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Original Article

Pathology Section

PD-L1 Expression by Tumour Cells and Tumour Infiltrating Lymphocytes in Gastric Carcinoma and Its Association with Clinicopathological Parameters: A Cross-sectional Study

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ABSTRACT

Introduction: According to the worldwide statistics on cancers, gastric carcinoma is in the fifth position. One of the most common risk factors is Helicobacter pylori. Hereditary factors also play a major role in the risk factors. Recently, the trend of using immunotherapy in a cancer treatment protocol has shown very promising results. Some types of cancer show an interaction between Programmed Death Ligand-1 (PD-L1) in cancer cells and Programmed Death-1 (PD-1) in T cells, which inhibits T cell function and thus aids the cancer cells to avoid entering the immune system.

Aim: To assess the expression of PD-L1 in tumour cells and tumour infiltrating lymphocytes in gastric carcinoma.

Materials and Methods: This was a hospital-based cross-sectional study conducted at the Department of Pathology, Amala Institute of Medical Sciences, Thrissur, Kerala, India, for a time period of 19 months from October 2022 to April 2024 among 33 gastric carcinoma cases, which included 20 gastric biopsies and 13 gastrectomy specimens. Histopathological and immunohistochemical results were recorded. Clinical details like age, gender and pathological details like gross appearance, histological type, depth of invasion, lymph node status, vascular invasion and TNM classification was studied, followed by PD-L1 immunohistochemistry and scored by Combined Positive Score (CPS) The data was entered into a Microsoft Excel worksheet and analysis was performed using Statistical Package for Social Sciences (SPSS) 23.0. Association between PD-L1 and clinicopathological parameters were analysed by Fisher's-exact Test. Descriptive statistics were carried out. Significance was assessed at a 5% level.

Results: Three of the 33 patients had both tumour cells and tumour-infiltrating lymphocytes that tested positive for PD-L1, which was suggestive of difficulty in statistical correlation. Combined positive score for case 1 was 42%, case 2 was 20%, and case 3 was 63%. The clinicopathological characteristics and PD-L1 expression were compared. The following clinicopathological parameters were examined: gender (p-value=0.629), age (p-value=1.000), gross appearance (p-value=1.000), histological type (p-value=0.775), vascular invasion (p-value=0.423), depth of invasion/T stage (p-value=0.159), and node involvement/N stage (p-value= 0.408). There was no discernible correlation.

Conclusion: Three of the gastric cancer patients examined in the current investigation had PD-L1 expression, suggesting a low incidence of PD-L1 positive in our cohort. There was no discernible correlation found between PD-L1 expression and the assessed clinicopathological characteristics. However, the capacity to identify significant connections might have been limited by the small sample size. Therefore, in order to precisely ascertain the prevalence of PD-L1 expression and its correlation with clinicopathological characteristics in gastric cancer, larger investigations with a higher number of cases are needed. Additionally, PD-L1 testing may be crucial in determining which patients may benefit from immune checkpoint inhibitor therapy, underscoring its potential utility as a predictive biomarker and a guide for individualised treatment plans in gastric cancer.

Keywords: Biomarkers, B7-H1 Antigen, Lymphocyte, Immune checkpoint inhibitors, Stomach neoplasm, Tumour

INTRODUCTION

Globally, gastric cancer is a major public health concern. It continues to be a major cause of cancer-related death globally, even if the total incidence has been falling in many areas [1].

Tumour microenvironment, particularly immune modulation, plays a crucial role in cancer progression. Programmed Death Ligand 1 or PD-L1 and its interaction with Programmed Cell Death-1 or PD-1 receptors in T cells that infiltrate the tumour, inhibits T cell function and helps tumour cells evade the immune system. Blockade of the PD-1/PD-L1 pathway restores anti-tumour immune responses and enhances T-cell mediated tumour cell destruction [2].

