

Review Article

Endocrine toxicity of cancer immunotherapy

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ABSTRACT

Immune checkpoint inhibitors (ICPIs) based on the efficacious anti-tumour immune response become an integral part of a number of cancer therapies. However, their widespread use has been linked to an increase in adverse events affecting almost every organ system. Common ICPIs include cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitors, programmed death 1 (PD-1) inhibitors, and PD ligand 1 inhibitors. Among the ICPIs induced immune-related adverse events, endocrine events are particularly common. Thyroid gland is the most common endocrine organ affected by ICPIs, followed by the pituitary gland. Hypophysitis is specifically linked to anti-CTLA-4 therapy, while thyroid dysfunction is associated with anti-PD-1 therapy. Rare endocrine adverse effects such as diabetes mellitus and primary adrenal insufficiency can also occur with ICPI therapy and, if not promptly addressed, may be life-threatening. Combination therapy with anti-CTLA-4 and anti-PD-1 inhibitors results in the highest incidence of endocrinopathies. Although most ICPI-related endocrine dysfunction emerges within 12 weeks of starting the therapy, some may develop months to years later. While some endocrine issues may resolve spontaneously, central adrenal insufficiency and primary hypothyroidism tend to persist. Management of ICPI-induced endocrine dysfunction primarily involves hormone replacement and control of symptoms. This article aims to review the endocrine complications of ICPI therapy and offer guidance on screening and managing patients experiencing endocrine dysfunction in daily clinical practice.

Keywords: Immune checkpoint inhibitors, Endocrine dysfunction, Immune-related endocrine events

INTRODUCTION

Immune checkpoint inhibitors (ICPIs) based on the efficacious anti-tumor immune response become an integral part of a number of cancer therapies. The use of ICPIs has been linked to an increase in adverse events affecting almost every organ system.^[1] Common ICPIs include cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitors such as ipilimumab and tremelimumab), programmed death 1 (PD-1) inhibitors such as nivolumab, cemiplimab, and pembrolizumab, and programmed death ligand 1 (PD-L1) inhibitors such as avelumab, atezolizumab, and durvalumab. CTLA-4 inhibits the proliferation and activation of T-cells by competing with CD28 for binding to CD80 and CD86.^[2,3] PD-1, present on immune cells, binds with its ligand PD-L1, presents on tumor cells macrophages, and induces immune tolerance.^[4,5] Activation of PD1-PDL1 inhibits the activation of T-cells, promotes apoptosis of tumor-infiltrating lymphocytes, reduces inflammatory cytokines, and increases the anti-inflammatory interleukin 10, thus allowing tumor cells to escape immune surveillance.^[5]

Non-specific T-cell activation induced by ICPIs can lead to side effects affecting up to 40–50% of treated patients.^[6-8] Common immune-related adverse events (irAEs) include skin reactions, diarrhea, colitis, and hepatitis. Immune-related endocrine events (free) occurring in 8.1% of all

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cases are among the most common irAEs.^[9-11] Thyroid gland is the most commonly affected endocrine organ, followed by pituitary, diabetes mellitus (DM), and primary adrenal insufficiency (PAI).^[12-14] Combination of anti-CTLA-4 and anti-PD-1 therapies results in a higher occurrence of thyroid dysfunction and hypophysitis compared to using either treatment alone patients with irAEs which have better clinical response and better survival.^[15]

It is suggested that immune activation induced by ICPIs destroys nearly all hormone producing cells, although there is a lack of histological evidence to confirm this hypothesis.^[11] This condition often begins with a lazy inflammatory phase that goes unnoticed until significant cell destruction occurs. Thus, unlike non-endocrine toxicities, irAEs are frequently irreversible and do not resolve with glucocorticoid therapy.

