Short Communication

PD-L1 Expression in Thyroid Cancer and Its Correlation with Different Clinical-Pathological Parameters among Some Iraqi Population

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Abstract

Background: thyroid cancer is the most common endocrine malignancy, particularly affecting women, and its incidence has been rising globally over the past two decades. Programmed cell death ligand 1 (PD-L1) is an immune checkpoint molecule known to contribute to tumour immune evasion. Its expression in thyroid cancer has been linked to tumour aggressiveness and poor prognosis, making it a potential biomarker and therapeutic target. **Objectives:** The aim of the Study is to investigate the expression of PD-L1in cases of thyroid cancer from Iraqi patients trying to correlate PD-L1 immunohistochemically expression and its correlation to clinical prognosis. **Materials and Methods:** retrospective cross-sectional study included 50 patients with thyroid cancer, whose formalin-fixed paraffin-embedded thyroid tissue blocks were retrieved from various hospitals in Hila. PD-L1 expression was evaluated immunohistochemically using the Tumour Proportion Score (TPS) method. Associations between PD-L1 expression and clinical features were analysed. **Results:** Among the 50 patients, 90% were female and 10% were male, mean age was 40.4 years. Papillary thyroid carcinoma was the most prevalent diagnosis (74%), PD-L1 was expressed in 46% of patients. PD-L1 expression was significantly associated with male gender ($P < 0.001$) and PTC histology ($P = 0.003$). There was no significant association between PD-L1 expression and age, tumour size, focality, or stage. **Conclusions:** PD-L1 could serve as a valuable biomarker for prognosis and potentially guide immunotherapy in thyroid cancer treatment.

Keyword: PD-L1, thyroid cancer, immunotherapy, endocrine malignancy

Introduction

Thyroid cancer represents the most common endocrine malignancy and the fifth most common cancer in women in the United States [1]. Its annual incidence has tripled over the last twenty years, with an average annual rate of 21.4% in female, and of 7.3% in male in the years 2011–2015 [2], Thyroid cancer is the fourth most common cancer in Iraq during 2022, the recorded new cases of thyroid cancer were 2402 (6.1%.) [3]. Thyroid cancer includes differentiated thyroid carcinoma (DTC), poorly DTC (PDTC), anaplastic thyroid carcinoma (ATC), and medullary thyroid carcinoma (MTC). MTC originates from parafollicular thyroid cells, whereas all other thyroid cancers originate from thyroid follicular epithelial cells. MTC occurs in 1% to 2% of cases of thyroid cancers [4]. DTC is the most common type thyroid cancer, accounting for 90% of all thyroid cancers; papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) account for 80% and 10% of thyroid cancers, respectively [5]. The incidence of PDTC is 2% to 15%, and its morphology and clinical behavior are usually between those of DTC and ATC. ATC is the most malignant and rare form of thyroid cancer (incidence, 1%). The routine treatments for thyr-

oid cancer include hormone suppression therapy, surgery, and radioiodine therapy [6]. The 10-year survival rate of radioiodine-refractory patients is approximately 19%, and the survival of patients with ATC is worse; moreover, 50%of patients with ATC die after onset [7]. Programmed cell death ligand 1 (PD-L1) is one of the immune checkpoints, which could be detected on the membrane of immune cells, epithelial cells, and tumor cells. Its main receptor, programmed cell death protein 1 (PD-1), acts as a co-inhibitory receptor on the surface of antigen-stimulated T-cells. When the extracellular domains of PD-L1 and PD-1 recognize each other, the PD-1 cytoplasmic immune receptor tyrosine–based inhibitory motif is activated to transfer a negative regulatory signal to T-cells, inhibiting proliferation, survival, and cytokine production. The PD-L1 pathway promotes immune escape of tumor cells through inducing T-cell apoptosis, anergy, and exhaustion [8]. In addition, PD-L1 has also been found to play a tumor-protective role in $CD8^+$ cytotoxic T-cell–mediated killing and apoptosis induced by Fas ligation or protein kinase inhibitor [9]. The aim of the Study is to investigate the expression of PD-L1in cases of thyroid cancer from Iraqi patients trying to correlate PD-L1 immunohistochemically expression and its correlation to clinical prognosis.

