Section: Pathology

Original Research Article

PD-L1 EXPRESSION IN THYROID CARCINOMA AND ITS ASSOCIATION WITH CLINICOPATHOLOGICAL FINDINGS: A HOSPITAL-BASED STUDY FROM SOUTH INDIA

Rajesh Kumar Mohan[1], Anusha Babu Rajendran[2], Rashmi Raveendran[3]

[1]Assistant Professor, Department of Pathology, Vels Medical College and Hospital, VISTAS University, Chennai, India.
[2]Associate Professor, Department of Pathology, Vels Medical College and Hospital, VISTAS University, Chennai, India.
[3]Assistant Professor, Department of Pathology, Vels Medical College and Hospital, VISTAS University, Chennai, India.

Received : 04/06/2023
Received in revised form : 15/07/2023
Accepted : 28/07/2023

Keywords:
Thyroid carcinoma, PD-L1 expression, clinicopathological findings, immunotherapy, prognostic biomarker, programmed death-ligand 1.

Corresponding Author:
Dr. Rashmi Raveendran,

DOI: 10.47009/jamp.2023.5.4.233

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (4); 1154-1159

Abstract

Background: Thyroid carcinoma comprises 1% of all cancers globally and its incidence rates are rising. Aggressive subtypes, including poorly differentiated and anaplastic carcinomas, present therapeutic challenges. Immunotherapy, particularly PD-1/PD-L1 axis blockade, has shown success in various cancers. PD-L1's role in thyroid carcinoma remains unclear, necessitating a comprehensive investigation to explore its prevalence and clinicopathological associations. Understanding PD-L1's impact may offer new immunotherapeutic strategies for improved patient outcomes. **Materials and Methods:** A retrospective cohort of thyroid carcinoma patients from a tertiary care hospital in South India was studied. Immunohistochemistry (IHC) staining for PD-L1 expression was performed on formalin-fixed paraffin-embedded (FFPE) tissue samples. PD-L1 expression was evaluated by two blinded pathologists using intensity and percentage scores. A PD-L1 score ≥10 indicated positivity. Clinicopathological data were collected, and statistical analysis was performed using SPSS 20.0. Chi-square and Fisher's exact tests were used to assess associations ($p<0.05$ considered significant). **Results:** The study included 157 thyroid carcinoma patients, with 81.5% male and 18.5% female. Most were younger than 45 years (57.3%, mean age 42.12±11.35 years). Papillary Thyroid Carcinoma (PTC) was the most common histopathological diagnosis (53.5%), followed by Poorly Differentiated Thyroid Carcinoma (PDTC) (30.6%). Papillary thyroid carcinoma (PTC) had the highest PD-L1 positivity (68.2%), while Anaplastic Thyroid carcinoma (ATC) had the lowest (4.5%). No significant associations were found between PD-L1 expression and age, tumor size, multiplicity, initial metastasis, recurrence, or death. PD-L1 expression was significantly associated with TNM stage 2 (22.7%) compared to stage 1 (45.5%) ($P = 0.014$). Overall, the study provides insights into PD-L1 expression in thyroid carcinoma and its potential prognostic significance. **Conclusion:** In conclusion, our study found that 14.0% of thyroid carcinoma patients showed PD-L1 positivity, with higher expression in females. PD-L1 expression varied across histopathological subtypes, being highest in Papillary Thyroid Carcinoma. TNM stage 2 had higher PD-L1 expression than stage 1.

INTRODUCTION

Thyroid carcinoma accounts for the most prevalent endocrine malignancy, comprising approximately 1% of all cancers worldwide.[1] The incidence rates have shown a steady rise over the past few decades, necessitating urgent efforts to understand the molecular underpinnings and identify novel therapeutic targets to improve patient outcomes. While conventional treatments, such as surgery, radiotherapy, and radioiodine therapy, have shown efficacy in well-differentiated thyroid cancers, aggressive subtypes, including poorly differentiated, anaplastic, and radioiodine-refractory cases, pose significant challenges and often exhibit poor prognosis.[2,3]

Immunotherapy has revolutionized the treatment landscape in several malignancies by harnessing the

