

Original Article

Cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) tumour expression in gastric carcinoma

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Background & objectives: Immune checkpoint inhibitor (ICI) therapy is an emerging therapeutic strategy for several malignancies, including gastric cancer, that hinges on immune checkpoint expression by the tumour infiltrating lymphocytes (TILs). Cytotoxic T lymphocyte associated antigen-4 (CTLA-4) is a well-known inhibitory T-cell co-receptor that functions as an immune checkpoint. CTLA-4 has also been found to be expressed by tumour cells making it a potential area of research for targeted therapy. We attempted to explore tumour cell CTLA-4 expression, and its correlation with programmed cell death receptor-1 (PD-1) and CD8 expression by the TILs and their correlations with histopathological parameters in gastric carcinoma.

Methods: A retrospective study carried out on archived paraffin blocks from 50 cases of gastric adenocarcinoma. Immunohistochemical (IHC) staining was performed and interpreted by grading the marker expression on the basis of its intensity and proportion of tumour cells stained. The relationship between tumour cell CTLA-4 expression, PD-1, CD8 expression in TILs and the histopathological features of gastric carcinoma was evaluated statistically.

Results: Most patients (n=37, 74%) were males and aged >60 yr (n=22, 44%). A statistically significant association was noted between high CTLA-4 expression in tumour cells and higher tumour stage ($P=0.017$). All cases with high CTLA-4 expression in tumour cells demonstrated nodal metastasis. CTLA-4 did not show a statistically meaningful association with other histopathological parameters. Positive PD-1 expression in TILs did not show a significant association with tumour aggression in terms of tumour grade, histologic type, nodal metastasis, lymphovascular and perineural invasion. Most TILs were found to be CD8+ T-cells.

Interpretation & conclusions: A higher CTLA-4 expression in tumour cells is linked to advanced tumour stage in our study. These findings can trigger research to elucidate a likely role of these markers as independent prognostic and therapeutic factors in determining overall outcome in gastric carcinoma.

Key words CTLA-4 - gastric carcinoma - immune checkpoint inhibitor therapy - PD-1 - TILs

Gastric carcinoma is the fifth most prevalent cancer diagnosed with associated cancer mortality ranking fourth worldwide. As per GLOBOCAN 2020

data, 1.1 million new gastric carcinoma cases were diagnosed globally in 2020¹. India has shown a trend towards increase in gastrointestinal malignancies and

gastric carcinoma is a significant contributor. Roughly 34,000 cases are diagnosed in India every year, with a male predominance². Five-year survival rates of early-stage gastric cancers treated with curative resection approaches 90 per cent, although a palliative approach is adopted for higher stage malignancies³. Advanced gastric carcinoma in India is associated with a reduced five-year survival rate (20%)⁴.

In recent years, there have been several developments in the therapeutic approach to advanced gastric cancer including chemotherapy and radiotherapy that are employed as adjuvant treatment or given post resection^{3,5}. Research is now focused on the development of immune checkpoint inhibitor (ICI) therapy against immunosuppressors. Extensive studies on tumour microenvironment have uncovered how cancer cells utilize multiple strategies to escape immune system surveillance including 'immunoediting' and expression of a plethora of immunosuppressive markers, some of which are also found on tumour infiltrating lymphocytes (TILs), the targets of ICI therapy⁶. ICI therapy acts by enhancing host immune response against tumour.

Cytotoxic T lymphocyte associated antigen-4 (CTLA-4) is an immunosuppressive receptor that is expressed on activated T-cells. CD80 and CD86 expressed on antigen-presenting cells (APCs) engage the CTLA-4 receptor resulting in the blockade of the early stages of T-cell activation in a physiological setting preserving peripheral tolerance. CTLA-4 is involved in tumour immunity via the same pathway leading to the downregulation of T-cells⁷. Anti-CTLA-4 therapies override the suppressive action of CTLA-4 receptor on T-cells. Ipilimumab and tremelimumab are Food and Drug Administration (FDA) approved anti-CTLA-4 drugs used for treatment of certain malignancies, including unresectable melanoma, non-small cell lung carcinoma (NSCLC), and hepatocellular carcinoma, in which they demonstrated significant improvement in progression free survival (PFS) of the patients⁸⁻¹⁰. Trials are in progress to evaluate their effectiveness in advanced gastric malignancies^{11,12}. Several studies have identified that occasionally malignant cells show surface expression of CTLA-4¹³. A literature search revealed contradictory data with regards to the significance of CTLA-4 tumour cell expression. It was shown to be associated with a better prognosis and improved overall survival in a few instances, while few studies reported tumour cell CTLA-4 expression to be associated with a poor prognosis and overall survival¹⁴⁻¹⁷. These findings reveal that the exact role

of CTLA-4 expression on tumour cell surface and its pathway of action in immune surveillance evasion, if any, remains poorly characterised¹³.