Immunotherapeutic agents targeting immunosuppressive proteins such as anti- PD-1 receptor and anti-PD-L1 have been chosen as treatment options for various cancers, including gastric carcinoma. In addition to their therapeutic role, the expression of PD-L1 has been used as a predictive biomarker for PD-L1 treatment response and has been shown to have a prognostic role in certain cancers [3].

Although PD-L1 serves as a predictive biomarker for response to immune checkpoint inhibitors, its association with clinicopathological parameters and prognosis in gastric carcinoma remains controversial [4].

Conflicting findings have been found in earlier research examining the relationship between PD-L1 expression and clinicopathological characteristics. While some authors have discovered no such associations, others have identified strong correlations with unfavourable pathology characteristics and poor clinical outcomes.

Similar to this, there is ongoing debate on the predictive importance of PD-L1 expression, with research showing both positive and negative effects on patient survival. Despite these contradictions, immune checkpoint drugs that target the PD-1/PD-L1 pathway have made PD-L1 a significant therapeutic target. The evaluation of PD-L1 expression has grown in significance in the treatment of gastric cancer as a predictive biomarker for identifying patients who might benefit from immunotherapy [2].

The present study evaluated the PD-L1 expression in tumour cells and tumour infiltrating lymphocytes in gastric carcinoma and assessed its association with clinicopathological parameters to understand its potential role as a prognostic and therapeutic biomarker.

The present study is unique in that it evaluates PD-L1 expression in tumour cells as well as tumour-infiltrating lymphocytes simultaneously in gastric carcinoma and correlates it with several clinicopathological parameters. Further, the study adds data from the Indian patient population where published evidence is still limited thus enhancing the understanding of the prognostic and therapeutic significance of PD-L1 in the gastric tumour microenvironment.

MATERIALS AND METHODS

This is a hospital-based cross-sectional study conducted at the Department of Pathology, Amala Institute of Medical Sciences, Thrissur, Kerala, India, over 19 months after the ethical clearance (IEC number: 17/EC/22/AIMS-65), from October 2022 to April 2024, enrolling histology-proven cases of both biopsies and gastrectomy specimens of gastric carcinoma during this period. A total of 33 cases, 13 gastrectomy and 20 gastric biopsies specimens were studied.

Inclusion criteria: All gastric specimens diagnosed with gastric carcinoma from those aged above 18 years, received in the Department of Pathology of the Institute during the stipulated time, are included in the study.

Exclusion criteria: Insufficient material received, patient lost to follow-up, incomplete data were excluded.

Sample size calculation: The sample size was calculated from the study by Ngoc Dung T et al., [2].

$$n = \frac{Z_{1-\alpha/2}^2 pq}{d^2}$$

p: Proportion of weak PD-L1 expression (77.8)

q: 1-p

d: Relative precision (20% of p)

α: Significance level 5%

n=27

However, 33 cases met the criteria by consecutive sampling in this stipulated time and were taken for study.

Study Procedure

Histopathological analysis was done followed by PD-L1 immunohistochemical analysis done using PD-L1 antibody- CAL 10 clone, manufactured by Biocare Medical. Placenta was used as control. Viable tumour cells, PD-L1 positive tumour cells and tumour infiltrating lymphocytes were counted manually. These values were used to calculate the CPS score.

$$CPS = \frac{\text{No. of PD-L1 staining cells (tumour cells, lymphocytes)}}{\text{Total no. of viable tumour cells}} \times 100$$

CPS score ≥5 is considered positive [5].

Clinicopathological parameters like age, gender, gross appearance (Borrmann classification), histopathological types, depth of invasion/T stage (AJCC 8th edition), Nodal status/N stage (AJCC 8th edition), and vascular invasion were studied.

STATISTICAL ANALYSIS

Data was entered in MS Excel worksheets and analysed using SPSS version 23.0 statistical software. Descriptive and inferential statistical analyses were carried out. Results on continuous measurements were presented on Mean ± Standard Deviation (SD) and results on categorical measurements were presented in number [%]. Significance is assessed at a 5 % level. Fisher's-Exact test analysed the association between PD-L1 expression and clinicopathological parameters.