ISSN (O): 2687-5365; ISSN (P): 2753-6556

host immune system to target tumor cells. Checkpoint inhibitors, particularly those targeting the PD-1/PD-L1 axis, have shown remarkable success in cancers such as melanoma, lung, and renal cell carcinoma.[4,5] PD-L1, an immune checkpoint ligand expressed on the surface of tumor cells, interacts with PD-1 on activated T cells, leading to T cell exhaustion and suppression of antitumor immunity. Blockade of this interaction by monoclonal antibodies has demonstrated promising clinical responses in various cancers, igniting enthusiasm for its potential application in thyroid carcinoma.[6,7]

Although studies investigating PD-L1 expression in thyroid carcinoma have yielded conflicting results, accumulating evidence suggests its involvement in tumor immune evasion and disease progression. Moreover, its association with clinicopathological features remains poorly understood, hampering the establishment of PD-L1 as a reliable prognostic and predictive marker in thyroid carcinoma.[8,9]

Hence, the aim of our study was to comprehensively evaluate the prevalence of PD-L1 expression in a diverse cohort of thyroid carcinoma cases and correlate it with clinicopathological findings. By addressing this research gap, we aspired to contribute critical insights into the role of PD-L1 in thyroid carcinoma, potentially paving the way for novel immunotherapeutic strategies and personalized treatment approaches.

MATERIALS AND METHODS

Study Cohort and Sample Collection

A retrospective cohort of patients diagnosed with thyroid carcinoma (January 2021 to June 2023) was selected for this study. Formalin-fixed paraffin-embedded (FFPE) tissue samples from primary thyroid tumors were obtained from the pathology archives of tertiary care hospital, South India. The inclusion criteria comprised patients with a confirmed diagnosis of thyroid carcinoma and adequate clinical and histopathological data. Patients with incomplete medical records or receiving neoadjuvant therapy were excluded from the study. Ethical approval for this research was obtained from the Institutional Review Board (IRB) of tertiary care hospital, South India and the period of study was 3 months (April 2023 to June 2023).

Immunohistochemistry (IHC) Staining for PD-L1 Expression

PD-L1 expression in thyroid carcinoma tissues was assessed using immunohistochemical staining. FFPE tissue sections (4 μm thick) were cut and mounted onto charged slides. Following deparaffinization and rehydration, antigen retrieval was performed using heat-induced epitope retrieval (HIER) with citrate buffer (pH 6.0). Endogenous peroxidase activity was quenched with 3% hydrogen peroxide, and non-specific binding was blocked with 5% bovine serum albumin (BSA) in phosphate-buffered saline (PBS). The slides were incubated with the primary anti-PD-L1 antibody (clone SP142, Ventana Medical Systems, dilution 1:100) overnight at 4°C. Subsequently, the sections were treated with the appropriate secondary antibody (anti-rabbit IgG, HRP-linked) for 30 minutes at room temperature. 3,3'-Diaminobenzidine (DAB) was used as the chromogen to visualize the bound antibodies, and the sections were counterstained with hematoxylin to aid in tissue visualization.

Evaluation of PD-L1 Expression

Two experienced pathologists, blinded to the clinicopathological data, independently evaluated PD-L1 expression in the thyroid carcinoma tissues. PD-L1 expression was assessed in both tumor cells and tumor-infiltrating immune cells. The staining intensity was graded as follows: 0 (no staining), 1+ (weak staining), 2+ (moderate staining), and 3+ (strong staining). The percentage of positively stained cells was recorded for each case.

The final PD-L1 score was calculated by multiplying the intensity score with the proportion of positive cells, yielding a value ranging from 0 to 300. Tumors with a PD-L1 score ≥10 were considered PD-L1 positive, while those with a score <10 were classified as PD-L1 negative, in line with previous studies [9,10].

Clinicopathological Data Collection

Clinicopathological data, including patient age, gender, tumor size, histological subtype, TNM stage, lymph node involvement, distant metastasis, and recurrence status, were collected from the electronic medical records and pathology reports. All patient information was de-identified and maintained confidentially.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0. The association between PD-L1 expression and clinicopathological parameters was evaluated using chi-square test and Fisher's exact test. A p-value of <0.05 was considered statistically significant.