Activated cytotoxic T-cells express another inhibitory co-receptor, programmed cell death receptor-1 (PD-1). The PD-1 receptor has two ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), expressed ubiquitously by macrophages and various other cell populations, including certain malignant cells. On binding by its ligands, PD-1 suppresses T-cell function in their effector phase and induces T cell apoptosis, limiting immune response and thus maintaining peripheral tolerance^{7,18}. Expression of PD-L1 by tumour cells is an important pathway of immune evasion by malignancies and constitutes the PD-1/PD-L1 axis¹⁹. Malignancies expressing PD-L1 often show a higher tumour size, presence of nodal metastasis and poorer overall survival, underscoring their utility as potential targets of ICI therapy^{11,20-23}. FDA has also approved ICI targeting PD-1 receptors, such as pembrolizumab and nivolumab, and these are implemented in tumours with PD-1 positive TILs^{8,22}. The potential synergistic benefits of combining anti-CTLA-4 and anti-PD-1 therapy is being investigated in the treatment of advanced gastric carcinoma^{12,24,25}.

In this study, we attempted to analyse the CTLA-4 expression by gastric tumour cells and the expression of PD-1 and CD8 by TILs and the potential correlations of these markers with other histopathological parameters.

Materials & Methods

Study design: This retrospective, observational analysis was conducted at the department of Pathology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India. The study was carried out on 50 archived paraffin blocks of cases diagnosed as primary gastric adenocarcinoma in resection specimens. The cases for the study were selected over a three-year period (July 2020 to July 2023). Institutional ethical clearance was secured prior to commencement of the study.

Case selection criteria and data collection process: Gastrectomy specimens diagnosed as primary gastric adenocarcinoma across all grades with the presence of tumour infiltrating immune cells (TILs), irrespective of adjuvant therapy status, were included in this study. Criteria for exclusion comprised endoscopic gastric biopsies, tumour resections lacking infiltrating

lymphocytes and tumour blocks with extensive necrosis. The sample size was established at 50, ensuring an absolute precision of 10 per cent. Relevant clinical data of the patient including age, gender, and tumour location were retrieved from the hospital information system. Histopathological details were obtained from histopathological case files.

Methodology: Haematoxylin and eosin (H&E) stained sections of cases diagnosed as primary gastric adenocarcinoma were retrieved, reviewed and appropriate blocks with representative sections of the tumour showing presence of TILs were selected.

IHC markers analysed were, monoclonal rabbit anti-human CTLA-4 antibody (Clone- IHC064), monoclonal mouse anti-human PD-1 antibody (Clone- IHC001), and monoclonal mouse anti-human CD8 antibody (Clone- IHC542) which were procured from GenomeMe Lab Inc. The IHC markers were pre-diluted, optimized and ready to use. The expression of each marker was standardized using tonsil as positive control tissue (as per provider recommendation). In the control tissue, CTLA-4 showed a membranous pattern of staining in the lymphocytes and PD-1 showed cytoplasmic and membranous staining. T-cells in the control tissue showed strong membranous staining for CD8.

IHC staining was performed on all 50 cases manually, in multiple batches along with controls, using 100 μ L of primary antibody per sample. The IHC expression was graded and scored by two pathologists independently.

Assessment of CTLA-4 expression in gastric tumour cells: The tumour cells showed cell surface expression of CTLA-4 in a cytoplasmic and membranous pattern. The scoring system utilized by Zhang *et al*¹⁶ was employed. CTLA-4 tumour cell expression was assessed based on intensity of staining and the proportion of tumour cells stained.

Intensity of CTLA-4 expression was scored as 0 (no expression), 1 (weak expression), 2 (moderate expression), and 3 (strong expression). Tumour cell proportion was scored as 0 (0-5% of tumour cells), 1 (5-25% of tumour cells), 2 (25-50 per cent of tumour cells), and 3 (>50% of tumour cells).