RESULTS

Of the 33 cases, 67% were in the 51–75 age group, 21% in the > 75 age group, and 12% in the 19–50 age group. The average age was 65.55 years. Males accounted for 73% of patients, while females accounted for 27%. There were three cases each of fungating and flat tumours, and seven cases of ulcerated neoplasm. There were nine cases of poorly cohesive carcinoma, including signet ring cell carcinoma; seven cases of well-differentiated adenocarcinoma; seven cases of moderately differentiated adenocarcinoma; six cases of poorly differentiated adenocarcinoma; three cases of mixed adenocarcinoma; and one case of mucinous adenocarcinoma. T4a accounted for 7 cases (54%), T3 for 4 cases (31%), and T2 for 2 cases (15%). There were no reports of T1 or T4b phases. Five (38.5%) of the cases were N1, three (23.1%) were N2, three (23.1%) were N3a, one (7.7%) was N3b, and one (7.7%) was N0. Vascular invasion was present in 77% (10 cases) and absent in 23% (3 cases).

Total of 30 cases had tumour cells that tested negative for PD-L1, while 3 cases had positive tumour cells. 30 cases had negative TILs, while 3 had positive TILs. The Combined Positive Score (CPS) for the 3 instances with PD-L1 positivity in both tumour cells and TILs was calculated using the formula [Table/Fig-1].

Cases	Positive tumour cells	Positive lymphocytes	Viable tumour cells	CPS (%)
1- Well differentiated adenocarcinoma	27	40	156	42
2- Moderately differentiated adenocarcinoma	14	6	100	20
3- Moderately differentiated adenocarcinoma	120	13	211	63

[Table/Fig-1]: Cases with positive PD-L1 tumour cells and tumour infiltrating lymphocytes and associated CPS Score

The expression of PD-L1 was compared across age groups. Of the three PD-L1-positive patients, two were in the 51–75 age range, and the third was in the >75 age range. In the 19–50 age range, there were no positive cases. Fisher's-exact test was used for statistical analysis, and the p-value was calculated as1.000 [Table/Fig-2].

Age group (in years)	PD-L1 expression		
	Negative	Positive	Total
19-50	4	0	4
51-75	20	2	22
>75	6	1	7
Total	30	3	33

[Table/Fig-2]: Comparison between age group and PD-L1 expression.

Of the three PD-L1 positive individuals, two were male and one was female. Fisher's-exact test was used for statistical analysis. The computed p-value is 0.629 [Table/Fig-3].

One of the three PD-L1 positive cases was excluded because it involved a gastric biopsy. PD-L1 positivity was observed in one instance of each fungating and ulcerated neoplasm. Fisher's-exact test was used for statistical analysis. The p-value was 1.000 [Table/Fig-4].

Gender	PD-L1 expression		
	Negative	Positive	Total
Female	8	1	9
Male	22	2	24
Total	30	3	33

[Table/Fig-3]: Comparison between gender and PD-L1 expression.

Gross appearance	PD-L1 expression		Total
	Negative	Positive	
Flat neoplasm	3	0	3
Fungating neoplasm	2	1	3
Ulcerated neoplasm	6	1	7
Total	11	2	13

[Table/Fig-4]: Comparison between the gross appearance of the tumour and PD-L1 expression.

Two of the three PD-L1 positive cases had moderately differentiated adenocarcinomas, and one had a well-differentiated adenocarcinoma. Statistical analysis used Fisher's-exact test. The p-value is 0.775 [Table/Fig-5].

Histopathological types	PD-L1 expression		Total
	Negative	Positive	
Mixed adenocarcinoma	3	0	3
Moderately differentiated Adenocarcinoma	5	2	7
Mucinous Adenocarcinoma	1	0	1
Poorly cohesive carcinoma	9	0	9
Poorly differentiated adenocarcinoma	6	0	6
Well-differentiated adenocarcinoma	6	1	7
Total	30	3	33

[Table/Fig-5]: Comparison between histopathological types and PD-L1 expression.

