CASE SERIES

10.2478/AMB-2026-0008

# AN INDIVIDUALIZED APPROACH IN THE MANAGEMENT OF THYROID DYSFUNCTION ASSOCIATED WITH CHECKPOINT INHIBITORS – A CLINICAL CASE SERIES

**R. Dimitrova, M. Siderova, Zh. Ruseva**

Medical University of Varna, UMHAT "Sveta Marina" – Varna, Bulgaria

***Abstract.*** *Immune checkpoint inhibitors (ICIs) are a revolutionary class of drugs for the treatment of a number of oncological diseases by harnessing the immune system to counteract malignant cells. However, their use as antitumor agents is accompanied by a wide range of immune-mediated adverse effects, including endocrinopathies. Among the latter, thyroid dysfunction stands out as one of the most common. This article presents six different clinical cases of thyroid damage with an emphasis on thorough clinical examination aided by imaging and precise interpretation of hormonal studies. The management of thyroid-related immune-mediated side effects requires an individualized approach, taking into account the severity and dynamics of the abnormalities, the clinical condition of the patient and the stage of the malignancy.*

***Key words:*** *checkpoint inhibitors, thyroid dysfunction, hypothyroidism, immune-related adverse events*

***Corresponding author:*** *Radina Dimitrova, Medical University of Varna, UMHAT "Sveta Marina", Varna, Bulgaria, email: dr.rsd1985@gmail.com*

***ORCID:*** *0000-0001-5897-2169*

***Received:*** *24 April 2025;* ***Revised/Accepted:*** *24 June 2025*

## INTRODUCTION

In recent years, immune checkpoint inhibitors (ICIs) have emerged as a powerful, innovative therapeutic strategy for treating various cancers [1]. Depending on the tumor type and stage, ICIs are used as first-, second- or third-line treatment, as well as for adjuvant or neoadjuvant therapy [2]. They can be administered alone or in combination with conventional treatments such as radiotherapy and chemotherapy. Their effect is exerted by targeting the immune response to malignant cells, blocking the usual inhibitory pathways of T-cell regulation, thereby allowing T-cell-mediated destruction of cancer cells [3, 4].

Cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death protein-1 (PD-1), as well as their ligand (PD-L1), are major immune checkpoints and targets for inhibition [5, 6]. Thus, the immune system can be manipulated at two levels, with CTLA-4 acting at the early stage of triggering the antigen response, whereas PD-1 and PD-L1 modulate the interactions with peripheral tissues [7]. Another promising therapeutic target in immunotherapy is lymphocyte activation gene-3 (LAG-3), which is also a receptor protein of the immune checkpoint family located on the surface of activated T-cells. It has a regulatory role comparable to that of PD-1/PD-L1 and CTLA-4 by occupying a major site in the

negative regulation of T-cell function and thus providing immune escape of the tumor into the microenvironment [8].

Along with the possibility of achieving significant success in the treatment of a number of cancers, ICIs therapy carries the risk of immune-related adverse events (irAEs), which can potentially affect any organ due to the hyperactivation of immune cells. This risk increases when immunotherapy is combined. The severity of irAEs can range from mild to life-threatening. In most cases, irAEs develop in the first few weeks or months after ICIs initiation, but they can occur at any other time, even after treatment discontinuation. These adverse events may be transient or associated with permanent loss of function of the affected organ [9].

Among the most common irAEs associated with ICIs therapy are colitis, pneumonitis, hepatitis and skin manifestations, followed by endocrine disorders [9]. Immune-related endocrinopathies affect approximately 10% of all patients on ICIs treatment [10], with the incidence increasing to 17% with combination immunotherapy [11]. In those receiving anti-PD-1/anti PD-L1 and anti-CTLA-4, thyroid abnormalities and pituitary involvement are most common [12, 13]. Adverse effects on the adrenal glands, pancreas and parathyroid glands are also reported, although less frequently [23].

Thyroid dysfunction is the prevalent endocrine irAEs associated with ICIs therapy. Anti-PD-1/anti-PD-L1 carries a higher risk compared to anti-CTLA-4, and their combined administration is associated with the highest risk [14]. Most cases are asymptomatic or mild.

Primary hypothyroidism is most common (mean incidence 2.5-3.8% for anti-CTLA-4, 3.9-8.5% for anti-PD-1/PD-L1 and 10.2-16.4% for combination treatment) and usually occurs over a period of 8-12 weeks after initiation of ICIs [15]. In a minority of cases, especially in patients treated with anti-CTLA-4, central hypothyroidism may develop, mostly together with secondary hypocorticism, which should not be missed and must always be treated before starting levothyroxine therapy.