Materials and Methods

This retrospective cross-sectional study was carried out in the Babylon Training Center for Histopathology during the period from December 2023 through September 2024. The study group comprises formalin-fixed paraffin-embedded tissue blocks collected from 50 patients diagnosed with thyroid carcinoma. The selected cases were obtained from the archives of the histopathology laboratory of Al-Hillah Teaching Hospital, Al-Imam Al-Sadiq Teaching Hospital, and private laboratories based in Hillah City. The sampling of cases includes the following: fifty patients with thyroid carcinoma, confirmed by hematoxylin and eosin stain, were included in this study. An expert pathologist did the re-evaluation of all the slides to confirm the histopathological diagnosis. The pathologic staging based on the 8th edition of the American Joint Committee on Cancer staging manual.

Immunohistochemistry technique

Immunohistochemical (IHC) staining was conducted on TMA sections using the Dako automated Autostainer Link 48 and the ZytoChem plus HRP Polymer Kit detection system. Briefly, 3 μm thick TMA sections were baked overnight at 58 °C, deparaffinized in xylene, and rehydrated through a series of graded ethanol solutions. Tissue sections then underwent heat-induced epitope retrieval (HIER) and were treated with a 3% hydrogen peroxide solution at 37 °C for 10 minutes to block endogenous peroxidase activity. This was followed by antigen retrieval using high-pressure cooking in citrate buffer (pH 6.0) for 10 minutes for PD-L1 detection. The sections were incubated at 37 °C for 60 minutes with rabbit IgG monoclonal antibodies against PD-L1 (1:100, Cat. No. RBK063-05, Zytomed Systems, Berlin, Germany). Immunostaining was carried out using the ZytoChem plus HRP Polymer (DAB) (POLHRP-006, Zytomed Systems, Berlin, Germany), resulting in the formation of a brown precipitate at the antigen site. Finally, the slides were counterstained with hematoxylin (Sigma Aldrich, St. Louis, MO, USA), followed by bluing and mounting in a non-aqueous medium [10].

Evaluation of immunostaining:

In this current study, we evaluate PD-L1 immunoreactivity in tumour cell. The evaluation of positive immunohistochemical reaction for

PD-L1 antibody is by complete circumferential or partial cell membranous staining of viable tumour cells of any intensity on ≥1% of all TCs. Since there is no standardized scoring system for thyroid cancer, we used Tumour Proportion Score of PD-L1 staining in NSCLC (non-small cell lung cancer) [11, 12] and the guidelines from the PD-L1 Kit (Dako PD-L1 IHC 22C3 pharmDx) as a reference.

Statistical analyses

Statistical analysis was carried out using SPSS version 27. Categorical variables were presented as numbers and percentages. Pearson Chi-Square test and Fisher's Exact test were used to find the association between categorical variables. P value ≤ 0.05 was considered as significant.

Ethical approval

The study was registered and approved by College of Medicine, University of Babylon and informed consents were taken from the parents.

Results

Clinical characteristics of patients

The baseline characteristics of 50 patients with thyroid cancer are presented in table 1, the majority of the patients were females, with 45 out of 50 being women, accounting for 90%. the mean age of the patients was 40.4 years, with a standard deviation of 9.9 years, and the age range spanned from 24 to 62 years, 10 patients (20%) were 20-30 years, 20 patients (40%) were 31-40 years, 13 patients (26%) were 41-50 years and 7 patients (14%) were above 50 years. For the histopathological diagnosis, 37 patients (74%) were diagnosed with papillary thyroid carcinoma (PTC), making it the most common diagnosis in the group. Follicular carcinoma (FC) was present in 10 patients, representing 20% of the study population. Invasive encapsulated follicular variant of PTC (IEFVPTC) was found in two patients (4%), while the oncocytic variant were diagnosed in one patient, accounting for 2%. When looking at tumour size 23 patients (46%) had tumours smaller than 2 cm, while 22 patients (44%) had tumours measuring between 2 and 4 cm. Only 5 patients (10%) had tumours larger than 4 cm. The mean tumour size was 2.19 cm with a standard deviation of 1.53 cm, and the range of tumour sizes varied between 0.5 cm and 7 cm regarding focality, 31 patients (62%) had unifocal tumour and the remaining 19 patients (38%) had multifocal tumours. All patients were classified as being in TNM stage 1, 18 patients (36%) had stage t1a, 6 patients (12%) had stage t1b, 19 patients (38%) had stage t2, 6 patients (12%) had stage t3a and one patient (2%) had stage t3b.