Regardless of the degree of vascular invasion, the three PD-L1 positive cases were evenly distributed between the two scenarios (one case each). Due to the small biopsy, one case was excluded from the study. Fisher's-exact test was used for statistical analysis. The p-value is 0.423 [Table/Fig-6].

Vascular invasion	PD-L1 expression		Total
	Negative	Positive	
Absent	2	1	3
Present	9	1	10
Total	11	2	13

[Table/Fig-6]: Comparison between vascular invasion and PD-L1 expression.

Among the three PD-L1-positive cases, one was classified as T2 and another as T4a. One case involved a small biopsy that was not taken for analysis. Fisher's-exact test was used for statistical analysis. The p-value is 0.159 [Table/Fig-7].

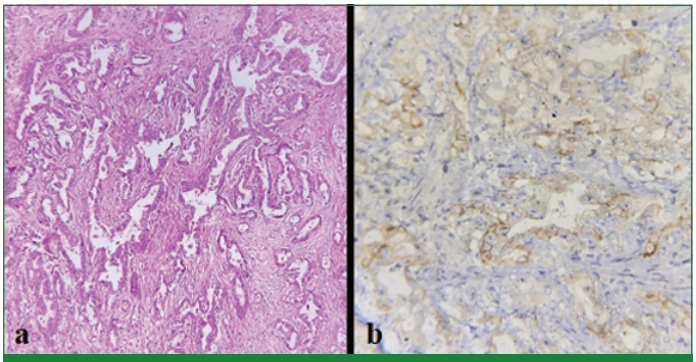
T staging	PD-L1 expression		Total
	Negative	Positive	
T1	0	0	0
T2	1	1	2
T3	4	0	4
T4a	6	1	7
Total	11	2	13

[Table/Fig-7]: Comparison between T Staging and PD-L1 expression.

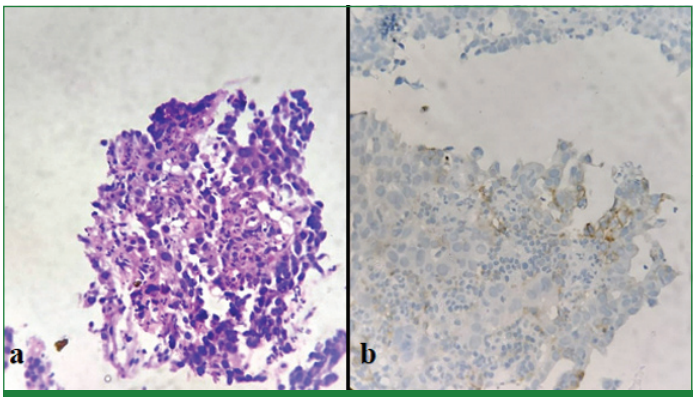
Of the three PD-L1-positive cases, one was reported as N1, and the other two were classified as N3a. Due to the small biopsy, a single case was excluded from the study. Fisher's-exact test was used for statistical analysis. The p-value is 0.408 [Table/Fig-8]. The histopathology and the immunohistochemical stain of corresponding cases are depicted in [Table/Fig-9,10].

N staging	PD-L1 expression		Total
	Negative	Positive	
N0	1	0	1
N1	4	1	5
N2	3	0	3
N3a	2	1	3
N3b	1	0	1
Total	11	2	13

[Table/Fig-8]: Comparison between N staging and PD-L1 expression.



[Table/Fig-9]: Case number 3- CPS score: 63%. a) Moderately differentiated adenocarcinoma (100x). b) PD-L1 positive tumour cells (400x).



[Table/Fig-10]: Case number 2 – CPS Score: 20%. a) Moderately differentiated adenocarcinoma (100x). b) PD-L1 positive tumour cells (400x).