Thyrotoxicosis is less common (mean incidence 0.2-5.2% for anti-CTLA-4, 0.6-3.7% for anti-PD-1/PD-L1 and 8.0-11.1% for combination treatment) [15]. It is thought to remain unrecognized as it is usually mild and transient, and often followed by hypothyroidism. Thyrotoxicosis has a rapid onset, usually 4-6 weeks after starting ICIs, and lasts approximately 6 weeks [16]. The time to onset of thyrotoxicosis is shorter in the case of combination treatment with ICIs. Rare cases of persistent hyperthyroidism in Graves' disease as well as thyroid-associated orbitopathy (TAO) have also been described [17, 18].

In this article, we present a case series with different types of thyroid dysfunction associated with the administration of various ICIs.

## CLINICAL CASE 1

A 50-year-old man was diagnosed with squamous cell carcinoma of the oropharynx (cT2pN3bcM1). After surgery, chemotherapy and radiotherapy, he had PET/CT evidence of progression, which led to the initiation of immunotherapy with Nivolumab (anti-PD-1). Two months later on anti-PD-1 treatment, severe overt hypothyroidism was detected with negative autoantibodies (Table 1). Ultrasound revealed diffuse changes in the thyroid parenchyma, as in autoimmune thyroid disease (ATD), despite negative autoantibody testing (Fig. 1). Levothyroxine therapy was initiated at a dose of 50 mcg. Currently, discontinuation of immunotherapy is not suggested. Follow-up and adjustment of the levothyroxine dose is recommended.

**Table 1.** Laboratory analysis

| | Two months after anti-PD-1 initiation | Reference range |
|---|---|---|
| TSH (μIU/ml) | **70.16** | 0.2-4.2 |
| FT4 (pmol/l) | **3.7** | 10.3-24 |
| FT3 (pmol/l) | **1.33** | 3.1-6.8 |
| Anti-TPO (U/ml) | 9.49 | <34 |
| Anti-TG (IU/ml) | 16.09 | <95 |

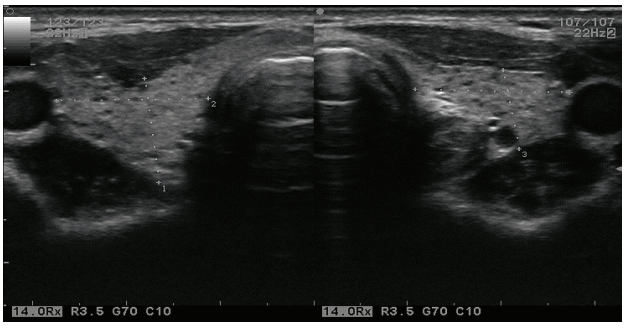


**Fig. 1.** Heterogeneous structure of the thyroid gland with small focal hypoechogenicity, as in autoimmune thyroid disease

## CLINICAL CASE 2

A 48-year-old man was diagnosed with poorly differentiated adenocarcinoma of the lung (pT1cN3M1). Combination targeted and immunotherapy with

Bevacizumab/Atezolizumab (anti-PD-L1) was initiated 13 months later. After four months of treatment, complaints of fatigue and significant weight reduction appeared, with no evidence of cancer progression. Suppressed TSH 0.005 mIU/ml was found, and thyrostatic treatment with Thiamazole 20 mg/day was started. A month later, a suboptimal response to the therapy was reported (Table 2), necessitating an increase in thyrostatic dose to 30 mg/day in combination with Prednisolone at a dose of 20 mg/daily. Atezolizumab treatment was then discontinued. It is important to note that, as in the previous case, anti-TG and anti-TPO were negative, and TRAb were at the upper limit. Three months after initiation of antithyroid therapy, there was a gradual control of thyrotoxicosis (Table 2). At follow-up, a sustained euthyroid state was recorded after discontinuation of thyrostatic and corticosteroid, allowing resumption of anti-PD-L1 therapy. One year later, with continued combination therapy for the underlying disease, but without antithyroid treatment, the euthyroid state and negative antibodies persisted (Table 2). Thyroid ultrasonography at the onset of thyrotoxicosis showed diffuse changes as in ATD despite negative autoantibodies (Fig. 2a). At follow-up, residual fibrotic changes with discrete hypoechogenicity of the parenchyma were observed (Fig. 2b).

