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Abstract

Immunohistochemical expression of programmed death-ligand 1 (PD-L1) has become a biomarker to predict the usefulness of cancer immunotherapy using PD-1/PD-L1 blockade in a variety of advanced-stage tumours. This emerging biomarker may serve to generate novel therapies for aggressive thyroid carcinoma (TC), which has not shown optimal results with existing treatments. The present study investigated the relevance of PD-L1 expression in aggressive histological types of TC compared with that found in less aggressive types. Surgically resected specimens were investigated, including 52 cases of TC consisting of 26 cases of aggressive histological types and 26 cases of less aggressive histological types. Immunohistochemical examinations were carried out on paraffin blocks of both groups using a mouse monoclonal primary antibody against PD-L1 (clone 22C3). PD-L1 expression was evaluated by calculating the tumour proportion score (TPS) in both groups. The results revealed a significant difference in the median TPS value of PD-L1 expression between the two groups. The TPS values were found to be higher in the group of aggressive histological types of TC compared with those in the group of less aggressive histological types. A significant difference in TPS value was also found for the extrathyroidal extension variable. In conclusion, the present study found a significant association between PD-L1 expression and the aggressive histological type of TC. In addition, a potential association between PD-L1 expression and the presence of extrathyroidal extension of TC was observed. These findings provide novel approaches for immunotherapy as a potential new treatment modality in patients with aggressive histological types of TC.

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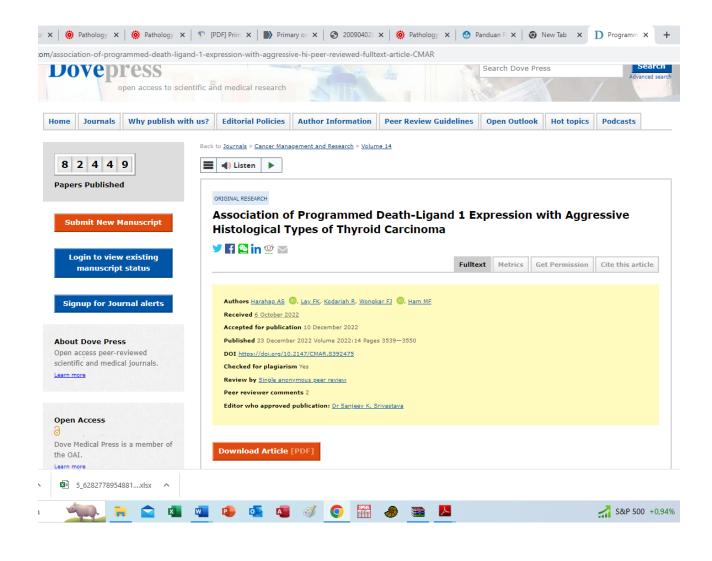
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Title: Association of programmed death-ligand 1 expression with aggressive histological types of thyroid carcinoma

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ORIGINAL RESEARCH

Association of Programmed Death-Ligand 1 Expression with Aggressive Histological Types of Thyroid Carcinoma

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Association of programmed death-ligand 1 expression with aggressive histological types of thyroid carcinoma

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Running title: HARAHAP *et al:* PD-L1 EXPRESSION IN AGGRESSIVE THYROID CARCINOMA

Abstract. Immunohistochemical expression of programmed death-ligand 1 (PD-L1) has become a biomarker to predict the usefulness of cancer immunotherapy using PD-1/PD-L1 blockade in a variety of advanced-stage tumours. This emerging biomarker may serve to generate novel therapies for aggressive thyroid carcinoma (TC), which has not shown optimal results with existing treatments. The present study investigated the relevance of PD-L1 expression in aggressive histological types of TC compared with that found in less aggressive types. Surgically resected specimens were investigated, including 52 cases of TC consisting of 26 cases of aggressive histological types and 26 cases of less aggressive histological types. Immunohistochemical examinations were carried out on paraffin blocks of both groups using a mouse monoclonal primary antibody against PD-L1 (clone 22C3). PD-L1 expression was evaluated by calculating the tumour proportion score (TPS) in both groups. The results revealed a significant difference in the median TPS value of PD-L1 expression between the two groups. The TPS values were found to be higher in the group of aggressive histological types of TC compared with those in the group of less aggressive histological types. A significant difference

in TPS value was also found for the extrathyroidal extension variable. In conclusion, the present study found a significant association between PD-L1 expression and the aggressive histological type of TC. In addition, a potential association between PD-L1 expression and the presence of extrathyroidal extension of TC was observed. These findings provide novel approaches for immunotherapy as a potential new treatment modality in patients with aggressive histological types of TC.