Sum of intensity and proportion scores were taken and graded as scores 0-1: negative, scores 2-3: weakly positive, scores 4-5: moderately positive, and score 6: strongly positive. Scores 4 and above were considered

as cases with high CTLA-4 expression in tumour cells. Scores below 4 were taken as low/no expression of CTLA-4.

Assessment of PD-1 expression in TILs: Immune cells with positive PD-1 expression showed uniform, membranous staining. A PD-1 positivity of 1 per cent and above was taken into consideration among the CD8+ TILs. Positivity less than 1 per cent was categorized as negative²⁶.

Assessment of CD8+ TILs: The CD8+ T-cells showed uniform, membranous staining. Only CD8+ T-cells infiltrating the tumour were considered as positive.

Statistical analysis of results and data: The data collected were tabulated using Microsoft Excel sheet (Microsoft Corp., Redmond, WA) and analysed using IBM SPSS Statistics, version 26 (IBM Corp., Armonk, NY). Fisher's exact test and Chi square test were employed to analyse the associations between CTLA-4 expression in tumour cells with PD-1, CD8 expression in TILs. The association between variables was considered significant when the *P* value was less than or equal to 0.05.

Results

Among our study population, the age group with the highest frequency was 61-70 yr, comprising 44 per cent (n=22). The mean age of the participants was 60.8 yr, with a standard deviation of 10.9 yr. Males comprised the majority of the study population (74%, n=37). Pyloric tumours were the most common, which includes antral tumours extending into the pylorus (each 24%, n=12), while tumours of the body and cardia were less common. The most prevalent histologic type was the intestinal type, observed in 58 per cent (n=29) of the sample. Moderately differentiated and poorly differentiated tumours were found in near equal proportions among the study population (Figs. 1A-D). A significant proportion of tumours belonged to the pT3 stage (penetrates subserosa connective tissue, no invasion of visceral peritoneum, adjacent structures) (46%, n=23). Most of the tumours demonstrated presence of lymphovascular invasion (58%, n=29) and nodal metastasis was present in 76 per cent (n=38) of the study population.

CTLA-4 expression on tumour cells (Figs. 2A-D) and PD-1 expression in TILs (Fig. 3; 3A) did not show a statistically significant association in this study population (Table I). PD-1 in TILs did not

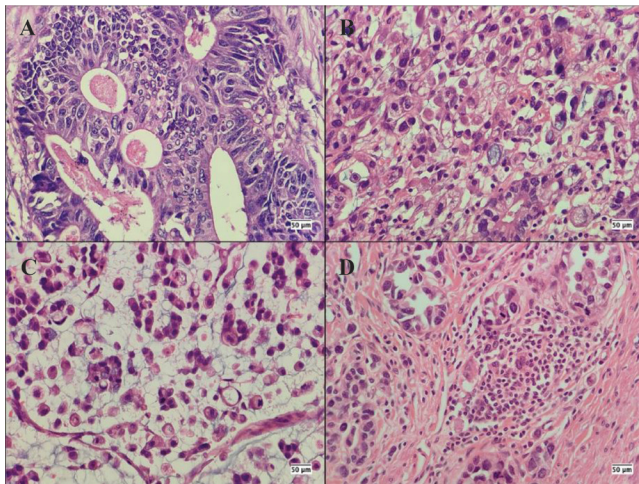


Fig. 1. (A and B) Sections from gastric carcinoma showing moderately differentiated, invasive neoplastic glands (H&E, 400 \times); (C) Poorly differentiated gastric carcinoma with occasional signet ring cells and extracellular mucin (H&E, 400 \times); (D) Invasive malignant glands with TILs (H&E, 400 \times). TILs, tumour infiltrating lymphocytes; H&E, hematoxylin and eosin.