## CLINICAL CASE 3

A 51-year-old man was diagnosed with malignant melanoma in the right deltoid region (pT4aN1Mx). He underwent surgery and adjuvant chemotherapy, but 7 years after diagnosis, PET/CT revealed progression (pT4aN1M1). It was considered to start combination immunotherapy with Nivolumab (anti-PD-1)/ Ipilimumab (anti-CTLA-4). Four months later, due to PET/CT evidence of stable disease, maintenance monotherapy with Nivolumab was switched. After one year of immunotherapy, hypothyroidism was noted with positive autoantibodies in a stable underlying disease (Table 3). Levothyroxine therapy was initiated with gradual dose titration to 200 mcg without discontinuation of immunotherapy. With replacement treatment, euthyroid status was maintained throughout the 9-month follow-up period to date (Table 3).

**Table 2.** Laboratory analysis

| | One month after anti-PD-L1 initiation | Two months follow-up | One year follow-up | Reference range |
|---|---|---|---|---|
| TSH (μIU/ml) | **0.005** | 1.62 | 2.84 | 0.2-4.2 |
| FT4 (pmol/l) | **53.15** | 12.72 | 18.39 | 10.3-24 |
| FT3 (pmol/l) | **10.3** | **2.28** | 3.88 | 3.1-6.8 |
| Anti-TPO (U/ml) | 10.52 | 15.96 | 15.96 | <34 |
| Anti-TG (IU/ml) | 30.86 | 18.39 | 18.39 | <95 |
| TRAb (IU/l) | **1.88** | 2.33 | 1.66 | <1.75 |

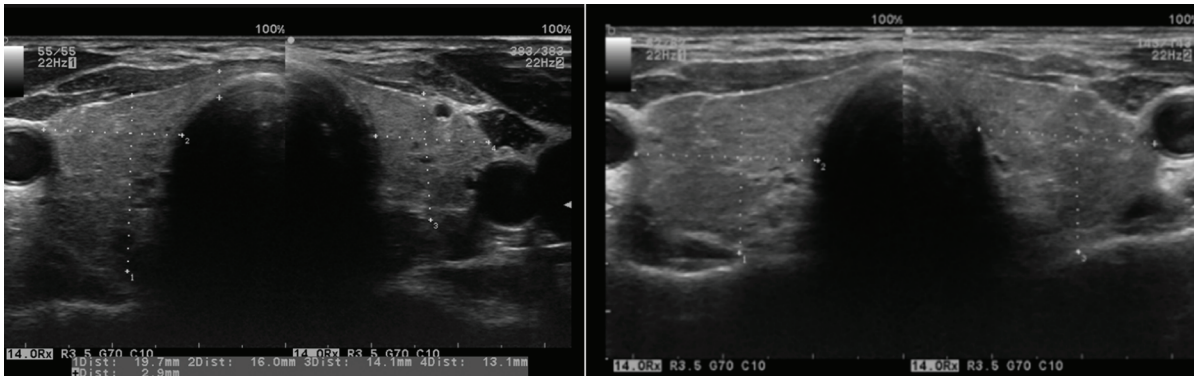


**Fig. 2. A.** Thyroid gland of the upper border size, with small- and medium-sized hypoechogenicity as in autoimmune thyroid disease. **B.** Thyroid ultrasonography in the same patient after 1 year – discrete inhomogeneity persists, with increasing fibrotic changes

**Table 3.** Laboratory analysis

| | One year after anti-PD-1/CLTA-4 initiation | Nine months follow-up | Reference range |
|---|---|---|---|
| TSH (μIU/ml) | **46.07** | 1.25 | 0.2-4.2 |
| FT4 (pmol/l) | **1.54** | 14.46 | 10.3-24 |
| FT3 (pmol/l) | **< 0.6** | 3.91 | 3.1-6.8 |
| Anti-TPO (U/ml) | **439.3** | - | <34 |

## CLINICAL CASE 4

An 88-year-old man was diagnosed with malignant melanoma of the right foot (pT3bN1Mx). Immunotherapy with Pembrolizumab (anti-PD-1) was initiated, and PET/CT data of progression were reported 9 months later (pT3bN1M1). Complaints of fatigue, polydipsia, polyuria and nausea appeared. Diabetes mellitus was diagnosed with depleted insulin reserve (Table 4), necessitating insulin therapy. Subclinical hypothyroidism was also recorded during the same period, but due to the patient's advanced age, it was considered to remain under surveillance. Subsequently, hypothyroidism worsened (Table 4) and Levothyroxine therapy was started with gradual titration to 75 mcg. No abnormalities were detected in the pituitary-adrenal axis.