THYROID

Thyroid dysfunction is the most prevalent endocrine disorder following ICPI therapy, ranging from overt hypothyroidism to hyperthyroidism. It affects 5% of patients treated with CTLA-4 inhibitors, 10% of patients treated with PD-1 or PD-L1 inhibitor monotherapy, and up to 15–20% on combination therapy.^[11] Dysfunction typically occurs within weeks of ICPI initiation, with a median onset occurring between 18 and 123 days.^[16-19] It initially presents as painless thyroiditis, progressing from a transient hyperthyroid phase to a euthyroid or hypothyroid phase. Furthermore, some patients initially present with subclinical or clinical hypothyroidism. Symptoms are usually mild and non-specific, often identified during regular monitoring, or may manifest with symptoms such as fatigue, depression, weight gain, constipation, and mental status alteration in severe cases.^[20-22] Myxoedema coma, although reported, is rare.^[23] Those presenting in the toxic phase of thyroiditis might exhibit symptoms such as weight loss, palpitations, anxiety, and tremors.^[20-22] However, thyroid storm is rare.^[24,25] Some patients have elevated autoantibodies, such as anti-thyroid peroxidase and anti-thyroglobulin.^[19,26] High levels of these antibodies before treatment seem to be associated with ICPI-induced thyroid dysfunction.^[27] Risk factors of ICPI-induced thyroid dysfunction include high baseline body mass index, baseline thyroid-stimulating hormone (TSH) levels, and prior use of tyrosine kinase inhibitors.^[28] ICPI-induced Graves' disease is much less common; however, it should be differentiated from the thyrotoxic phase of thyroiditis by measuring the TSH receptor antibody titer or an uptake scan. Also, the presence of Thyroid eye disease favors Graves' disease. Graves' disease is managed by anti-thyroid drugs.^[29,30]

TSH level is the most sensitive and preferred test for diagnosing thyroid dysfunction in patients treated with ICPI. Primary hypothyroidism is indicated by TSH elevation with low free thyroxine (FT4) whereas central hypothyroidism

secondary to pituitary disorder is diagnosed by low FT4 along with low normal to suppressed TSH. In case of thyrotoxicosis, low TSH is seen with elevated FT4 and triiodothyronine (T3). Thyroid function should be evaluated every 4–8 weeks or more frequently if indicated clinically in all patients treated with ICPI.^[31,32] In hypothyroidism, if TSH is elevated above 10 mIU/mL on two separate occasions or mildly elevated along with low FT4 level without going for further investigations thyroid hormone should be replaced. Subclinical hypothyroidism is characterized by elevated TSH below 10 mIU/mL and a normal FT4 level. In such cases, treatment decisions should be personalized according to symptoms, age, and comorbidities.^[33]

Hypothyroidism is treated with levothyroxine, with the dose adjusted based on age comorbidities, with a lower starting dose for advanced age. After initiating treatment, TSH levels should be checked 6–8 weeks later. For most patients with primary hypothyroidism, the dose of levothyroxine should be adjusted to achieve a normal TSH level. However, in central hypothyroidism, monitoring of FT4 is recommended instead of TSH, and cortisol levels should be checked and replaced if found low before initiating thyroid hormone to prevent adrenal crisis precipitation. Hyperthyroidism due to thyroiditis is managed symptomatically by beta-blockers and steroids in selected cases with close monitoring for progression to hypothyroidism, while hyperthyroidism secondary to Graves' disease is treated with anti-thyroid drugs such as carbimazole, methimazole, surgery, or radioactive iodine based on clinical presentation and patient's preference.

HYPOPHYSITIS

Hypophysitis, the inflammation of the pituitary gland is often resulting from infections, infiltrations, tumors, or autoimmune processes. ICPI-induced hypophysitis is most frequently triggered by CTLA-4 Inhibitor ipilimumab, with an incidence rate ranging from 1.8% to 17%^[34] followed by anti-PD1/PD-L1 therapy at 0.5–1%.^[35,36] Combination therapy with anti-CTLA-4 and anti-PD-1 increases the risk of hypophysitis compared to using anti-CTLA-4 therapy alone.^[6] No specific risk factors have been identified for ICPI-induced hypophysitis, although some studies suggest potential risk factors such as age, male gender,^[35] anti-pituitary antibodies, and certain human leukocyte antigen (HLA) alleles.^[37] The higher incidence in male may be due to the frequent use of ICPI therapy in melanoma, which is more common in men. Symptoms usually present between 9 and 12 weeks after starting anti-CTLA-4 therapy and around 26 weeks for anti-PD-1/L1 therapy.^[35] Symptoms are often non-specific, including headache and fatigue,^[35,38] while signs from mass effects like visual defects are rare. Other symptoms include dizziness, poor appetite, nausea, weight loss, and decreased libido. The primary consequence of ICPI-induced

