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REVIEW

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Immunotherapy-induced thyroid dysfunction: an updated review

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Abstract

Immunotherapy medicines (immune checkpoint inhibitors, ICIs) that work directly on the immune system have shown vastly increased survival for people with cancer in phases 2 and 3 clinical studies during the past few years. Nevertheless, ICI treatment (irAEs) may trigger immune-related adverse effects. An underactive thyroid is among the most frequent endocrine irAE, affecting about 40% of individuals who received ICIs. Our review aims to collect and organize the most recent data on immunotherapy-induced thyroid dysfunction in cancer patients, including its prevalence, diagnostic criteria, and treatment options and to summarize those findings in a comprehensive review article. The incidence of irAEs varies depending on the type of cancer and the treatment regimen. Thyroid ultrasound, radioactive uptake scan, and PET CT scan can aid in diagnosing thyroid dysfunction. Thyroid dysfunction treatment necessitates collaboration between specialists in oncology, endocrinology, and primary care in a multidisciplinary team discussion. The prognosis of patients who suffered from thyroid dysfunction while on ICIs treatment is reasonably good. Suboptimal baseline thyroid function was linked with decreased overall survival (OS) among ICI-treated patients, but initiating replacement hormonal therapy after ICI initiation was associated with enhanced OS. More research work is required to identify these links and mechanisms of action.

Keywords Immunotherapy, Thyroid dysfunction, Cancer, Management, Ipilimumab, Nivolumab, PD-1 inhibitors

Introduction

Immune checkpoint inhibitors (ICIs) stimulate (switch on) the immune system to recognize and attack cancer cells. However, these medications have been linked to various autoimmune disorders, such as thyroid dysfunction [1]. Thyroid dysfunction induced by ICIs depends on the type of immunotherapy administered. According to an intriguing 2022 meta-analysis by Muir et al., programmed cell death protein 1 (PD-1) inhibitors (nivolumab and pembrolizumab) caused 3.2% of hyperthyroidism, while combo immunotherapy with ipilimumab caused 8.0% [2]. Combination therapy caused 13.2% more hypothyroidism than PDL-1 inhibitors alone. PD-1 inhibitors alone took 70 days, and combined therapy took 63 days to onset [3].

Haanen et al. (2017) found an incidence of 1–5 to 10% for individuals receiving 3 mg/kg and 10 mg/kg ipilimumab [4]. In a more recent retrospective investigation by Girimonte et al. (2022), 29.6% (53 out of 179) of metastatic cancer patients taking ICIs developed hypothyroidism, with 44 of those instances experiencing transient thyrotoxicosis followed by hypothyroidism [5]. While treating cancer with anti-PD-1 or anti-PD-L1, the risk of thyroid abnormalities is 5–10%, with a higher prevalence in combination therapy patients.

In recent years, research has aimed to understand better the endocrine toxicities arising from ICI therapy and the side effects patients can expect. These events rarely exceed 20% severity [4]. Several studies on immunotherapy-induced endocrinopathy have found these results. Lecoq et al. (2022) thoroughly reviewed

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the relevant literature and analyzed their clinical observations from treating 80 patients. Their findings showed that thyroiditis and hypothyroidism were the most common endocrinopathies reported with ICI treatment, particularly when using anti-PD-1 medication. Patients taking anti-CTLA-4 and anti-PD-1 medicines were at a higher risk of developing endocrinopathies [6].

Similarly, Storm et al. (2022) investigated the real-world safety profile of ICIs in younger and older participants between September 2016 and September 2019. The study enrolled 217 patients who received ICIs and found no statistically significant difference in the cumulative incidence of immunotherapy-related toxicities between the two age groups, although thyroid gland problems occurred in 20.3% of patients. These results suggest that older adults are less likely to experience immune-related adverse medication responses from ICIs [7].

In another study, among 24 cancer patients receiving ICI, Patrizio et al. (2022) observed that using these medications raised the incidence of thyroid disease, including subclinical illness, with the latter being more common in women than in males [8]. Degtiareva et al. (2022) also found that immune-related toxicity was more common with combination ICIs than with monotherapy (70.6% vs. 23.6%) among Russian patients in a retrospective study [9]. Additionally, Ochenduszko et al. (2022) found that among 36 patients with advanced melanoma receiving either nivolumab or pembrolizumab monotherapy, 5 of them (13.9%) developed hypothyroidism [10].