Table 1: Baseline characteristics of the patients with thyroid cancer (N=50)

Variables		Frequency	percent
Gender	Female	45	90
	Male	5	10
Age years	20-30	10	20
	31-40	20	40
	41-50	13	26
	>50	7	14
	Mean ± SD	40.4 ± 9.9	
	Range	24-62	
Histopathological diagnosis	PTC	37	74
	FC	10	20
	ANCOCYTIC	1	2
	IEFVPTC	2	4
Tumour Size cm	<2 cm	23	46
	2—4 cm	22	44
	>4 cm	5	10
	Mean ± SD	2.19 ± 1.53	
	Range	0.5 – 7	
TNM stage	1	50	100
Focality	Unifocal	31	62
	Multifocal	19	38
Stage	t1a	18	36
	t1b	6	12
	t2	19	38
	t3a	6	12
	t3b	1	2

Immunohistochemical expression of PD-L1

Overall, tumoural PD-L1 was expressed in 23 (46%) of 50 cases at a 1% threshold. Regarding cancer types, PD-L1-positive staining (Figure 1, 2) was found in 56.8% of papillary thyroid carcinomas (21 of 37), 10% of follicular thyroid carcinomas (1 of 10). The distribution of PD-L1 positivity was significantly different according to cancer histology types ($P < 0.001$) (Table 2). Other variables such as age, size, primary tumour (pT) and tumour focality were of no significance.

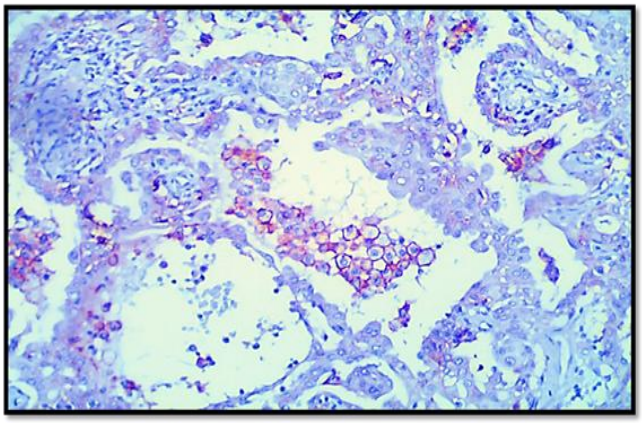

Figure 1: Programmed cell death ligand-1 immuno-histochemical expression in thyroid cancer (original magnification, ×400). Positive membranous PD-L1 expression (≥1% of stained cell).

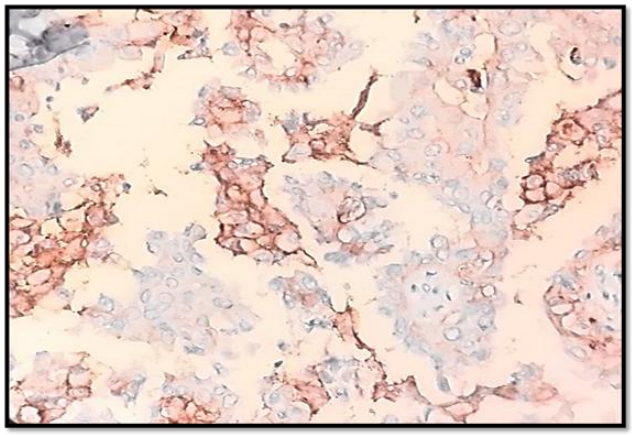

Figure 2: Programmed cell death ligand-1 immuno-histochemical expression in thyroid carcinoma (original magnification, ×400). positive PD-L1 expression >50%

Table 2: IHC expression of PD-L1 in tumour cells (TC)

Variables		PDL1 -VE (n=27)		PDL1+VE (n=23)		Total	P Value
		Frequency	percent	Frequency	percent		
Gender	Female	26	57.8	19	42.2	45	<0.001
	Male	1	20.0	4	80.0	5	
Age Group	20-30	4	40.0	6	60.0	10	0.781 Not significant
	31-40	12	60.0	8	40.0	20	
	41-50	6	46.2	7	53.8	13	
	>50	5	71.4	2	28.6	7	
Histopathological Diagnosis	PTC	16	43.2	21	56.8	37	0.003
	FC	9	90.0	1	10.0	10	<0.001
	ONCOCYTIC	0	0.0	1	100.0	1	Not applicable
	IEFVPTC	2	100.0	0	0.0	2	Not applicable
Tumour Size (cm)	<2cm	13	56.5	10	43.5	23	0.233 Not significant
	2—4 cm	10	45.5	12	54.5	22	
	>4cm	4	80.0	1	20.0	5	
Focality	Unifocal	16	51.6	15	48.4	31	0.572 Not significant
	Multifocal	11	57.9	8	42.1	19	
PT. stage	t1a	11	61.1	7	38.9	18	0.094 Not significant
	t1b	2	33.3	4	66.7	6	
	t2	8	42.1	11	57.9	19	
	t3a	5	83.3	1	16.7	6	
	t3b	1	100.0	0	0.0	1	