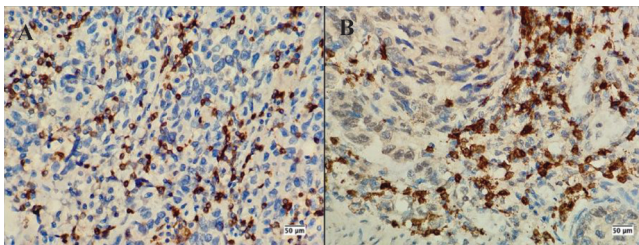


Fig. 3. (A) PD-1 positive TILs (IHC, 400 \times); (B) CD8+ TILs (IHC, 400 \times). PD-1, programmed cell death receptor 1; TILs, tumour infiltrating lymphocytes.

show statistically significant correlation with the histopathological parameters (Table II). Among the cases studied, 98 per cent ($n=49$) showed presence of CD8+ TILs (Fig. 3B).

High CTLA-4 expression on tumour cells was seen in 9/50 cases (18%). The tumours invading the lamina propria (pT1a) or limited to the submucosa (pT1b) did not express CTLA-4 (Table II). High CTLA4 expression was observed in 2 out of 23 cases (8.7%) among the pT3 group and in 6 out of 14 cases (42.9%) among the pT4a group. There was no significant association between CTLA-4 expression and tumour extent ($P=0.076$). On reassessing the CTLA-4 expression among high stage tumours (pT3 and pT4a), a statistically significant association ($P=0.017$) was observed between high tumour CTLA-4 expression and tumour invasiveness (Table III). CTLA-4 expression did not correlate significantly with the other histopathological parameters (Table II).

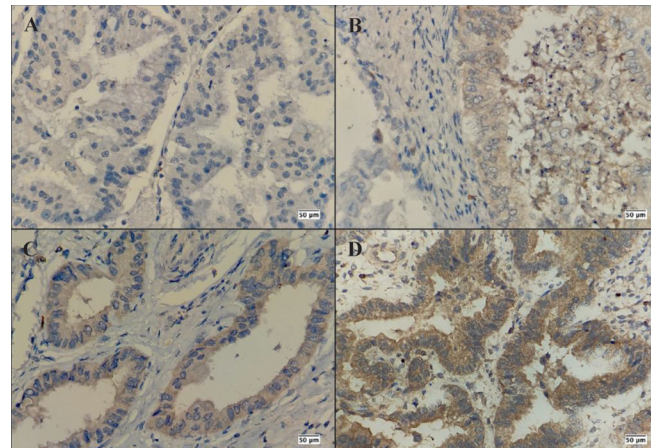


Fig. 2. CTLA-4 expression in tumour cells (A) Score 0 (No expression) (IHC, 400 \times); (B) Score 1 (Weak expression) (IHC, 400 \times); (C) Score 2 (Moderate expression) (IHC, 400 \times); (D) Score 3 (Strong expression) (IHC, 400 \times). CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; IHC, immunohistochemistry.

Discussion

In our study population, tumours with high CTLA-4 expression on correlation with tumour extent suggested a trend ($P=0.076$) towards meaningful association. Higher CTLA-4 expression was predominantly documented in tumours invading serosa (pT4a), followed by tumours invading the subserosal connective tissue (pT3). Strikingly tumours with invasion limited to the lamina propria or submucosa did not show high CTLA-4 expression. A revised analysis for CTLA-4 expression among only high stage tumours revealed a statistically significant association ($P=0.017$). A study published in 2018 explored the expression of CTLA-4 in NSCLC tumour cells and its role in tumourigenesis. CTLA-4 tumour expression resulted in the upregulation of EGFR pathway, increased tumour PD-L1 expression and tumour proliferation, in the presence of anti-CTLA-4 antibodies²⁷. High tumour CTLA-4 expression has been associated with poorer prognosis and overall survival in oesophageal and thymic malignancies^{16,17}. Similar results have not, however, been replicated in prior research done on gastric carcinoma. Occasional publications have reported an association between low/no CTLA-4 expression in tumour cells of gastric carcinoma and aggressive tumour characteristics (such as a higher tumour grade and diffuse Lauren histological type), a finding not reflected in our data²⁸. In other studies, high CTLA-4 expression in the tumour has been linked to less aggressive features, such as lower tumour stage, better differentiation and intestinal-type histology^{29,30}. However, bearing in mind

Table I. Association between CTLA-4 expression in tumour cells and PD-1, CD8 expression in TILs

		CD8+ TILs			PD-1		
		Positive	Negative	<i>P</i> value	Positive	Negative	<i>P</i> value
CTLA-4	Low/no	41	0	0.18	28	13	0.467
	High	8	1		5	4	
PD-1	Positive	33	0	0.34			
	Negative	16	1				