Mechanism and risk factors

The exact mechanisms underlying immunotherapy-induced thyroid dysfunction remain unclear. ICIs are typically harmless, but some evidence suggests they may provoke an autoimmune reaction in the thyroid gland by disturbing the delicate balance of immune cells or by producing cross-reactive cancer cell antigens. ICIs may also change thyroid-related gene expression, causing hypothyroidism [11]. Several researchers have investigated possible risk factors for endocrinopathies in patients receiving ICIs to better understand this phenomenon's origins. In 2022, Amara et al. examined the causes of immune-related thyroid dysfunction during ICIs treatment [12]. The study found that among cancer patients taking PD-1/PD-L1 inhibitors, a history of smoking, hypertension, or opioid use was all associated with adverse events involving the thyroid [12]. Another study found that immunotherapy-related thyroid dysfunction may be linked to a hereditary predisposition to autoimmune thyroid disease [13].

Screening and monitoring for thyroid dysfunction

It is essential to regularly check for thyroid dysfunction in patients receiving ICIs, as early detection and treatment can prevent more serious consequences. While there are various screening recommendations, most suggest baseline thyroid function testing and regular monitoring of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) levels both before and after ICI therapy [14]. The American Thyroid Association (ATA) recommends monitoring thyroid dysfunction symptoms/signs and checking TSH and FT4 levels at least every 4 to 8 weeks while on ICI treatment therapy and every 3 to 6 months afterward [3].

Monitoring thyroglobulin (Tg) and anti-TgAb can assist in diagnosing thyroid autoimmune reactions and track a patient's response to thyroid dysfunction treatment [15]. However, the frequency of checks should be determined by the patient's status and risk factors. It is important to note that patients receiving ICIs may develop thyroid dysfunction at any point during or after treatment. Thus, thorough monitoring is crucial throughout the treatment [16]. The most recent recommendations from the European Society for Medical Oncology (ESMO) suggest measuring TSH and FT4 levels periodically before starting immunotherapy and before each cycle at least monthly intervals [17]. Recent studies have also examined the clinical trajectories and risk factors for enduring immune-related toxicities in cancer patients receiving anti-PD-1, anti-PD-L1, and/or combination with anti-CTLA-4 therapy. Chieng et al. (2022) studied 66 patients and followed them for a median of 15.7 months [18]. The study found that the average duration of thyroid dysfunction prior to diagnosis was 1.8 months. The study also found that persistent thyroid disorder was linked to positive thyroperoxidase antibodies (TPOAb) and/or thyroglobulin antibodies (TgAb) status at the onset. Interestingly, the study also found that patients who developed endocrinopathies had a longer median survival [18]. This suggests that early screening is crucial given the large median time to onset of endocrinopathies, and that the screening and follow-up strategy for endocrine irAEs should be tailored to each endocrinopathy's clinical history [18].

Clinical manifestations

Immunotherapy-induced thyroid dysfunction can cause fatigue, weight gain, heart rate changes, and thyroid hormone abnormalities [19]. Hence, ICI patients must be monitored regularly. Latif et al. (2022) examined thyroid dysfunction in advanced cancer patients treated with ICIs at two United Arab Emirates (UAE) tertiary cancer centers from November 2015 to January 2019 [20]. Of the

43 people who received ICI, 44% or more had some form of thyroid malfunction, either hypothyroidism (57%), hyperthyroidism, or subclinical hypothyroidism (21%). ICI caused most thyroid dysfunction after 6 weeks [20].

Role of thyroid ultrasound to detect and ICIs-induced thyroid dysfunction

Thyroid ultrasonography can detect thyroid gland changes in immunotherapy patients on immune checkpoint inhibitors (ICIs). Thyroid nodules, a larger or smaller gland, may suggest hyperthyroidism or hypothyroidism. Ultrasound can detect autoimmune disorders such as diffuse or localized thyroiditis [21]. Furthermore, thyroid ultrasonography can also be utilized to monitor the effectiveness of treatment in patients with thyroid dysfunction who are receiving ICIs. For instance, ultrasonography can be used to evaluate the effectiveness of antithyroid medication in treating hyperthyroidism by determining whether the size and shape of the thyroid gland have returned to normal [21]. However, thyroid ultrasound results should be reviewed with other diagnostic methods, such as blood tests and clinical examinations, and analyzed by a skilled physician for proper and accurate diagnosis. It is crucial to remember that thyroid ultrasound is an auxiliary tool.