Introduction

Thyroid carcinoma (TC) is the most common malignant endocrine neoplasm and can originate from follicular or parafollicular cells [1]. TCs arising from follicular cells are classified into well-differentiated TC (WDTC), poorly differentiated TC (PDTC) and anaplastic TC (ATC) [1]. Another type of TC that arises from parafollicular cells is medullary TC (MTC) [1, 2]. The incidence of TC significantly increased over the last three decades [3]. The highest increase has occurred in papillary TC (PTC) [3], which is included in the WDTC group along with follicular TC (FTC) and Hurthle cell carcinoma (HCC) [1, 4]. PTC is also the most common type of TC, which accounts for 65-90% of cases in adults and children, with an incidence rate of 13.5 cases per 100,000 individuals per year [1, 3, 5]. The second most common type is FTC, which accounts for 6-10% of TC cases [1]. Other less common types of TC, including PDTC, ATC and MTC, only account for 2-3% of all TC cases [1, 2, 5].

TC has generally a good prognosis, with a 10-year survival rate of 90-95% in the WDTC group, particularly for PTC and FTC [1]. Several factors can worsen patient's prognosis, including advanced age, male sex, increased tumour size, aggressive histological types, presence of extrathyroidal extension, and lymph node or distant metastasis [5, 6]. The worst prognosis is found in ATC, with a disease-specific mortality rate of almost 100% [1].

Therapeutic modalities that can be used in the treatment of TC include surgery, I-131 radiotherapy and systemic medication [7]. Surgery remains the main treatment for patients with common TC, but its role as a curative measure may have limited benefit for patients with more aggressive TCs, such as ATC, PDTC, MTC and several aggressive variants of PTC [6]. TCs with these histological types usually show an infiltrative appearance, extrathyroidal extension and lymph node or distant metastasis [4, 5]. A number of these TC types also tend to show resistance to I-131 radiotherapy [1, 6]. These treatment problems may deteriorate the patient's condition and worsen the prognosis. Therefore, it is necessary to identify other therapeutic modalities to increase the life expectancy of patients.

In the past decade, numerous clinical trials have been conducted on programmed death-1 (PD-1)/PD ligand-1 (PD-L1) inhibitors as immunotherapy agents in patients with lung carcinoma, melanoma, urothelial carcinoma, renal cell carcinoma and Hodgkin's lymphoma [8]. These studies have led to the development of several types of drugs that have been approved by the Food and Drug Administration as PD-1 or PD-L1 inhibitors. These inhibitors are used as immunotherapy in patients with cancer who exhibit positive immunohistochemical PD-L1 expression [8].

Several studies on the role of PD-L1 in TC have been conducted in recent years [9-20]. These studies are mostly based on immunohistochemical examination and also evaluations at the mRNA level. The results of these studies generally indicate a role of PD-L1 in the diagnosis, prognosis and identification of patients with TC who may benefit from immunotherapy using PD-1 or PD-L1 inhibitors [9]. Positive correlations between PD-L1 and certain histological types, clinical aggressiveness, recurrence and advanced stage of TC have been described in several studies [10, 14, 15, 18-22]. However, there are limited studies on immunohistochemical PD-L1 expression in aggressive histological types of TC.

The present study aimed to investigate the immunohistochemical expression profile of PD-L1 in TCs and the association of PD-L1 with aggressive histological types vs. less aggressive types. The results are expected to serve as a basis for novel immunotherapy approaches for patients with aggressive TCs, which are generally difficult to treat.