RESULTS

The study included 157 patients with thyroid cancer, with 81.5% being male and 18.5% female. The majority of patients (57.3%) were younger than 45 years, with a mean age of 42.12±11.35 years. Papillary Thyroid Carcinoma (PTC) was the most common histopathological diagnosis (53.5%), followed by Poorly Differentiated Thyroid Carcinoma (PDTC) (30.5%). Tumors of 2-4 cm size constituted 72.6% of cases. Most patients (76.4%) had solitary tumors, and 8.9% presented with initial metastasis. The majority (56.7%) were at TNM stage 1, while 22.3% experienced recurrence, and 11.5% succumbed to the disease during follow-up (Table 1).

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 1: Baseline characteristics of the patients with thyroid cancer (N=157)

Variables	Frequency	%
Gender		
Male	128	81.5
Female	29	18.5
Age group		
<45 years	90	57.3
>45 years	67	42.7
Mean age (in years)	42.12+11.35	
Histopathological diagnosis		
Papillary Thyroid Carcinoma (PTC)	84	53.5
Poorly Differentiated Thyroid Carcinoma (PDTC)	48	30.5
Follicular Thyroid Carcinoma (FTC)	18	11.5
Anaplastic Thyroid Carcinoma (ATC)	7	4.5
Tumour size		
<2 cm	18	11.5
2-4 cm	114	72.6
>4 cm	25	15.9
Multiplicity		
Yes	37	23.6
No	120	76.4
Initial metastasis		
Yes	14	8.9
No	143	91.1
TNM stage		
1	89	56.7
2	14	8.9
3	45	28.7
4	9	5.7
Recurrence		
Yes	35	22.3
No	122	77.7
Death		
Yes	18	11.5
Alive	139	88.5

In the Figure 1., histological examination, papillary thyroid carcinoma (PTC) displayed a predominant papillary structure. The background thyroid tissue of PTC exhibited dense lymphoplasmacytic infiltrates and germinal center formation, indicating the presence of chronic lymphocytic thyroiditis. Immunohistochemical analysis revealed diffuse PD-L1 expression on both the cell membrane and cytoplasm of tumor cells. However, it is important to note that there was also staining on the tumor-infiltrating lymphocytes (TILs), which should not be considered as positive staining of the tumor cells. Additionally, focal PD-L1 expression was observed on the tumor cell membrane.

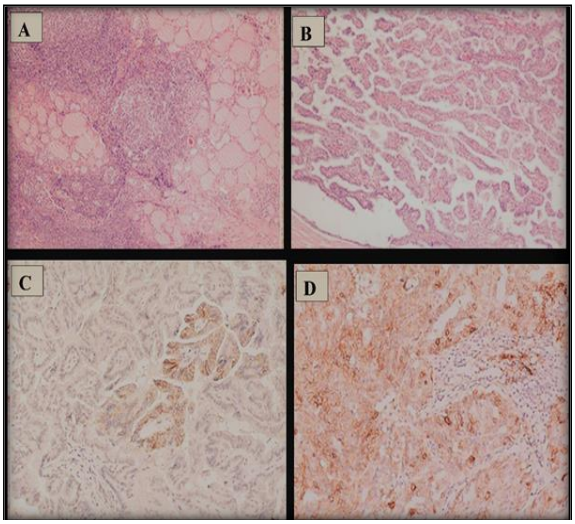

Figure 1. Papillary thyroid carcinoma. A: Dense lymphoplasmacytic infiltrates and germinal center formation. B: Predominant papillary structure, C: PD-L1 was focally expressed. D: Diffuse PD-L1 expression

The Figure 2., for PD-L1 expression in tumor cells showed that 86.0% of patients had no tumor cells stained with PD-L1, while 14.0% of patients had stained tumor cells. Among the PD-L1 positive cases, the distribution of staining percentage was as follows: 36.4% had less than 1% of tumor cells stained, 22.7% had 1-10% stained cells, 18.2% had 11-33% stained cells, 13.6% had 34-66% stained cells, and 9.1% had 67-100% stained cells.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

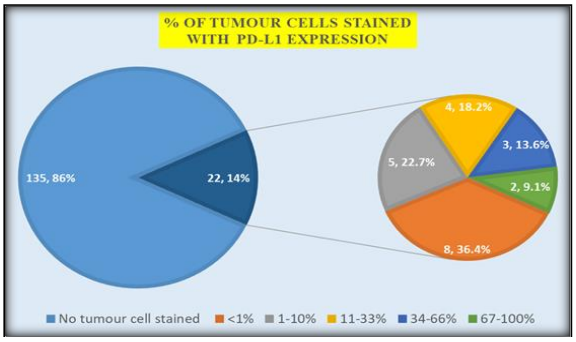

Figure 2. Percentage of tumour cells-stained PD-L1 expression.