Role of thyroid radioactive uptake scan with ICIs

A radioactive thyroid uptake scan can play a crucial role in assessing patients who have developed hyperthyroidism or hypothyroidism in immunotherapy. This diagnostic method can pinpoint thyroid dysfunction's etiology, such as a toxic nodule or Graves' disease. The scan can also reveal whether the thyroid is hyperactive or underactive. The test can also detect autoimmune responses by measuring thyroid gland radioactivity uptake. For example, reduced radioactive material uptake in patients with autoimmune thyroiditis may indicate autoimmune alterations in the thyroid gland [22].

Role of inflammatory markers and biomarker on thyroid disease-related ICIs

Inflammatory indicators such as cytokines, TNF-alpha, IL-6, and IFN-gamma, all of which can damage tissue through the recruitment, activation, and invasion of inflammatory cells into the thyroid gland, have been linked recently to thyroid dysfunction [23]. In terms of biomarkers, a recent trial conducted in 2022 by Amara et al. found that 9 out of 20 patients with lung cancer who received immunotherapy developed irAEs, including thyroid dysfunction [12]. The study discovered that the CD4/CD8 ratio consistently dropped by 30–40% just before the onset of ICI-induced toxicities. The study suggests that biomarkers such as the serum CD4/CD8 ratio may be crucial for early management in cases of irAEs [12]. These findings highlight the importance of monitoring inflammatory markers and biomarkers in managing and monitoring patients with thyroid dysfunction related to ICIs.

Role of PET CT scan

Tatar et al. studied [18F]-fluoro-2-deoxy-D-glucose (F-FDG) PET/CT for detecting immune-related adverse events (irAEs) in immune checkpoint inhibitor patients in 2022 (ICIs). The study enrolled 46 patients with diverse forms of advanced cancer, and their treatment responses were monitored using PET/CT scanning [24]. The study found that among the most frequently observed adverse effects, colitis (28.1%) stood out, while among the least often observed adverse effects, thyroiditis and myositis/arthritis (13.0%) affected only about six individuals. The study also found that the appearance of irAEs on PET/CT occurred a median of 4.3 months after the start of immunotherapy. The study's results suggest that F-FDG PET/CT is an important aspect of cancer immunotherapy, as it can detect serious irAEs during diagnosis and follow-up. irAEs were detected on PET/CT scans in more than 50% of the trial patients [24]. The study concludes that implementing F-FDG PET/CT scans in the management and follow-up of patients receiving ICIs is essential for the early detection and management of irAEs [24].

Treatment

Treating thyroid dysfunction caused by immunotherapy requires a multidisciplinary approach [21]. Patients with thyroid dysfunction should delay immunotherapy until their symptoms improve, according to the latest ESMO guidelines. Antithyroid drugs, beta-blockers, and even radioactive iodine can be used in protocols to treat hyperthyroidism. Levothyroxine is usually used to cure hypothyroidism. Subclinical hypothyroidism does not preclude thyroid hormone replacement therapy for patients with fatigue and weight gain symptoms. Propranolol and atenolol are also used in the treatment of hyperthyroidism. Such medicines provide long-term advantages in controlling symptoms and improving tolerability to ICIs [4].

An American Association of Clinical Endocrinology Disease review article provides healthcare professionals with a helpful method for managing patients who develop endocrinopathies due to immunotherapy. These agents frequently affect the thyroid and pituitary glands, and the authors conduct a literature search and review methods for their diagnosis and treatment. The researchers emphasize the need for all healthcare professionals caring for these cancer patients to have a high index of clinical suspicion and stress the