Materials and methods

Clinicopathological features. The present study retrospectively evaluated the clinicopathological data of 52 patients in two groups of histological types of TC: i) A group of aggressive histological types; and ii) another group of less aggressive histological types. Each group contained 26 samples randomly selected from all patients who had undergone total or partial thyroidectomy for TC at Dr. Cipto Mangunkusumo National Central Public Hospital (Jakarta, Indonesia), in the period January 2015-December 2019. Each case should have an adequate paraffin block of the tumour tissue for additional immunohistochemical examination in order to be enrolled in the current study. TCs with lymphocytic thyroiditis background were excluded from the study. The patients' clinical data were obtained from electronic health records. The original haematoxylin and eosin slides from all cases were reviewed by two pathologists (FKL and ASH), and a paraffin block containing sufficient representative tumour and adjacent/normal tissue of each case was selected for additional immunohistochemical

examination. The histological types of TC were classified according to the criteria of the latest World Health Organization thyroid tumour classification [1] . TCs with histological diagnosis of ATC, PDTC or MDTC as well as various aggressive variants of PTC (tall cell, columnar, solid and hobnail variant) were categorized as a group of aggressive histological types, whereas other types (including FTC, HCC and the remaining variants of PTC) were categorized as a group of less aggressive histological types. The present study was conducted according to the Declaration of Helsinki and was approved (approval no. KET-1295/UN2.F1/ETIK/PPM.00.02/2019) by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (Jakarta, Indonesia).

Immunohistochemical examination. Paraffin-embedded tumour samples were sliced at a thickness of 3-5 μm, placed on poly-L-lysine coated slides and dried on a slide warmer at 60˚C for 60 min. All slides were subjected to deparaffinization in three serial xylene incubations, followed by rehydration in gradually decreasing alcohol concentration, and then eventually washed in running water for 3 min in room temperature. Blocking of endogenous peroxidase was carried out using a solution of 5% H_2O_2 in methanol for 45 min. A Tris EDTA-based solution (pH 9) was used under high pressure to retrieve the antigen. Immunohistochemical staining using a mouse monoclonal primary anti-PD-L1 antibody (clone 22C3; Dako; Agilent Technologies, Inc.) was performed at a dilution of 1:75 overnight in room temperature. Subsequently, the slides were rinsed in PBS (pH 7.4) and incubated for 15 min with Novolink Polymer Detection System as a secondary antibody (Novocastra (Leica Microsystems, Inc.). A solution of 3'3-diaminobenzidine was used as the chromogen to visualize the antigen as dark brown colour. A single in-house quality control derived from non-cancerous tonsil tissue block was provided as the positive control, and was prepared for each batch of slides in the immunostaining process. The negative control was generated by omitting the above primary antibody during immunohistochemical staining, and was prepared for each tumour slide.

Immunohistochemical expression of PD-L1 was determined by using the tumour proportion score (TPS), which is defined as the percentage of PD-L1-stained tumour cell count over the total number of viable tumour cells [23]. Tumour cells that were considered PD-L1 positive were any viable tumour cells that had total or partial linear membrane staining from weak to strong intensity, which was perceived as distinct from cytoplasmic staining and therefore was included in the scoring. The number of PD-L1 staining tumour cells was explored throughout the entire slide area and counted manually with the help of a cell counter. The total number of viable tumour cells (stained and non-stained tumour cells) in the entire tumour field

4

on a slide was calculated by using ImageJ software version 1.53f (National Institutes of Health). A cut-off score ≥1% was used to define PD-L1 positivity in addition to numerical TPS data.

Assessment of PD-L1 immunohistochemistry was accomplished independently by two investigators (FKL and ASH) to determine TPS. Cohen's κ coefficient and Bland Altman analysis were employed to evaluate the reliability of the examination conducted by the above two investigators, both categorically and numerically.

Statistical analysis. Mann-Whitney U test was used to evaluate the statistical significance of differences in numerical TPS data, which were not normally distributed, between two groups. Data are presented as the median and range. $P<0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS 20.0 software (IBM Corp.).