The analysis of PD-L1 expression intensity revealed that 135 cases (86.0%) had negative staining, while 22 cases (14.0%) showed positive staining. Among the positive staining cases, 3 cases (13.6%) exhibited strong intensity, 8 cases (36.4%) showed intermediate intensity, and 11 cases (50.0%) displayed weak intensity (Figure 3).

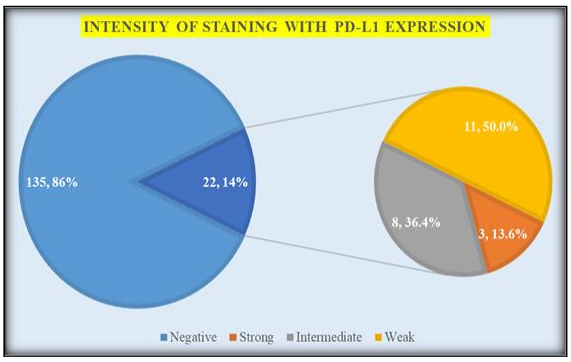

Figure 3. Intensity of staining with PD-L1 expression.

PD-L1 positivity was significantly higher in females (72.7%) compared to males (27.3%) (P < 0.0001). There was no statistically significant difference in PD-L1 expression between patients younger than 45 years (45.5%) and those older than 45 years (54.5%) (P = 0.224). PD-L1 positivity varied significantly across different histopathological subtypes. Papillary Thyroid Carcinoma (PTC) had the highest PD-L1 positive cases (68.2%), followed by Follicular Thyroid Carcinoma (FTC) (22.8%), Anaplastic Thyroid Carcinoma (ATC) (4.5%), and Poorly Differentiated Thyroid Carcinoma (PDTC) (4.5%) (all P < 0.05). There was no significant association between PD-L1 expression and tumor size, irrespective of whether the tumor size was less than 2 cm, 2-4 cm, or greater than 4 cm (all P > 0.05). No significant difference in PD-L1 expression was observed between patients with solitary tumors (68.2%) and those with multiple tumors (31.8%) (P = 0.325). PD-L1 positivity did not significantly differ between patients with initial metastasis (4.5%) and those without metastasis (95.5%) (P = 0.437). PD-L1 expression showed a significant association with TNM stage 2 (22.7%) compared to stage 1 (45.5%) (P = 0.014). However, there were no significant differences in PD-L1 expression between other stages (all P > 0.05). While there was no statistically significant association between PD-L1 expression and recurrence (P = 0.087), there was also no significant association between PD-L1 expression and death (P = 0.730) (Table 2).

Table 2. Distribution of various clinicopathological variables and their association with PD-L1 expression in thyroid carcinoma patients

Variables	Frequency	%	Frequency	%	P value
	Group A (n=22)		Group B (n=135)		
Gender					
Male (n=128)	6	27.3	122	90.4	<0.0001
Female (n=29)	16	72.7	13	9.6	
Age group					
<45 years (n=90)	10	45.5	80	59.3	0.224
>45 years (n=67)	12	54.5	55	40.7	
Histopathological diagnosis					
PTC (n=84)	15	68.2	77	57	<0.0001
PDTC (n=48)	1	4.5	47	34.8	0.004
FTC (n=18)	5	22.8	13	9.6	0.073
ATC (n=7)	1	4.5	6	4.4	<0.0001
Tumour size					
<2 cm (n=18)	2	9.1	16	11.9	0.706
2-4 cm (n=114)	16	72.7	98	72.6	0.989
>4 cm (n=25)	4	18.2	21	15.6	0.754
Multiplicity					
Yes (n=37)	7	31.8	30	22.2	0.325
No (n=120)	15	68.2	105	77.8	
Initial metastasis					
Yes (n=14)	1	4.5	13	9.6	0.437
No (n=143)	21	95.5	122	90.4	
TNM stage					
1 (n=89)	10	45.5	79	58.5	0.251
2 (n=14)	5	22.7	9	6	0.014
3 (n=45)	5	22.7	40	29.6	0.506
4 (n=9)	2	9.1	7	5.1	0.085
Recurrence					