Table 4. Laboratory analysis

| | 9 months after anti-PD-1 initiation | One month follow-up | Reference range |
|---|---|---|---|
| TSH (μIU/ml) | **5.87** | **18.88** | 0.2-4.2 |
| FT4 (pmol/l) | - | 11.4 | 10.3-24 |
| C-peptide (ng/ml) | **0.18** | - | 3.1-6.8 |

## CLINICAL CASE 5

A 45-year-old man with known type 2 diabetes mellitus on treatment with metformin, Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) and GLP-1RA was diagnosed with low-grade non-small cell lung cancer (T2N3M0). After 6 courses of chemotherapy and radiotherapy, immunotherapy with Ipilimumab (anti-CTLA-4) and Nivolumab (anti-PD-L1) was started. After the 5th course of immunotherapy, laboratory and imaging evidence of ATD developed (Fig. 3), but with a hormonal constellation of secondary hypothyroidism (Table 5) Levothyroxine treatment was started with gradual dose titration to 100 mcg. After the 6th course of immunotherapy, complaints of general fatigue and dizziness appeared. Further laboratory investigations revealed hypoglycemia (blood glucose level 2.1 mmol/l), uncompensated hypothyroidism and secondary hypocorticism without evidence of hypogonadism and hyposomatotropism (Table 5). Magnetic resonance imaging showed mild overall inhomogeneity of the pituitary, corresponding to hypophysitis, explaining the secondary (central) hypothyroidism and hypocorticism (Fig. 4). We initiated treatment with Methylprednisolone i.v. at a dose of 20 mg/day until stabilization, after which we switched

**Table 5.** Laboratory analysis

| | After 5th course of anti-PD-L1/CTLA-4 treatment | After 6th course of anti-PD-L1/CTLA-4 treatment | Reference range |
|---|---|---|---|
| TSH (μIU/ml) | 0.818 | **61.05** | 0.2-4.2 |
| FT4 (pmol/l) | **6.7** | **5.69** | 10.3-24 |
| Anti-TPO (U/ml) | **68.97** | - | <34 |
| ACTH (pg/ml) | - | **<5** | 0-46 |
| Cortisol 08 a.m. (nmol/l) | - | **22.22** | 145.4-619.4 |
| LH (m[IU]/ml) | - | **8.38** | 0.8-7.6 |
| FSH (m[IU]/ml) | - | 6.48 | 0.7-11.1 |
| Testosterone (nmol/l) | - | 12.5 | 4.47-26.59 |
| GH (ng/ml) | - | 0.27 | 0.05-3 |
| IGF-1 (ng/ml) | - | 154 | 48-209 |

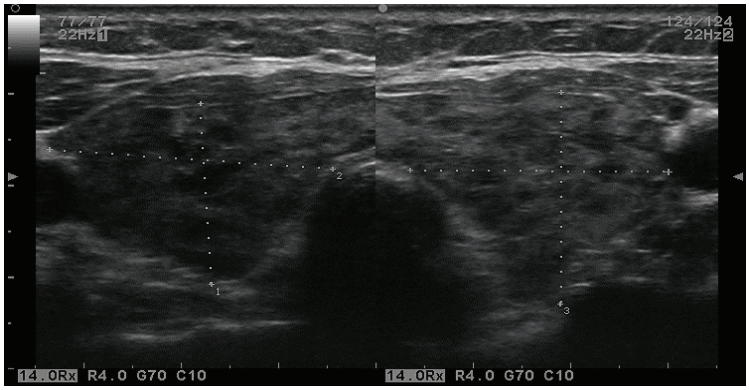


**Fig. 3.** Typical ultrasound image of autoimmune thyroid disease with marked diffuse hypoechogenicity of the parenchyma and fibrotic changes

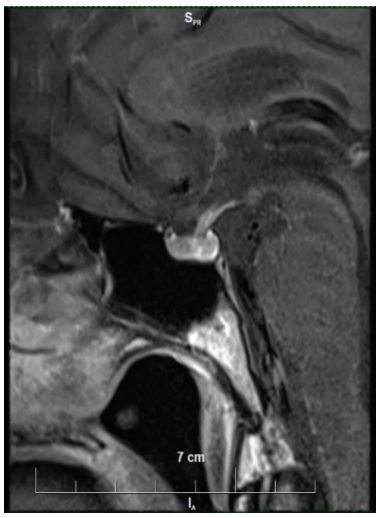


**Fig. 4.** Magnetic resonance imaging of the pituitary gland with evidence of hypophysitis

to oral Hydrocortisone with gradual dose reduction to 20 mg/day. After secondary adrenal insufficiency was coped with, the dose of Levothyroxine was increased to 150 mcg. During hospitalization, laboratory evidence of immune-mediated hepatitis was also noted, necessitating discontinuation of antidiabetic therapy and temporary acceptance of a long-acting insulin analogue until normalization of liver function.