Results

From 2015 to 2019, among 800 patients who had diagnoses of TC, 568 patients underwent partial or total thyroidectomy, and the remaining were subjected to biopsies only. Aggressive histological type of TC was found in 272 cases, and less aggressive histological type was found in 296 cases of all the subjects who underwent surgery.

The present study evaluated a total of 52 samples of patients with TC. There were 40 females (76.9%) and 12 males (23.1%), with a predominant female to male ratio of 3.3:1. The age range of patients was 18-70 years, with a median age of 48.5 years. In total, 32 patients (61.5%) were ≥45 years of age. The tumour size exhibited a range of 0.5-20.0 cm, with a median size of 3.3 cm, and 31 patients (59.6%) had a tumour size ≤4 cm. There were 19 patients (36.5%) with lymph node metastases, 13 (25%) with distant organ metastases and 24 (46.2%) with tumour expansion to surrounding tissues outside the thyroid gland at the time of surgery. Complete data regarding the demographic and pathological characteristics of the present cohort are shown in Table I.

Evaluation was carried out by two observers independently with a good level of conformity based on the Cohen's κ coefficient (0.86) and Bland Altman analysis [limit of agreement, -3.66 to 4.68; 95% confidence interval (-0.67–1.69)] for the categorical (PD-L1 positivity) and numerical (TPS) results, respectively. In the majority of cases, PD-L1 staining

revealed the presence of partial or total linear membrane staining, varying from a few tumour cells to almost all tumour cells as shown in Figure 1. The smallest TPS percentage value obtained was 0.01% which was found in 4 cases (2 cases in each group). The largest TPS percentage value obtained was >90%, which was found in 3 cases (91.17, 91.36 and 95.00%) in aggressive histological type group. Research samples with no PD-L1 positivity at all (TPS=0.00%) were also found in 10 cases, of which 3 cases belonged to the aggressive histological type group and 7 to the less aggressive histological type group. TPS values in each group of TC type are shown in Table II.

A bivariate statistical test, the Mann-Whitney U test, was performed to compare the non-normally distributed TPS data between two groups, namely the aggressive histological type and the less aggressive histological type. The results revealed significant differences (P=0.01), as shown in Table III. This suggested that there was a significant difference in TPS values between the two groups of TC, where the aggressive histological type exhibited higher PD-L1 immunoexpression positivity than the less aggressive histological type.

Additional analyses were also performed on all other demographic and pathological characteristics to evaluate their potential association with PD-L1 immunoexpression as expressed in TPS values (Table IV). Only the extrathyroidal extension variable showed a significant difference (P=0.02).

Discussion

The present study revealed a total of 52 TC cases with a predominant ratio of female to male ratio of 3.3:1, and 61.5% (32/52) of patients were aged ≥45 years old. This is consistent with the incidence rate of TC, which is 3-fold more commonly found in women than in men, and usually patients are >50 years old [1]. The most frequent tumour size found in the present study was ≤4 cm, since the most common type of carcinoma is PTC, which usually measures 2-3 cm on diameter. Larger tumour sizes are generally found in PDTC and ATC, which tend to have a lower incidence than PTC [1].

The majority of TC cases in the present study exhibited no metastasis in distant organs at the time of surgery; however, almost 50% showed tumour expansion into surrounding tissues outside the thyroid gland. These findings are in line with several previous studies, which frequently found stage I-II of TC cases without lymph node or distant metastases. Tumour extension out of the thyroid gland was commonly found in almost 50% of cases in various studies, although a number of studies reported a lower or higher percentage [11, 12, 14, 15].

Previous studies on the role of PD-L1 on TC commonly classified the PD-L1 staining results into positive or negative, based on the TPS and/or combined positive score (CPS) values with different cut-off points. There is currently no agreement on the TPS and/or CPS PD-L1 cut-off points for TC, contrarily to other carcinomas such as lung, breast and urothelial carcinoma. This leads to variations in the cut-off value used when evaluating the TPS value for TC. Previous studies on PD-L1 immunoexpression in TC mainly use a TPS cut-off point of 1 and/or 5% to determine PD-L1 positivity [11-13, 15, 24], while a study by Cantara *et al* (18) used a higher TPS cut-off point (25%) to assess PD-L1 immunoexpression in ATC.