Table 1 Immunotherapy-thyroid disease case reports during 2022–2023

Study name	Age	Sex	Cancer type	Drug name	Adverse events	Lab findings	Recommendation	Others
Marinides et al. (2022) [30]	76	Not mentioned	Not mentioned	Teprotumumab	Graves' disease	MRI brain showed CAA with subacute bleeds, negative CSF studies, negative paraneoplastic panel	Contraindication of IGF-1R inhibitors in the presence of underlying cerebrovascular disease	Rapid cognitive decline, response to immune-modulatory treatments
Vilaca et al. (2022) [31]	62	Male	Metastatic NSCLC	Immunotherapy	Graves' disease	Current smoker, EGFR, and ALK wild types	Caution when interpreting results due to single patient	Long-lasting response, no immune-related adverse events
Duminuco et al. (2022) [32]	N/A	N/A	N/A	Nivolumab	Thyroid disorder	N/A	Temporarily ineligible for transplantation	Adverse effects involving multiple organs
Najjar & Yu (2022) [33]	N/A	N/A	Various	ICIs (including nivolumab and ipilimumab)	Immune-mediated endocrinopathies	Varies depending on the type of endocrinopathy (thyroid and pituitary gland involvement common)	A high index of clinical suspicion and a multidisciplinary team approach with endocrinologists	Case-based clinical review
Kataoka et al. (2022) [34]	72	Female	Non-small cell lung cancer (NSCLC)	Nivolumab and ipilimumab	Thyroid storm	Positive for antithyroid antibodies, prominent hyperthyroidism with gastrointestinal symptoms and signs of heart failure	Evaluate thyroid function and symptoms of suspected thyroid storm within 3 weeks from the initiation of therapy when combination therapy is administered in patients with NSCLC positive for antithyroid antibodies	The patient had no history of thyroid disease
De Filette et al. (2022) [35]	63	Female	Non-small cell lung carcinoma	Durvalumab	Thyrotoxicosis followed by hypothyroidism	HLA-DR4 and DR13	Proactive monitoring of thyroid hormone levels	Identification of biomarkers for better patient selection and understanding of mechanisms
Bao & Jiang (2022) [36]	59	Female	Non-small cell lung cancer	Pembrolizumab	Immune-induced autoimmune thyroiditis	Continuously monitor thyroid function and provide thyroxine replacement therapy	Carefully monitor patients with underlying thyroiditis before deciding on immunotherapy treatment	It discusses features and general mechanisms of immune-related endocrine toxicity
Bao & Jiang (2022) (the same patient) [36]	59	Female	Non-small cell lung cancer	Pembrolizumab	Immune-induced autoimmune diabetes, diabetic ketoacidosis	Discontinue immunotherapy, diagnosed with insulin-dependent diabetes mellitus	Carefully monitor patients for signs of autoimmune diabetes	
Chen et al. (2022) [37], tw cases	65/52	Male/female	Relapsed refractory B-cell lymphoma	CAR-T-cell therapy	Hashimoto's thyroiditis	N/A	Further investigation of the mechanisms of CAR-T therapy on the thyroid tissue	A rare adverse effect, complete remission achieved at 1 and 3 months

Table 1 (continued)

Study name	Age	Sex	Cancer type	Drug name	Adverse events	Lab findings	Recommendation	Others
Braga et al. (2022), case 1 [38]	44	Female	Metastatic melanoma	Nivolumab	Acute thyroiditis, hypothyroidism	TSH: 310 µUI/mL, FT4, and FT3 under the detection limit, positive for anti-TG 471 UI/mL and nti-TPO 172 UI/mL	Continue nivolumab under continuous levothyroxine supplementation	Acute thyroiditis with suppression of thyroid hormone synthesis
Braga et al. (2022), case 2 [38]	72	Female	Lung adenocarcinoma	Pembrolizumab	Diabetic ketoacidosis, autoimmune thyroiditis, hypothyroidism	Hyperglycemia (> 658 mg/dL), ketoacidosis (pH < 7.0, HCO3 — 5.2 mmol/L), TSH: 11.2 µUI/mL, FT4: 0.569 ng/dL, TT4: 2.97 µg/dL, FT3: 0.666 pg/mL, TT3: 32.77 ng/dL, positive for anti-TPO 319 UI/mL	Admit to the intensive care unit	Life-threatening multi-organic compromise with neurological repercussions

ALK anaplastic lymphoma kinase, *CAA* cerebral amyloid angiopathy, *CSF* cerebrospinal fluid, *CAR-T* chimeric antigen receptor T cell, *EGFR* epidermal growth factor receptor, *FT4* free thyroxine, *HLA-DR4* human leukocyte antigens DR4, *ICIs* immune checkpoint inhibitors, *IGF-1R* the insulin-like growth factor 1 receptor, *MRI* magnetic resonance imaging, *N/A* not available, *NSCLC* non-small cell lung carcinoma, *PD-L1* programmed death-ligand 1, *TSH* thyroid-stimulating hormone

significance of multidisciplinary team discussion in managing patients receiving immunotherapy and exhibiting endocrinopathies [21].