hypophysitis is one or more pituitary hormone deficiencies, most commonly being central hypothyroidism, central adrenal insufficiency, and hypogonadotropic hypogonadism. In central hypothyroidism, low or low normal FT4 levels with low or inappropriately normal TSH levels are seen.^[39] This condition is usually transient, and the thyroid axis recovers spontaneously in most of the cases. It is also important to note that non-thyroidal illness syndrome (NTIS) can present with similar biochemical thyroid function test abnormality; however, in NTIS, serum T3 decline is progressive, and T4 and TSH also decrease if the underlying illness does not improve. Central adrenal insufficiency, which is characterized by low cortisol and low adrenocorticotropic hormone (ACTH) levels, presents with hypotension and hyponatremia and sometimes can be life-threatening.^[40] Cosyntropin (ACTH) stimulation test helps to diagnose adrenal insufficiency, although it may not rule out recent-onset central adrenal insufficiency and concurrent corticosteroid therapy. Central adrenal insufficiency is often permanent. Hypogonadotropic hypogonadism is characterized by low or inappropriately normal follicle-stimulating hormone and luteinizing hormone levels in the setting of low serum testosterone and low estradiol levels in men and women, respectively. Hypogonadotropic hypogonadism is usually transient and recovers spontaneously; however, it is difficult to distinguish it from functional hypogonadism secondary to underlying illness. Growth hormone deficiency^[41] and abnormal prolactin levels are rare. The posterior pituitary is usually spared, and diabetes insipidus has rarely been reported in the literature.^[42,43] Magnetic resonance imaging (MRI) often shows an enlargement of the pituitary, which may precede clinical diagnosis and usually resolves within weeks to months.^[35] Mild-to-moderate pituitary enlargement with homogeneous or heterogeneous contrast enhancement with or without stalk thickening is usually seen on imaging.^[44] However, a normal imaging does not rule out hypophysitis.^[45] Treatment includes glucocorticoid replacement for adrenal insufficiency most commonly with hydrocortisone or prednisone with patient education about sick day dosing to prevent a crisis. For central hypothyroidism, glucocorticoids to be given before initiating thyroid hormone to avoid adrenal crisis.^[46] Although monitoring in central hypothyroidism is based on FT4 levels, with a goal of keeping the value in middle half of reference range, TSH can also be monitored because an increase in TSH level after the diagnosis of central hypothyroidism may indicate recovery of the thyrotrophs. Higher doses of glucocorticoid therapy (prednisone 1–2 mg/kg followed by tapering dose) are indicated in patients with severe compressive symptoms such as headache and vision change.^[32,47] Testosterone replacement is considered in men with hypogonadotropic hypogonadism and estrogen therapy in women based on individual risk assessment. Desmopressin is used for diabetes insipidus

if severe dehydration and hypernatremia occur.^[48] Severe dehydration and hypernatremia are classified as grade 4 toxicity, requiring temporary suspension of therapy.^[47,49,50] High-dose glucocorticoids are usually given for severe hyponatremia.