Discussion

In this study immune-reactivity for PD-L1 expression revealed that7 of the patients (54%) were negative while 23atients (46%) were positive. ese findings are similar to the results of Mizuki Sekinoet al.'s (11) study on the Japanese population, which reported that 20 (60.6%) patients were PD-L1 negative, while 13 (39.4%) patients were positive usingPD-L1 staining cut-off value of 1%. Additionally, Angellet al. (12) Bastman et al. (13) andd Rui Li et al. (1414) observed the PD-L1 expression in their studies n

tumour tissue, which was 53% 53% from patients 64% of DTC and59.7% (40/67), respectively. Conversely, a study by Sara al. (15) on the Egyptian population reported a much higher positive PD-L1 expression rate (82.5%, 33/40), with only 17.5%. This aligns with findings from an IHC study by Cunha et al. which suggested that over 80% of DTCs expressedPD-L1 (16). This difference in the results may be attributed to variation in sample sizes, geographical locations, genetic differences, and different scoring systems used. The age of patients at the time of diagnosis in our study ranged from 24 to 62 years (median 40.4 years). This is comparable to the finding in Ahnt al.'s.'s (17) study, where the median was 43.8 years. similarly, Sara et al. (15) reported that patients' ages ranged from 17 to 66 years, with a mean age of 40±13.00 years. In contrast, the mean age in Limet al.'s (18) study conducted in the US was 48 years, slightly higher than in our study, but still indicating that thyroid cancer commonly affects middle-aged individuals. he current study did not find a significant correlation betweenPD-L1 expression and patient age (P = 0.781). This is in in agreement with Cunha et al. (16), Rajesh Mohan et al. (19), and Ahnhn et al. (17), who also evaluatedPD-L1 expression and reported a non-n-significant correlation with patient age, reporting P values of (P=0.192), (P=0.224), d (P=0.44),, respectively. These findings suggest that PD-L1 expression is independent of age in thyroid cancer patients, implying that age may not be a determining factor for PD-L1-mediated immune evasion in thyroid cancer. The study included50 patients with thyroid cancer, of which 90%were female and 10% were male; these proportions are consistent with those found in a study by Hyeyen Limet al. (18), which analysed data from 77,276 patients and found that 75%f patients were female and 25% were male. Similarly, Stephanie Harahap et al. (20). It was reported that 76.9% their 52 thyroid cancer samples were female, and Ahnet al. (1717) observed that 83%re females and 17% were males. Additionally, in Saraet al.'s. (15) study, there were 67.50% ale and 32.50%male. reflecting the global trend of higher thyroid cancer incidence in women, likely hormonal and genetic factors influence it. Our results revealed that80% of male patients were PD-L1 positive, compared to only42.2% of female patients, a difference that was highly statistically significant (P < 0.001). While, Ahn et al. (17), in their study of 407atients, did not observe a significant association between PD-L1 expression and gender (P = 0.192). This discrepancy between our study and Ahn's might be attributed to the small number of male patients in our sample (only 5 males), which could have led to a different statistical significance. Additionally, Saraet al. (15) found no significant association between PD-L1 expression and gender with p value (P= 0.365). While BaiYuhana et al. (21) conclude that PD-L1 expression was significant associated with female gender (p value = 0.004),, with 60.41% female patients exhibiting PD-L1 positivity. This is consistent with the finding of Mohanet al. (19), who observed a significant association between PD-L1 expression and gender, with markedly higher PD-L1 positivity in female patients (72.7%) compared to males (27.3%). The majority of patients in our study were diagnosed with papillary thyroid carcinoma (PTC) at 74%, followed by follicular carcinoma (FC) at 20%. This aligns closely with findings from Lim's study where 84% of patients had PTC, and 11% had Ahn et al. reported proportions of 80% for PTC, 16.2% for FC, 1.5% for PDTC and 2.2% for anaplastic carcinoma (154, 124). . Boruah's (222) study included 1149 thyroid carcinoma cases of which