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Yes (n=35)	8	36.4	27	20.0	0.087
No (n=122)	14	63.6	108	80.0	
Death					
Yes (n=18)	3	13.6	15	11.1	0.730
Alive (n=139)	19	86.4	120	88.9	

DISCUSSION

The assessment of PD-L1 expression in cancer has emerged as a pivotal aspect of immunotherapy research, providing valuable insights into tumor-immune interactions and potential treatment targets. Several studies, including Hasio et al., Chen et al., and Wu et al., have investigated PD-L1 expression in various cancers.[9,10,11] In this study, we aimed to investigate PD-L1 expression in thyroid carcinoma and its association with various clinicopathological parameters to shed light on its prognostic and predictive significance.

In our study, we observed that Papillary Thyroid Carcinoma (PTC) exhibited the highest percentage of PD-L1 positive cases (68.2%), followed by Follicular Thyroid Carcinoma (FTC) (22.8%), Anaplastic Thyroid Carcinoma (ATC) (4.5%), and Poorly Differentiated Thyroid Carcinoma (PDTC) (4.5%) (all $P < 0.05$). These findings indicate a selective presence of PD-L1, suggesting its potential role in modulating the immune response within the tumor microenvironment. These results are consistent with previous studies conducted by Rosenbaum et al., Chintakuntlawar et al., Zwaenepoel et al., Chowdhury et al., Bastman et al., Tamimi et al., and Ulisse et al.[12-18]

An intriguing finding in our study was the significant association between PD-L1 expression and gender. PD-L1 positivity was markedly higher in female patients (72.7%) compared to males (27.3%). This gender-based discrepancy may imply potential hormonal influences on PD-L1 expression, warranting further investigation. Additionally, this observation prompts us to explore whether gender-specific immunotherapeutic approaches could be beneficial in PD-L1 positive thyroid carcinoma patients.

Although the association between PD-L1 expression and age was not statistically significant, our study revealed a substantial correlation with histopathological subtypes. Specifically, Papillary Thyroid Carcinoma (PTC) exhibited the highest PD-L1 positivity (68.2%), while Anaplastic Thyroid Carcinoma (ATC) and Poorly Differentiated Thyroid Carcinoma (PDTC) showed the lowest (4.5 %). These findings are in line with previous studies by Shi et al., Zhang et al., Bi et al., and Bongiovanni et al., indicating varied PD-L1 expression patterns among different thyroid carcinoma subtypes.[19-22] The distinct PD-L1 expression suggests the presence of diverse immune evasion mechanisms and potential immunotherapeutic vulnerabilities unique to each histological variant. These results align with the observations But Ingenwerth et al., found that PD-L1 expression was not detected in either tumor cells or lymphocytes/macrophages.[23]

Tumor size and multiplicity did not show any significant association with PD-L1 expression. This observation suggests that PD-L1 expression might not be directly linked to tumor aggressiveness in thyroid carcinoma, contrasting findings from certain other cancer types (3). However, the impact of PD-L1 expression on tumor growth, invasion, and metastasis cannot be entirely ruled out, and further studies are warranted to clarify these associations. Studies by Cunha et al., Angell et al., Shi et al., and Bi et al., reported a significant correlation between PD-L1 positivity and distant metastases at the time of surgery.[19,21,24,25] They also found that co-expression of PD-1 and PD-L1 was associated with a more advanced TNM stage.

An interesting finding in our study was the significant association between PD-L1 expression and TNM stage 2 compared to stage 1. Although the overall differences in PD-L1 expression among various TNM stages were not statistically significant, the observation of higher PD-L1 positivity in stage 2 raises intriguing questions about the potential dynamic changes in PD-L1 expression during tumor progression. Teng et al.[26] This finding emphasizes the need for longitudinal studies to explore the temporal alterations in PD-L1 expression in thyroid carcinoma.

Regarding clinical outcomes, our study did not find a statistically significant association between PD-L1 expression and recurrence or death. However, the relatively small number of events in our study might have affected the statistical power, highlighting the need for larger patient cohorts to draw more conclusive assessments.