The present study on the role of PD-L1 in TC used a TPS value with a cut-off point of ≥1% positivity. The TPS values were quantitatively compared between the aggressive histological type and less aggressive histological type groups. The use of TPS instead of CPS to assess PD-L1 immunoexpression in the present study was carried out to avoid the influence of lymphocytes, which can increase PD-L1 immunoexpression positivity, for example in cases of TC accompanied by lymphocytic thyroiditis. A previous study that supported this finding, which was carried out by Fadia *et al* (19), revealed that PTCs with lymphocytic thyroiditis showed significantly higher PD-L1 immunoexpression (39.1%) than PTC without lymphocytic thyroiditis (6.1%). A meta-analysis conducted by Girolami *et al* (20) also reported the same findings.

In agreement with our working hypothesis, PD-L1 immunoexpression in the present study was found to be more abundant, and exhibited higher TPS values in the aggressive histological type of TC compared with those in the less aggressive histological type ($P < 0.05$). Based on the cut-off point of TPS ≥1% in determining PD-L1 positivity status, the number of positive PD-L1 cases was 46.2% (12 of 26 cases) in the aggressive histological type of TC group and 15% (4 of 26 cases) in the less aggressive histological type of TC group. TPS values in the aggressive histological type were also found to be significantly higher than those in the less aggressive histological type. These findings are consistent with a previous study conducted by Chowdhury *et al* (21) using an anti-PD-L1 antibody (clone E1L3N), which demonstrated a significant difference in the number of positive PD-L1 cases between the aggressive variant (53/74 cases) and the non-aggressive variant (21/111 cases) of TC. The aggressive variants involved in that study were ATC, PDTC and the tall cell variant of PTC. The authors also found a greater rate of recurrence in TCs with positive PD-L1 status.

The highest PD-L1 immunoexpression found in the present study (TPS >50.00%) was detected in 4 cases of aggressive histological type of TC. Of them, 3 cases were ATC (TPS=84.87, 91.17 and 91.36%) and 1 case was a mixed variant of PTC (solid and tall cell)

with certain anaplastic components (TPS=95%). Other cases of aggressive histological type that also showed positive PD-L1 status included 1 case of hobnail variant of PTC (TPS=3.07%), 2 cases of tall cell variant of PTC (TPS=5.57 and 21.14%), 2 cases of mixed variant of PTC (solid and tall cell) with anaplastic components (TPS=9.81 and 36.60%) and 3 cases of ATC (TPS=1.15, 4.12 and 21.72%). The present study did not find PD-L1 immunoexpression in any of the MTC cases (TPS=0.00%). In the less aggressive histological type, positive PD-L1 immunoexpression with TPS ≥1% was found in 4 cases, including 2 cases of the follicular variant of PTC (TPS=3.31 and 14.10%), 1 case of the classic variant of PTC (TPS=8.94%) and 1 case of HCC with minimal invasion (TPS=19.53%). The difference in TPS values in various types of TC found in the present study was in line with the findings of a previous study conducted by Ahn *et al* (12), which showed differences in PD-L1 immunoexpression among different histological types of TC using tissue microarray samples with anti-PD-L1 antibody clone SP142 and a TPS cut-off point of ≥1% to define PD-L1 positivity. The authors found positive PD-L1 immunoexpression status in 6.1% (20/326) of PTC cases, 7.6% (5/66) of FTC cases and 22.2% (2/9) of ATC cases. All the ATC cases in their study showed much higher TPS values (80-90%) than other types of TC. Positivity of PD-L1 immunoexpression in MTC was not found in the current study. This may be due to the small sample number of MTC in the present study, since only 1 sample was included, and the frequency of PD-L1 positivity in this type of carcinoma is low according to the results of previous studies [15, 25]. One of those studies was conducted by Kemal *et al* (22), who used an anti-PD-L1 antibody (clone SP263) with a TPS cut-off point of ≥1% to explore the PD-L1 positivity in 41 MTC cases and found PD-L1 positivity in only 5 cases.