In terms of levothyroxine dosing for patients developing de novo hypothyroidism, particularly hypophysitis, a recent retrospective study in 2022 by Kristan et al. suggests a more conservative approach, such as starting at 0.9–1.2 mcg/kg and monitoring thyroid function tests (TFTs) every 4 weeks and spacing out TFT surveillance to every 12 weeks after [25].

Prognosis

A study conducted by von Itzstein et al. in 2022 found that suboptimal baseline thyroid function was associated with decreased overall survival (OS) among patients treated with ICIs. However, initiating replacement hormonal therapy with levothyroxine after ICI initiation was associated with enhanced OS [26]. The study suggests that existing thyroid problems may predict worse outcomes for individuals undergoing ICI therapy [26]. A 2022 study by Trudu et al. found that patients treated with ICIs for spread lung cancer had a median progression-free survival of 9.5 months [27]. Thyroid dysfunction was the most common immune-related adverse event (30.7%).

Those who had immune-related adverse events (irAEs) had a significantly longer median progression-free survival (PFS) [28]. Improvements in overall survival were seen (*HR* 0.63, 95% *CI* 0.43–0.89) [28]. irAEs in immunotherapy-treated cancer patients may indicate better treatment efficacy and survival [28]. Zheng et al. found that 40% of anti-PD-1-treated hepatocellular carcinoma (HCC) patients in his trial had hypothyroidism; however, this did not impair survival [29]. These relationships and mechanisms need further study.

Case reports

The following table presents immunotherapy-thyroid disease case reports during 2022–2023 (Table 1).

Conclusion

Thyroid dysfunction, which may arise as a side effect of immunotherapy, should be managed cautiously by a multidisciplinary group of oncologists, endocrinologists, and primary care physicians, as highlighted in the article. Treatment options — subject to symptoms — may include using beta-blockers, antithyroid drugs, radioactive iodine, or hormone replacement therapy after proper counseling with patients. The use of thyroid ultrasonography, radioactive uptake scan, inflammatory markers, biomarkers, and PET-CT scans can aid in diagnosing and monitoring thyroid dysfunction. The initiation of replacement hormonal therapy with levothyroxine after ICI initiation was associated with enhanced overall survival. The emergence of irAEs in cancer patients treated with immunotherapy may indicate greater treatment success and overall survival; however, further research is needed to validate these connections and mechanisms of action. Having a high index of clinical suspicion and a multidisciplinary team discussion in managing patients receiving immunotherapy and exhibiting endocrinopathies is essential.

Abbreviations

ALK	Anaplastic lymphoma kinase
anti-CTLA-4	Anti-cytotoxic T-lymphocyte-associated antigen-4
anti-PD-L1	Anti-programmed cell death 1 ligand
CAA	Cerebral amyloid angiopathy
CAR-T	Chimeric antigen receptor T cell
CSF	Cerebrospinal fluid
EGFR	Epidermal growth factor receptor
ESMO	European Society for Medical Oncology
F-FDG	Fluoro-2-deoxy-D-glucose
FT4	Free thyroxine
HLA-DR4	Human leukocyte antigen DR4
ICIs	Immune checkpoint inhibitors
IFN-gamma	Interferon-gamma
IGF-1R	The insulin-like growth factor 1 receptor
IL-6	Interleukin 6
irAEs	Immune-related adverse event
MRI	Magnetic resonance imaging
N/A	Not available
NSCLC	Non-small cell lung carcinoma
OS	Overall survival
PD-1	Anti-programmed cell death 1
PD-L1	Programmed death-ligand 1
PET/CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
TFTs	Thyroid function tests
Tg	Thyroglobulin
TgAb	Anti-thyroglobulin antibodies
TNF-alpha	Tumor necrosis factor-alpha
TSH	Thyroid-stimulating hormone

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