown in [Table/Fig-2] [5]. Score was divided into three groups: CPS <1: no PD-L1 expression. CPS ≥1 and <20%: Low expression. CPS ≥20%: High PD-L1 expression.

CPS Score	PD-L1 expression
<1	No
≥1 to <20	Low
≥20	High

[Table/Fig-2]: Expression of PDL 1 using CPS score.

STATISTICAL ANALYSIS

Data were compiled and analysed using SPSS version 24.0. Continuous variables were expressed as Mean ± Standard Deviation (SD), while categorical variables were expressed as frequency and percentage. Associations between PD-L1 expression and clinicopathological parameters were evaluated using the Chi-square test or Fisher's exact test.

RESULTS

The results were derived from 60 biopsy-confirmed cases of HNSCC processed and stained with PD-L1 IHC. Age of the patients ranged from 31-90 years with a median age of 58.0 years. Maximum no. of cases 21 (35.0%) was in the age group of 51-60 years. The age distribution of the study population is shown in [Table/Fig-3]. Total of 47 cases (78.3%) were male and 13 cases (21.7%) were female. The gender distribution of the study population is shown in [Table/Fig-4]. Patients presented with various complaints most common being difficulty in swallowing 44 (73.3%) and change in voice accounting for 10 cases (16.7%), respectively. Growth at base of tongue (5%), hoarseness of voice (1.7%) and tongue ulcer (3.3%) were other presenting complaints.

Age	n (%)
31-40 years	6 (10.0%)
41-50 years	10 (16.7%)
51-60 years	21 (35.0%)
61-70 years	14 (23.3%)
71-80 years	7 (11.7%)
81-90 years	2 (3.3%)
Total	60 (100%)

[Table/Fig-3]: Distribution of the cases according to age (N=60).

Gender	n (%)
Male	47 (78.3%)
Female	13 (21.7%)
Total	60 (100%)

[Table/Fig-4]: Distribution of the cases according to gender (N=60).

On routine histopathological examination using H&E stain, 13 (21.7%) cases were graded as well differentiated SCC, 37 (61.7%) cases were graded as moderately differentiated and 10 (16.7%) cases graded as poorly differentiated SCC. Cases were also categorised according to Anneroth's multiparametric grading system which evaluated six parameters as shown in [Table/Fig-5]: degree of keratinisation, nuclear pleomorphism, number of mitoses per high-power field, pattern of invasion, stage of invasion and lymphoplasmacytic infiltrate. Out of 60 cases 37 (61.7%) were grade II, 12 (20.0%) were grade I, 10 (16.7%) and 1 (1.7%) were grade III and grade IV, respectively.

All the cases were assessed for PDL-1 expression as shown in [Table/Fig-6]. 45 cases (75%) were PDL-1 positive and 15 cases (25%) were PDL-1 negative. As per intensity of PDL-1 expression, 15 cases (25%) had negative PD-L1 expression, 26 (43.3%) had low and 19 (31.7%) had high expression. All the cases were assessed for CPS score. 15 cases (25%) had CPS score: <1%, 26 (43.3%) had CPS Score:1-20% and 19 cases (31.7%) had CPS score: >20%. Association between PDL-1 expression and histopathological grade of the tumour shown in [Table/Fig-7].

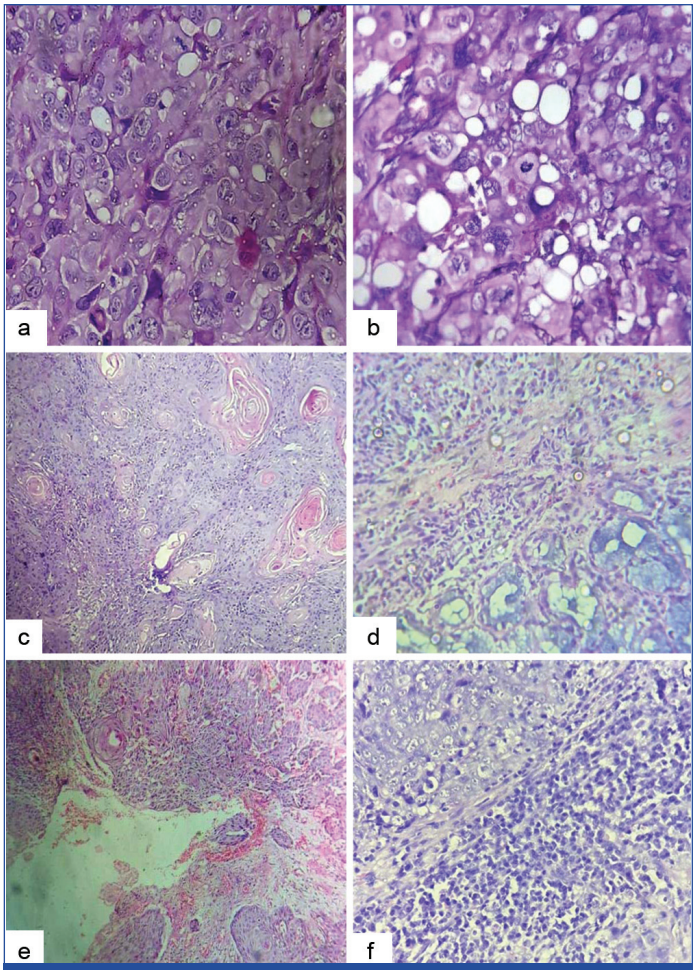
PDL-1 expression was associated with Anneroth's grade and there was statistically significant association (p=0.020) as shown in [Table/ Fig-8].