(70%)ere PTC, (9.4%)were FTC, (1.9%)were oncocytic carcinoma, (2.3%)were PDTC, (1.7%) were ATC, and (14.6%) were medullary thyroid carcinoma. this study, 56.8% of PTC patients were PD-L1 positive, while only 10% of FC patients were PD-L1 positive. Mohan et al. (19) investigatedPD-L1 expression in different histological types of thyroid cancer and found similar results with higher PD-L1 expression in PTC (68.2%) compared to FC (22.8%) (all $P < 0.05$), sporting our findings. These findings suggest that PD-L1 may play a more significant role in the pathogenesis of PTC, possibly due to its distinct molecular and genetic characteristics. Studies by Rosenbaum et al., Chowdhury et al., and, and Bastman et al. (23, 24, 13) have also supported this observation, with PDL-1 being more prevalent in PTC. Similar studies showed PDL-1expression in PTC. Angell et al.'s study noted PDL-1 expression in 53% of cases (9 from17) (12). And Shi et al. reported PDL-1positivity in 52.3% of cases (136 from 260), with significantly higher positivity in tumour than non-tumour tissue (25). However, Ahn et al. evaluated PDL-1 expression in 407 patients. They found it present in (6.1%) of PTC, (7.6%) of FC and (22.2%) of ATC; the distribution of PDL-1 PD-L1 positivity different according to cancer histology types. (17) Zhang et al. reviewed several studies and noted that PD-L1positivity ranged from 6.1% to 82.5% in papillary thyroid cancer (PTC) patients and from 22.2% to 81.2% in anaplastic thyroid cancer (ATC) patients, with significantly stronger PD-L1 expression in tumour tissues compared to adjacent non-tumour thyroid tissues (26). The mean tumour size was 2.19 cm, and all patients were classified as TNM stage 1. This aligns with the findings of Bastman et al., who reported a mean tumour size was 2.3 ± 1.8 suggesting that early detection and diagnosis are becoming more common.. And that most patients present with early-stage disease (13). Similarly, arahap et al. (20) reported of tumour sizes from 0.5 to 0.5 to 20.0 with a median size of 3.3 cm, which is larger than the mean tumour size of this study. Larger tumour sizes are generally found in PDTC and ATC, while most of these study cases are PTC, which usually measure2–3 cm in diameter. Regarding tumour size, wee, we did not find a significant correlation between PD-L1 expression and tumour size,e, which agrees with Ahn et al. (17) Mohan et al.. (19), and Mizukiki Sekino et al. (11). In contrast, Rong Shi al. (255) reported that higher PD-L1 expression was in those with primary tumours larger than 4 cm ($p = 0.002$). This difference might result from variations in sample sizes, tumour size distributions, or population differences. Regarding focality, 31 patients (62%) had unifocal tumours and the remaining 19 patients (38%) had multifocal tumours. This aligns with Ahn et al.'s (17) study that showed most malignant cases do not have multiplicity. However, Cunha (1616) showed multimodality in 130 (51.4%) of the PTC cases, whereas 123 (48.6%) were unifocal tumours. Furthermore, no significant association between PD-L1 expression and tumour focality was observed in our study. This is consistent with Rajeshsh Mohan et al. (19) and Ahnt al. (17), who also found no significant correlation between PD-L1 expression and multifocalityin thyroid cancer with p values (P=0.325) and (P=0.706),6), respectively. However, a study by RuliLi et al. (14) on 52 patients with thyroid cancer found a significant association between PD-L1 expression and multifocality (P=0.031), although no association was found with age (P=0.71) or gender (P=0.31). The current study shows no significant correlation between PD-L1 expression and tumour stage ($P = 0.094$). This

could be due to the limited staging variation in our study, as all patients were TNM stage 1. In contrast, Shi et al.'s (25) study included patients with a broader range of stages, which may explain the observed associations between higher PD-L1 expression and advanced tumour stages in PTC patients ($P < 0.01$). They also found that positive PD-L1 staining in tumour tissue was linked to poorer recurrence-free survival (RFS) in males ($p = 0.001$), older patients (aged 45 and above; $p = 0.001$), multifocal tumours ($p = 0.031$), extra thyroidal extension ($p = 0.012$), and lymph node metastasis ($p = 0.004$) (19). Similar to our finding, Rajesh Mohan et al.'s study on 157 thyroid carcinoma patients found no significant correlations between PD-L1 expression and factors such as age, tumour size, multiplicity, initial metastasis, recurrence, or mortality. However, PD-L1 expression was significantly associated with TNM stage ($P = 0.014$) (19).

Conclusion

PD-L1 was positive in 46% of patients, PD-L1 could be a valuable biomarker during therapy, and among patients with PTC, 56.8% were PD-L1 positive, indicating a significant association between PD-L1 expression and PTC histology ($P = 0.003$). With only 10% of patients with FC were PD-L1 positive, showing a significant inverse association ($P < 0.001$). Also, no significant association was found between PD-L1 expression and patient age ($P = 0.781$), tumour size ($P = 0.233$), Tumour Focality ($P = 0.572$) or tumour stage ($P = 0.094$).

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