## DISCUSSION

Thyroid dysfunction has emerged as the most common endocrinopathy associated with ICIs therapy. The clinical cases presented show that thyroid impairment can result in hypothyroidism or thyrotoxicosis, isolated (cases 1, 2 and 3) or combined with another endocrinopathy (cases 4 and 5). Hypothyroidism comprises the majority of cases, which may be accompanied by the presence of positive antibodies (case 3), and is then more severe, requiring a higher dose of replacement therapy. However, antibody-negative cases are also common. Immune-mediated destruction of the thyroid tissue is the most common underlying mechanism for ICI-induced hypothyroidism. Typically, the clinical presentation begins with a transient thyrotoxicosis followed by irreversible hypothyroidism. Associated immune-related damage to the gastrointestinal tract may impair the enterohepatic circulation of thyroid hormones and reduce thyroid-binding globulin synthesis, potentially accelerating the development of hypothyroidism. Hypothyroidism may be secondary to pituitary toxicity or combined primary and secondary (case 5 – ultrasonography changes and antibody positivity as in primary and hormonal constellation with low TSH and FT4 as in secondary).

Because of the high incidence of immune-related thyroid dysfunction, international consensus recommends screening for TSH and FT4 before initiating ICIs [2, 19]. In cases of overt thyroid dysfunction at baseline or a history of severe thyroid disease, initiation of ICIs should be discussed in a multidisciplinary team that includes an endocrinologist [2, 19].

During treatment with ICIs, it is recommended to monitor TSH and FT4 before each cycle of ICIs for the first 6 months, after which the interval can be increased to every 2-3 months for 6 months, then to every 6 months thereafter [2, 19]. In the case of hypothyroidism, anti-TPO testing is appropriate as it indicates an autoimmune etiology. Most guidelines do not recommend anti-TG testing [19]. In the case of thyrotoxicosis, TRAb testing is recommended. Given the cases of baseline disease without elevated TRAb levels described in the literature [17], the differential diagnosis of severe or persistent thyrotoxicosis requires further evaluation of FT3, thyroid scintigraphy and ultrasound [2].

There is conflicting data on the gender-related predisposition to develop immune-mediated thyroid dysfunction with ICIs treatment. The presented case series includes only men. Nevertheless, most studies suggest an association with female sex, although their cohorts were over 60% male [20, 21, 22].

The occurrence of adverse immune-mediated thyroid-related side effects does not usually require interruption or discontinuation of ICIs therapy, except in cases of severe thyrotoxicosis and/or TAO [4, 19]. Patients with marked hypothyroidism should be started on Levothyroxine therapy. Recovery of thyroid function without replacement is unlikely, although it is possible in cases of subclinical hypothyroidism [14]. On the other hand, in patients already being treated for hypothyroidism, Levothyroxine dose adjustment may be necessary after initiation of ICI therapy [19].

In patients with destructive thyroiditis, the initial thyrotoxic phase is usually transient and is followed by hypothyroidism. Close follow-up is recommended. In symptomatic patients, β-blockers may be considered. However, if thyrotoxic symptoms are severe, a short course of glucocorticoids may be used. Antithyroid drugs should be initiated in thyrotoxicosis caused by Graves' disease. In thyrotoxic storm, combined treatment with β-blockers, thyrostatics, and glucocorticoids may be necessary [2, 19].

## CONCLUSION

ICIs are a revolutionary class of drugs that can make an enormous contribution to the treatment of

various types of cancers by harnessing the immune system to fight malignant cells. Their successful use as antitumor agents is associated with a wide range of irAEs, including endocrinopathies. Among these, thyroid disorders are one of the most common. Identifying these abnormalities requires vigilance and regular monitoring of thyroid function. Early detection requires both a thorough clinical examination and laboratory evaluation. The management of thyroid-related irAEs requires an individualized approach that considers the severity of the abnormality, the clinical condition of the patient and the stage of the malignancy [23].