A significant association of PDL-1expression was also seen with intensity of expression (p-value <0.001) and CPS score (p-value <0.001).

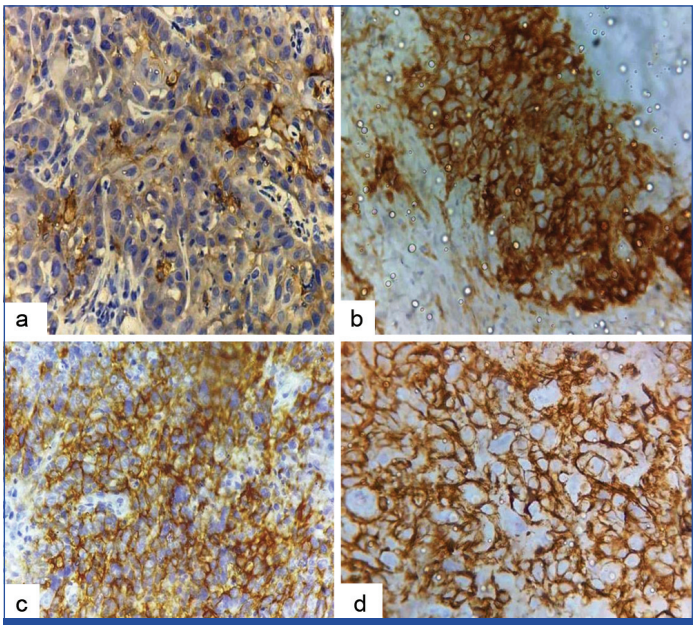
PDL-1 expression was not significantly associated with age (p-value=0.079) and chief complaints (p-value=0.764).

DISCUSSION

The PD-L1, a key component of the PD-1/PD-L1 immune checkpoint axis, plays a crucial role in tumour immune evasion by downregulating T-cell activity within the tumour microenvironment. In recent years, its expression has emerged as both a prognostic



[Table/Fig-5]: a) Nuclear Pleomorphism (H&E; 400X); b) Mitosis/HPF (H&E; 400X); c) Keratinisation (H&E; 400X); d) Infiltrating into saliary gland (H&E; 400X); e) Infiltrating cords (H&E; 100X); f) Lymphocytic Infiltrate (H&E; 400X).



[Table/Fig-6]: a) Grade I PDL-1 Positive (IHC; 400X); b) Grade 2 PDL-1 Positive (IHC; 400X); c) Grade 3 PDL-1 Positive (IHC; 400X); d) Grade 4 PDL-1 Positive (IHC; 400X).

Histopathological grade	PDL-1			p-value
	Positive	Negative	Total	
WDSCC (Grade I)	6 (13.3%)	7 (46.7%)	13 (21.7%)	0.037
MDSCC (Grade II)	31 (68.9%)	6 (40.0%)	37 (61.7%)	
PDSCC (Grade III)	8 (17.8%)	2 (13.3%)	10 (16.7%)	
Total	45 (100.0%)	15 (100.0%)	60 (100.0%)	

[Table/Fig-7]: Association between PDL-1 expression and histopathological grade of the tumour (N=60) Values are expressed as n (%).

Anneroth's grade	PDL-1			p-value
	Positive	Negative	Total	
Grade I	5 (11.1%)	7 (46.7%)	12 (20.0%)	0.020
Grade II	30 (66.7%)	7 (46.7%)	37 (61.7%)	
Grade III	9 (20.0%)	1 (6.7%)	10 (16.7%)	
Grade IV	1 (2.2%)	0 (0.0%)	1 (1.7%)	
Total	45 (100.0%)	15 (100.0%)	60 (100.0%)	

[Table/Fig-8]: Association between PDL-1 expression and Anneroth's grade (n=60).
*Association was evaluated using Fisher's-Exact test. p-value less than 0.05 was accepted as statistically significant.

marker and a predictive biomarker for immune checkpoint blockade therapies in various cancers, including HNSCC.

In the present study, 75% of patients with HNSCC showed PD-L1 expression, with 33.3% demonstrating low expression (CPS 1-20) and 41.7% showing high expression (CPS ≥20). This aligns with findings from Wusiman A et al., who documented PD-L1 positivity in 76% of HNSCC patients using CPS scoring, particularly among laryngeal squamous cell carcinoma cases [12].