A study conducted by Girolami et al. reported a significant correlation between PD-L1 expression and decreased disease-free survival, but no significant association was observed with overall survival.[27] But in studies by Basak et al., Cortellini et al., Peters et al., and Lim et al., found significant association between PD-L1 expression and clinical outcomes in their respective cohorts.[28,29,30,31] These varying results emphasize the importance of considering larger sample sizes and conducting further research to better understand the potential impact of PD-L1 expression on clinical outcomes in thyroid carcinoma.

Limitations

Limitations of our study include its retrospective design, small sample size, and single-center setting. The heterogeneity of thyroid carcinoma subtypes and the use of immunohistochemistry for PD-L1 assessment could introduce variability. Additionally, the study did not evaluate the response to

ISSN (O): 2687-5365; ISSN (P): 2753-6556

immunotherapy or consider other immune checkpoints. Future research with larger, prospective cohorts and multi-center collaborations is needed to overcome these limitations and provide more comprehensive insights.

CONCLUSION

In conclusion, our study found that 14.0% of thyroid carcinoma patients showed PD-L1 positivity, with higher expression in females. PD-L1 expression varied across histopathological subtypes, being highest in Papillary Thyroid Carcinoma. TNM stage 2 had higher PD-L1 expression than stage 1. Although no significant associations were observed with clinical outcomes, our findings indicate the potential of PD-L1 as a biomarker for tailored immunotherapeutic approaches in thyroid carcinoma. Further research with larger cohorts is warranted to validate these findings and optimize treatment strategies.