DISCUSSION

Many tumours exhibit the feature of increased expression of PD-L1 because its association with the PD-1 receptor on activated T cells reduces anti-tumour immunity by neutralising T cell stimulatory signals. PD-L1 overexpression plays a major role in immune evasion. Beyond its immunological interface, PD-L1 also has inherent properties that directly influence oncogenic processes, promoting the growth and survival of cancer cells. PD-L1's dual nature raises suspicion about the effectiveness of immune checkpoint inhibitors and emphasises its potential use as a direct therapeutic target [6].

In carcinoma immunotherapy, one of the important checkpoint inhibitors is the PD-1 pathway. NK cells, B cells, activated monocytes, dendritic cells, and activated T cells are among the immune cells whose surface expresses PD-1 for a brief period of time. When PD-1 interacts with its ligand, PD-L1, which is expressed by a multitude of cell types, PD-1 expressing cells undergo apoptosis. In the tumour microenvironment, PD-L1 is upregulated on the tumour cells, causing a defect in the anti-tumour immune response which results in the escape of the malignant cells from the detection by cytotoxic T cells [7].

High TIL densities have been linked to a favourable prognosis in certain immunogenic tumours, including gastric cancer, according

to studies. In patients with gastric cancer, these TILs may serve as a possible biomarker and a reliable indicator of a favourable prognosis [8]. Calculation of CPS has better prognostic significance which emphasises the importance of TILs as well [2]. Studies have shown that oesophageal, oesophagogastric, gastric and colon carcinoma can benefit from an immune checkpoint inhibitor treatment. As per the current European Society of Medical Oncology (ESMO) in the treatment of gastric carcinoma, they have included checkpoint inhibitors [9].

Out of 33 cases taken, 3 cases (9%) showed positive PD-L1 staining and a Combined Positive Score was calculated. In a study done by Ngoc Dung T et al., out of 54 cases, 22 cases (22%) were PD-L1 positive [2]. In another study done by Tamura T et al., out of 431 cases, 128 cases (29.6%) were PD-L1 positive [10]. These studies show that the percentage of positivity of PD-L1 was less. A similar finding was noted in the current study also.

PD-L1 positive cases was found in 51-75 year age group, with a p-value of 1. In a study done by Attia S et al., the age group with positive PD-L1 was >58 years (p-value: 0.006), showing association and statistically significant [11]. In another study done by Liu X et al., the mean age was 64 years (p-value=0.13), no association was seen and was statistically insignificant [12]. These studies and the current study show that the most common age group was >50 years. However, no association was seen in most of the studies.

Two out of three positive cases were males with a p-value of 0.629. In a study conducted by Boger C et al., the incidence of gastric carcinoma was most common in males (290 cases out of 465 cases) and PD-L1 positivity was most common in the male population (80 cases) (p-value: 0.018), showing a statistically significant association [13]. In another study done by Amirmoezi F et al., out of 50 cases, 42 were males, and PD-L1 positive cases were predominantly in the male population (12 cases) (p-value: 0.342). No association was seen and was statistically insignificant [14]. The current study study is comparable in gender predilection with the other studies.

Borrmann classification and gastrectomy specimens (n=13 cases) were used to categorise the gross appearance of the neoplasm. PD-L1 positive cases were reported in both fungating and ulcerated neoplasm. A p-value in the present study was 1. In the study done by Ngoc Dung T et al., most of the positive cases were in the ulcerated neoplasm category, but no association was reported (p-value=0.473) [2]. In another study done by Lian J et al., no association was reported between PD-L1 expression and the gross appearance of tumours (p-value=0.86) [15]. All these studies and the current study show no association between PD-L1 expression and the gross appearance of gastric carcinoma, however, the association between them cannot be established.

The PD-L1 positive cases showed a morphology of moderately differentiated and well-differentiated adenocarcinoma with a p-value of 0.775, which was statistically insignificant. In a study done by Ali S et al., most of the positive cases were Moderately differentiated adenocarcinoma (p-value=0.273) and no association was reported [7]. A similar study was conducted by Ngoc Dung T et al., most of the positive cases were adenocarcinoma (p-value: 0.903) and no association was reported [2]. All these studies and the current study show that the most common histopathological type with PD-L1 positivity was moderately differentiated adenocarcinoma, however, the association between them could not be established.