A prospective observational study is the best method to evaluate the risk of recurrence of TC and its association with PD-L1 immunoexpression; however, this methodology requires extensive resources and time. The simple but reasonable approach of evaluating the presence or absence of tumour extension outside the thyroid gland can be used as an alternative method to predict the recurrence of TC, as suggested by Bai *et al* [26]. Tumour expansion outside the thyroid gland is one of the clinicopathological factors assessed in the present study. Additional analyses performed found a significant association between PD-L1 immunoexpression and extrathyroidal extension. This finding is in line with the results of several other studies, including that by Aghajani *et al* (13), who found that 11 of 15 cases of PTC with positive PD-L1 immunoexpression (TPS ≥1%) showed tumour expansion outside the thyroid gland. A similar result was also reported in a study conducted by Shi *et al* (24), who found extrathyroidal extensions of the thyroid tumour in 60 of 136 cases of PTC with positive PD-L1 status. The

association between PD-L1 immunoexpression and the presence of extrathyroidal extension found in the present and previous studies may suggest an association between PD-L1 immunoexpression and the risk of recurrence, which could affect the patient's prognosis, as suggested by Chowdhury *et al* [18]. Further studies with a more suitable research design should be considered in the future to validate this potential association.

In the present study, other demographic or pathological factors, such as sex, age, tumour size, lymph node metastases or distant metastases, did not show a significant association with PD-L1 immunoexpression based on the bivariate statistical tests performed in the additional analyses, using Mann-Whitney U test. These findings were also reported by other studies that assessed the same clinicopathological factors [12, 13, 15]. One of those studies was conducted by Ahn *et al* (12), and included a large sample size of TC (407 cases). The authors found no association between PD-L1 immunoexpression and clinicopathological variables such as age, sex, tumour size, multifocality or stage[12]. Similarly, another study with a smaller sample size (110 cases of PTC stained with anti-PD-L1 antibody clone SP142) conducted by Bai *et al* (16) did not reveal significant associations between PD-L1 immunoexpression and clinicopathological factors [13].

In conclusion, the present study found a clinically and statistically significant association between PD-L1 immunoexpression and aggressive histological types of TC. PD-L1 immunoexpression, as evaluated by the TPS value, was found to be significantly higher in the aggressive histological type group compared with that in the less aggressive histological type group. The histological types of TC that showed the highest PD-L1 positivity were ATC, tall cell variant of PTC and other aggressive histological types of TC with anaplastic components involved. Only a few TC cases from the less aggressive histological group showed PD-L1 immunoexpression (follicular variant of PTC, classic PTC and HCC with minimal invasion). Other demographic/pathological factor that also appeared to show a significant association with PD-L1 immunoexpression was extrathyroidal extension of TC. Other factors such as sex, age, tumor size, lymph node metastasis or and distant metastasis did not show a significant association with PD-L1 immunoexpression. These findings provide novel approaches for immunotherapy as a potential new treatment modality in patients with aggressive histological types of TC.

Funding

Availability of data and materials

All data are available from the corresponding author upon reasonable request.

Authors' contributions

MFH, ASH, FKL and RK designed the study. FKL and ASH carried out the study including the data collection and data analysis. RK evaluated data analysis. FKL wrote the manuscript. FKL and ASH confirmed the authenticity of the raw data. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by The Ethics Committee of the Faculty of Medicine, Universitas Indonesia.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figure legends

Figure 1. Immunohistochemical PD-L1 expression in TC samples using a mouse monoclonal anti-PD-L1 antibody (clone 22C3) (A) Aggressive histological type: PD-L1 expression in anaplastic TC showed positive linear membrane staining, from weak to strong intensity (TPS ≥90%). (B) Less aggressive histological type: Absent PD-L1 expression was observed in classic papillary TC (TPS 0%). TC, thyroid carcinoma; TPS, tumour proportion score; PD-L1, programmed death-ligand 1.