***Conflict of interest statement:*** *The authors declare no conflicts of interest related to this work.*

***Funding:*** *The authors did not receive any financial support from any organization for this research work.*

***Ethical statement:*** *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.*

***Consent for publication:*** *Consent form for publication was signed by the patients and collected.*

## REFERENCES

1. Basudan AM. The Role of Immune Checkpoint Inhibitors in Cancer Therapy. Clin Pract. 2022; 13(1): 22-40.
2. Husebye ES, Castinetti F, Criseno S, et al. Endocrine-related adverse conditions in patients receiving immune checkpoint inhibition: an ESE clinical practice guideline. Eur J Endocrinol. 2022; 187(6): G1-G21.
3. Castinetti F, Borson-Chazot F. Introduction to expert opinion on endocrine complications of new anticancer therapies. Ann Endocrinol (Paris) 2018; 79:535-8.
4. Byun DJ, Wolchok JD, Rosenberg LM, et al. Cancer immunotherapy – immune checkpoint blockade and associated endo crinopathies. Nat Rev Endocrinol 2017; 13:195–207.
5. Lugowska I, Teterycz P, Rutkowski P. Immunotherapy of melanoma. Contemp Oncol (Pozn) 2018; 22:61–7.
6. González-Rodríguez E, Rodríguez-Abreu D, Spanish Group for Cancer Immuno-Biotherapy (GETICA). Immune checkpoint inhibitors: review and management of endocrine adverse events. Oncologist 2016; 21:804–16.
7. Ibrahim R, Saleh K, Chahine C et al. LAG-3 Inhibitors: Novel Immune Checkpoint Inhibitors Changing the Landscape of Immunotherapy. Biomedicines. 2023; 11(7):1878.
8. Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncology. 2018; 4: 1721–1728.
9. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol 2018; 4:173–82.
10. Elantably D, Al Armashi AR, Hammad F, et al. Immune checkpoint inhibitor-related endocrinopathies: A nationwide population-based study. JCO 2022, 40: 2653-2653.
11. de Filette J, Andreescu CE, Cools F, et al. A systematic review and meta-analysis of endocrine-related adverse events associated with immune checkpoint inhibitors. Horm Metab Res 2019; 51:145–56.
12. Bai X, Chen X, Wu X, et al. Immune checkpoint inhibitor-associated thyroid dysfunction: a disproportionality analysis using the WHO adverse drug reaction database, VigiBase. European Journal of Endocrinology. 2020; 182:1–9.
13. Stelmachowska-Banas M, Czajka-Oraniec I. Management of endocrine immune-related adverse events of immune checkpoint inhibitors: an updated review. Endocrine Connections. 2020; 9: R207–R228.
14. Iyer PC, Cabanillas ME, Waguespack SG et al. Immune-related thyroiditis with immune checkpoint inhibitors. Thyroid. 2018; 28: 1243–1251
15. Brancatella A, Viola N, Brogioni S, et al. Graves' disease induced by immune checkpoint inhibitors: a case report and review of the literature. European Thyroid Journal. 2019; 8:192–195.
16. Sagiv O, Kandl TJ, Thakar SD, et al. Extraocular muscle enlargement and thyroid eye disease-like orbital inflammation associated with immune checkpoint inhibitor therapy in cancer patients. Ophthalmic Plastic and Reconstructive Surgery. 2019; 35: 50–52.
17. Yuen K, Samson S, Bancos I, et al. American Association of Clinical Endocrinology Disease State Clinical Review: Evaluation and Management of Immune Checkpoint Inhibitor-Mediated Endocrinopathies: A Practical Case-Based Clinical Approach. Endocrine Practice. 2022; 28(7): 719-731.
18. Li X, Song Z, Chen Y, et al. Immune checkpoint inhibitors-related thyroid dysfunction: influencing factor analysis, prediction model development, and management strategy proposal. Cancer Immunol Immunother 2025, 74 (2).
19. Lu D, Yao J, Yuan G, et al. Immune Checkpoint Inhibitor-related New-onset Thyroid Dysfunction: A Retrospective Analysis Using the US FDA Adverse Event Reporting System. Oncologist. 2022;27(2):e126-e132.
20. Kennedy OJ, Ali N, Lee R, et al. Thyroid dysfunction after immune checkpoint inhibitors in a single-centre UK pan-cancer cohort: A retrospective study. European Journal of Cancer, 2024; 202, 113949.
21. Karaviti D, Kani ER, Karaviti E, et al. Thyroid disorders induced by immune checkpoint inhibitors. Endocrine. 2024; 85(1):67-79.