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell death receptor-1; TILs, tumour infiltrating lymphocytes

Table II. Association of CTLA-4, PD-1 and CD8 expression with histopathological parameters

		CTLA-4			PD-1			CD8	
		Low/No	High	<i>P</i> value	Positive	Negative	<i>P</i> value	Positive	Negative
Histological type	Intestinal	25	4	0.084	18	11	0.651	28	1
	Diffuse	16	4		14	6		20	0
	Mixed	0	1		1	0		1	0
Grade	Grade 2	20	4	1.000	16	8	0.126	23	1
	Grade 3	21	5		17	9		26	0
T stage	T1a (Invades lamina propria)	1	0	0.076	0	1	0.586	1	0
	T1b (invades submucosa)	4	0		2	2		4	0
	T2 (invades muscularis propria)	7	1		6	2		8	0
	T3 (Penetrates subserosal connective tissue, no invasion of visceral peritoneum, adjacent structures)	21	2		16	7		22	1
	T4a (Invades serosa/visceral peritoneum)	8	6		9	5		14	0
Lympho vascular invasion	Present	22	7	0.271	16	12	0.238	29	0
	Absent	19	2		17	5		20	1
Perineural invasion	Present	14	6	0.13	11	9	0.229	20	0
	Absent	27	3		22	8		29	1
Lymph node status	Involved	29	9	0.092	25	13	1.000	37	1
	Uninvolved	12	0		8	4		12	0

T stage, tumour stage

that there is lacunae in published research of similar studies undertaken in India and therefore among a comparable study population, our findings suggest significance. While our findings show discord from those previously reported in gastric carcinoma, the role of targeted therapy against CTLA-4 in high stage tumours would be a question of profitable debate in terms of patient management.

Anti-PD-1 therapy is yet another ICI therapeutic option that enhances anti-tumour immunity by overcoming the inhibitory effect of PD-1 receptor expressed by activated T-cells⁸. PD-1 is especially notorious since the tumour cells in gastric carcinoma are

Table III. Association of CTLA-4 expression with high tumour stage

T stage	CTLA-4 expression		<i>P</i> value
	Low/No expression	High expression	
pT3	21	2	0.017
pT4a	8	6	

known to express its ligand PD-L1¹⁹. PD-1 expression was analysed by IHC in the same zones showing presence of CD8+ TILs. All cases with PD-1 positive TILs (33/50) were positive for CD8. Significantly higher PD-1 expression in tumours has been observed with increased CD4+ and CD8+ TILs. Existing

publications have correlated higher PD-1 expression in TILs with tumour progression¹⁹. The association between PD-1 and CD8+ TILs and clinicopathological features in gastric carcinoma has been explored in prior research, generally finding no statistically significant correlation between PD-1 expression on TILs and factors such as histologic type, tumour aggression and extent, lymph node status, lymphovascular invasion, and perineural invasion. Our results are in alignment with these observations³¹.

CD8+ TILs were observed in 98 per cent cases (n=49) in our study group. Previous studies have linked the presence of increased CD8+ TILs with good prognosis and their presence also qualifies them as potential candidates for ICI therapy³².

As previously outlined, CTLA-4 is an inhibitory co-receptor that acts during T-cell activation and is expressed by tumour cells of several malignancies although its functional path remains unclear. In our study, high CTLA-4 expression in tumour cells demonstrated a statistically significant association with gastric tumours of advanced stage. Though in conflict with prior studies, we can conclude that this finding indicates the need for further research conducted on a larger cohort with the goal to analyse the potential relationship between gastric tumour CTLA-4 expression and prognosis as well as its effect on overall survival. The utility of these markers on small gastric biopsies in order to identify targets for ICI therapy to downstage the disease also remain to be explored.

Our study is not without its limitations. These include the potential inconclusive nature of the results obtained due to the limited sample size. Since ICI therapy was not employed in treatment of the patients, its benefit among the cases with CD8+ TILs could not be examined. Furthermore, correlation of IHC expression of CTLA-4, PD-1 and CD8 in TILs could not be comprehensively evaluated pertaining to their effect on prognosis due to the limited availability of long-term clinical follow-up data for the study cohort.

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Conflicts of Interest: None.

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