REFERENCES

1. Katoh H, Yamashita K, Enomoto T, Watanabe M. Classification and general considerations of thyroid cancer. Ann Clin Pathol. 2015;3(1):1045.
2. Carlomagno F, Santoro M. Thyroid cancer in 2010: a roadmap for targeted therapies. Nat Rev Endocrinol. 2011;7(2):65-7.
3. Sun WY, Lee YK, Koo JS. Expression of PD-L1 in triple-negative breast cancer based on different immunohistochemical antibodies. J Transl Med. 2016;14(1):173.
4. McLaughlin J, Han G, Schalper KA, et al. Quantitative Assessment of the Heterogeneity of PD-L1 Expression in Non-Small-Cell Lung Cancer. JAMA Oncol. 2016;2(1):46-54.
5. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat Immunol. 2007;8(3):239-45.
6. Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer immunotherapy with antibodies to the PD-1 and PD-L1 pathway. Trends Mol Med. 2015;21(1):24-33.
7. Phillips T, Simmons P, Inzunza HD, et al. Development of an automated PD-L1 immunohistochemistry (IHC) assay for non-small cell lung cancer. Appl Immunohistochem Mol Morphol. 2015;23(8):541-9.
8. Scheel AH, Dietel M, Heukamp LC, et al. Harmonized PD-L1 immunohistochemistry for pulmonary squamous-cell and adenocarcinomas. Mod Pathol. 2016;29(10):1165-72.
9. Hsiao SJ, Nikiforov YE. Molecular approaches to thyroid cancer diagnosis. Endocr Relat Cancer. 2014;21(5):T301-13.
10. Chen J, Jiang CC, Jin L, Zhang XD. Regulation of PD-L1: a novel role of pro-survival signalling in cancer. Ann Oncol. 2016;27(3):409-16.
11. Wu H, Sun Y, Ye H, Yang S, Lee SL, de las Morenas A. Anaplastic thyroid cancer: outcome and the mutation/expression profiles of potential targets. Pathol Oncol Res. 2015;21(3):695-701.
12. Rosenbaum MW, Gigliotti BJ, Pai SI, et al. PD-L1 and IDO1 Are Expressed in Poorly Differentiated Thyroid Carcinoma. Endocr Pathol. 2018;29(1):59-67.
13. Chintakuntlawar AV, Rumilla KM, Smith CY, et al. Expression of PD-1 and PD-L1 in Anaplastic Thyroid Cancer Patients Treated With Multimodal Therapy: Results From a Retrospective Study. J Clin Endocrinol Metab. 2017;102(6):1943-50.
14. Zwaenepoel K, Jacobs J, De Meulenaere A, et al. CD70 and PD-L1 in anaplastic thyroid cancer - promising targets for immunotherapy. Histopathology. 2017;71(3):357-65.
15. Chowdhury S, Veyhl J, Jessa F, et al. Programmed death-ligand 1 overexpression is a prognostic marker for aggressive papillary thyroid cancer and its variants. Oncotarget. 2016;7(22):32318-28.
16. Bastman JJ, Serracino HS, Zhu Y, et al. Tumor-Infiltrating T Cells and the PD-1 Checkpoint Pathway in Advanced Differentiated and Anaplastic Thyroid Cancer. J Clin Endocrinol Metab. 2016;101(7):2863-73.
17. Tamimi DM. The association between chronic lymphocytic thyroiditis and thyroid tumors. Int J Surg Pathol. 2002;10(2):141-6.
18. Ulisse S, Tuccilli C, Sorrenti S, et al. PD-1 Ligand Expression in Epithelial Thyroid Cancers: Potential Clinical Implications. Int J Mol Sci. 2019;20(6):1405.
19. Shi X, Yu PC, Lei BW, et al. Association Between Programmed Death-Ligand 1 Expression and Clinicopathological Characteristics, Structural Recurrence, and Biochemical Recurrence/Persistent Disease in Medullary Thyroid Carcinoma. Thyroid. 2019;29(9):1269-78.
20. Zhang GQ, Wei WJ, Song HJ, et al. Programmed Cell Death-Ligand 1 Overexpression In Thyroid Cancer. Endocr Pract. 2019 Mar;25(3):279-86.
21. Bi Y, Ren X, Bai X, et al. PD-1/PD-L1 expressions in medullary thyroid carcinoma: Clinicopathologic and prognostic analysis of Chinese population. Eur J Surg Oncol. 2019;45(3):353-8.
22. Bongiovanni M, Rebecchini C, Saglietti C, et al. Very low expression of PD-L1 in medullary thyroid carcinoma. Endocr Relat Cancer. 2017;24(6):L35-L38.
23. Ingenwerth M, Goetz M, Schmid KW, Theurer S. The mismatch repair system is not affected in medullary thyroid carcinoma independent of stromal desmoplasia or ret proto-oncogene mutation. Ann Diagn Pathol. 2020;44:151445.
24. Cunha LL, Marcello MA, Morari EC, et al. Differentiated thyroid carcinomas may elude the immune system by B7H1 upregulation. Endocr Relat Cancer. 2013;20(1):103-10.
25. Angell TE, Lechner MG, Jang JK, Correa AJ, LoPresti JS, Epstein AL. BRAF V600E in papillary thyroid carcinoma is associated with increased programmed death ligand 1 expression and suppressive immune cell infiltration. Thyroid. 2014;24(9):1385-93.
26. Teng MW, Ngiow SF, Ribas A, Smyth MJ. Classifying Cancers Based on T-cell Infiltration and PD-L1. Cancer Res. 2015;75(11):2139-45.
27. Girolami I, Pantanowitz L, Mete O, et al. Programmed Death-Ligand 1 (PD-L1) Is a Potential Biomarker of Disease-Free Survival in Papillary Thyroid Carcinoma: a Systematic Review and Meta-Analysis of PD-L1 Immunoexpression in Follicular Epithelial Derived Thyroid Carcinoma. Endocr Pathol. 2020;31(3):291-300.
28. Basak EA, van der Meer JWM, Hurkmans DP, et al. Overt Thyroid Dysfunction and Anti-Thyroid Antibodies Predict Response to Anti-PD-1 Immunotherapy in Cancer Patients. Thyroid. 2020;30(7):966-73.
29. Cortellini A, Friedlaender A, Banna GL, et al. Immune-related Adverse Events of Pembrolizumab in a Large Real-world Cohort of Patients With NSCLC With a PD-L1 Expression ≥ 50% and Their Relationship With Clinical Outcomes. Clin Lung Cancer. 2020;21(6):498-508.e2.
30. Peters S, Gettinger S, Johnson ML, et al. Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With Programmed Death-Ligand 1-Selected Advanced Non-Small-Cell Lung Cancer (BIRCH). J Clin Oncol. 2017;35(24):2781-9.
31. Lim SM, Shin SJ, Chung WY, et al. Treatment outcome of patients with anaplastic thyroid cancer: a single center experience. Yonsei Med J. 2012;53(2):352-7.

ISSN (O): 2687-5365; ISSN (P): 2753-6556