Out of 3 cases positive for PD-L1, the association between depth of invasion and PD-L1 could be evaluated in 2 cases only third case was a small biopsy. When comparing with the PD-L1 positivity 1 case with T2 staging and 1 case with T4a staging was positive. The p-value was 0.159, there was no association and was statistically insignificant. In a study conducted by Menon D et al., the positive cases were most commonly seen in higher grades, T4a and T4b (p-value=0.159) [16]. In another study conducted by Yamashita K et al., higher-grade tumours which include T3 and T4 were positive for PD-L1 (p-value=0.26) [17]. All these studies show no association and are statistically insignificant. The majority of the studies and the current study show that most of the positive cases were seen in the higher grades. However, no association between the PD-L1 expression and depth of invasion/ T staging could be established.

Lymph node metastasis was staged according to the American Joint Committee on Cancer (AJCC) 8th edition guidelines for N staging. When comparing with PD-L1 positivity, 1 case was in N1 stage and the other in N3a stage. The p-value was 0.408, there was no association and was statistically insignificant. In a study conducted by Ali S et al., most of the positive cases were in N3 (p-value: 0.87) but no association could be explained and was statistically insignificant [7]. Another study conducted by Lian J et al., where the lymph node metastasis was classified as present or absent (p-value: 0.89) also showed no association and was statistically insignificant [15]. These studies and the current study show that a higher grade of lymph node metastasis can show PD-L1 positivity in the tumour. However, no association between the PD-L1 expression and lymph node metastasis can be established.

When comparing PD-L1 positivity and vascular invasion, vascular invasion was noted in one positive case. The p-value was 0.423and was statistically insignificant. In a study conducted by Tamura T et al., 43 cases showed vascular invasion was positive for PD-L1 (p-value: 0.05), showing an association between the PD-L1 expression and vascular invasion [10]. In a study conducted by Ngoc Dung T et al., 2 cases which showed vascular invasion were PD-L1 positive and 10 cases which showed no vascular invasion were positive for PD-L1(p-value: 0.122), however, the association cannot be established and was statistically insignificant [2]. The majority of the studies and the current study show that PD-L1 positivity can be seen in cases with vascular invasion; however, no association can be made between them.

Limitation(s)

The present study include an inadequate sample size and topographical variations in PD-L1 expression. PD-L1 expression is dynamic because of the tightly regulated expression of PD-L1 at multiple molecular levels in a tumour, so a single slide may not be representative of the entire expression. Loss of antigenicity on prolonged storage of formalin-fixed paraffin-embedded sections is also to be considered. In the case of gastric biopsies, the sample may not be representative of the whole tumour, thereby producing negative results.

CONCLUSION(S)

Gastric carcinoma is a highly heterogeneous illness that is still treatable; one unmet need is systemic therapy. Recently, in the treatment plan for gastric carcinoma, targeted immunotherapy with immune checkpoint inhibitors has gained interest and PD-L1 is one among them. The purpose of the present study was to determine the relationship between the clinicopathological characteristics and the expression of PD-L1 by tumour cells and TILs in gastric carcinoma. There are only a few studies which showed an established association between PD-L1 expression and clinicopathological parameters. The current study expected that there would be a positive correlation between the expression of PD-L1 and clinicopathological parameters. Though PD-L1 positive cases was undertaken, a positive correlation between the PD-L1 expression and clinicopathological parameters could not be established. Overcoming various limitations, more studies are necessary to establish a positive correlation between the PD-L1 expression and clinicopathological parameters and to bring targeted immunotherapy into the mainstream treatment regimen of gastric carcinoma because the available studies show that there is a better outcome in patients with positive PD-L1 expression.

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