When associating PD-L1 expression with WHO histological grade, this study found a statistically significant association, especially among moderately differentiated tumours (grade II), where most PD-L1 positive cases clustered (p=0.037). This suggests that tumour differentiation may influence or reflect immune escape mechanisms. Yang W et al., similarly observed higher PD-L1 expression in moderately differentiated oral squamous cell carcinomas [13].

Majority of cases with PDL-1 expression were moderately differentiated (grade II). PDL-1 expression was significantly associated with histopathological grade of tumour (p-value 0.037). The significant association between PD-L1 expression and histopathological tumour grade (p=0.037) holds meaningful clinical relevance. Although moderately differentiated (Grade II) tumours constituted the largest proportion of cases, the association reflects a biological pattern rather than merely numerical distribution. As tumour differentiation decreases, the malignant cells tend to exhibit greater aggressiveness and enhanced capacity for immune evasion, including increased PD-L1 expression. Thus, the observed trend suggests that PD-L1 upregulation is linked to the progressive dedifferentiation of tumour cells. This supports the notion that PD-L1 plays a role in facilitating immune escape in more aggressive tumour phenotypes and may serve as a useful biomarker for identifying patients who are more likely to benefit from immune checkpoint inhibitor therapy.

However, not all studies have reached a consensus. Troiano G et al., through a meta-analysis, noted inconsistent correlations between PD-L1 and tumour grade, suggesting other molecular or microenvironmental factors may modulate PD-L1 expression beyond traditional histological parameters [14].

Anneroth's grading offers a more detailed assessment of tumour aggressiveness by incorporating parameters such as keratinisation, nuclear pleomorphism, mitotic activity, invasion pattern, invasion depth, and lymphoplasmacytic infiltration. In the present study, PD-L1 expression positively correlated with higher Anneroth's grades (grade II and III), reinforcing the link between tumour biological behaviour and immune checkpoint activation (p=0.020). Tumours with higher Anneroth's scores often exhibit increased mitotic index, nuclear atypia, and invasive potential, all of which contribute to an immunosuppressive tumour microenvironment where PD-L1 may be upregulated to facilitate immune escape.

Similarly, Rasmussen JH et al., highlighted the spatial heterogeneity of PD-L1 expression in HNSCC and noted that more aggressive, poorly differentiated tumours had higher PD-L1 expression levels. This matches the finding that even a single poorly differentiated (grade IV) case in the current study expressed high PD-L1 [15].

Importantly, PD-L1 expression has been proposed as a dynamic marker, influenced by prior therapies such as radiation and chemotherapy. Delafoy A et al., observed that PD-L1 expression varied in recurrent tumours, often increasing after treatment, suggesting that higher-grade or treatment-resistant tumours may upregulate PD-L1 as an adaptive resistance mechanism [16].

The present study indicates that approximately one-third (31.7%) of HNSCC patients could be eligible for immune checkpoint therapy targeting PD-L1. The KEYNOTE-048 trial demonstrated a survival advantage in HNSCC patients treated with pembrolizumab monotherapy, particularly when CPS ≥20 [5]. Similarly, Ferris RL et al., demonstrated a survival benefit using nivolumab in PD-L1-positive recurrent or metastatic [17].

Additionally, Kim HR et al., noted that PD-L1 expression on immune cells rather than tumour cells correlated with improved prognosis, suggesting that not just expression level but localisation and cellular source of PD-L1 are essential factors for prognosis and therapy selection. The present study's use of CPS- capturing PD-L1 on both tumour and immune cells-provides a more comprehensive picture of PD-L1 activity and is aligned with current clinical practice [11].

This integrative analysis reinforces the value of combining Anneroth's histological scoring with PD-L1 immunoprofiling to identify high-risk tumours and guide immunotherapy decisions.

Limitation(s)

The sample was drawn from a single tertiary care centre, which may restrict the broader applicability of the findings. HPV status, an important biological variable known to influence tumour behaviour and immune response, was not assessed and therefore its relationship with PD-L1 expression could not be explored. Additionally, interpretation of PD-L1 IHC can vary depending on antibody clones, staining protocols, and observer judgment, potentially affecting reproducibility across settings. The use of biopsy specimens alone may not fully capture intratumoural heterogeneity in PD-L1 expression. Furthermore, clinical outcome data and response to therapy were not included, limiting the ability to evaluate the prognostic or predictive implications of PD-L1 expression.

CONCLUSION(S)

The PD-L1 expression in HNSCC reflects the interaction between tumour aggressiveness and host immune response. Its association with higher Anneroth's grades highlights its relevance as a potential prognostic marker and therapeutic target. Incorporating PD-L1 evaluation into routine histopathological assessment may assist in more precise patient selection for immunotherapy and support individualised treatment planning.

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