PAI

The development of PAI induced by ICPI (ICPI-PAI) is rare.^[51,52] However, combination therapy with PD-1 and CTLA-4 inhibitors carries a higher risk of PAI compared to monotherapy using PD-1 inhibitors.^[53] Men and older adults are more susceptible to ICPI-PAI. Symptoms in patients with PAI include fatigue, nausea, vomiting, poor appetite, weight loss, nausea, hypotension, or adrenal crisis secondary to mineralocorticoid deficiency.^[51,53,54] Diagnosed is confirmed by low morning cortisol levels along with an elevated ACTH level. Common findings include hyponatremia, metabolic acidosis, hyperkalemia (due to mineralocorticoid deficiency)^[54] with hypoglycemia, and hypercalcemia being less frequent. Plasma renin is usually elevated; however, it should be interpreted correctly, especially if IV fluids are administered, as they can affect renin and aldosterone levels.^[20] Patients with PAI should be initiated on glucocorticoid replacement. The dosage and method of administration (oral/parenteral) should be determined based on the clinical status of the patient. In acute phases, treatment is started with an initial bolus parenteral dose of 100 mg of hydrocortisone, followed by 50 mg every 6 hours, and then gradually tapered as the patient stabilizes. Long-term treatment involves lifelong glucocorticoid replacement therapy, typically 15–25 mg of hydrocortisone in divided doses or 5 mg prednisolone once daily. Mineralocorticoid replacement is also needed to prevent hypotension and hyperkalemia, with an initial fludrocortisone dose is 50–100 ug daily orally, adjusted based on clinical response and electrolytes.^[55] ICPI-PAI should be differentiated from adrenal insufficiency due to adrenal metastasis or adrenal hemorrhage by adrenal imaging. ICPI-induced adrenalitis typically shows bilaterally enlarged adrenals with smooth borders in contrast to metastasis, which presents with a nodular appearance with a distorted adrenal margin.^[21]

DIABETES

DM has been observed in 0.2–1.4% of patients receiving ICPI therapy.^[56,57] Studies indicate that ICPI-induced DM occurs in approximately 71% of individuals treated with anti-PD-L1 or anti-PD-1 monotherapy, 15% with combination therapy involving PD-1/PD-L1 and CTLA-4 blockade, and 3% with anti-CTLA-4 monotherapy.^[11,57] ICPI-DM arises from autoimmune destruction of pancreatic b-cells, which express PD-L1.^[11,58] Patients with ICPI-DM who tested positive for islet autoantibodies typically develop diabetes shortly after beginning therapy in contrast to those without

these autoantibodies.^[58] In addition, HLA DR4 has been strongly associated with the development of ICPI-DM.^[59] Pancreatic inflammation induced by ICPI therapy can also lead to exocrine. The median age at diagnosis is 63 years. The onset of diabetes has been observed after a single dose or up to 17 doses and within a time frame ranging from 1 week to 12 months.^[60-63]

ICPI-related DM is marked by acute onset of hyperglycemia, rapid progression to endogenous insulin deficiency, and a high risk of developing diabetic ketoacidosis (DKA) if not detected and treated with insulin. DKA symptoms include polyuria, polydipsia, nausea, vomiting, pain abdomen, and coma, while hyperglycemia may also be detected through blood tests. As hyperglycemia develops suddenly, hemoglobin A1c levels might appear normal. This type of DM results in complete endogenous insulin deficiency accompanied by low or undetectable C-peptide levels. Pancreatic imaging using ultrasound, computed tomography (CT), or MRI in certain studies has either been normal or indicated atrophy, enlargement, or signs of widespread inflammation.^[64-66] Screening for ICPI-DM includes monitoring random blood glucose levels during each treatment cycle. Approximately 60–85% of ICPI-DM cases present with DKA.^[67] Patients with DKA should promptly undergo treatment according to DKA protocol. This includes continuous intravenous insulin infusions, fluid resuscitation, and correction of electrolyte imbalances.^[68] Lifelong insulin therapy is necessary for these patients, and their management should parallel that of classic type 1 DM.

HYPOPARATHYROIDISM

ICPI-induced hypoparathyroidism is an exceedingly uncommon endocrine complication.^[69,70] Patients exhibit mild hypocalcemia and hyperphosphatemia with symptoms such as perioral tingling, numbness, muscle cramp, spasms, and tetany. Diagnostic evaluation should involve assessing serum calcium, albumin, and phosphorus.^[71] On confirming hypocalcemia, measuring parathyroid hormone (PTH) levels can confirm hypoparathyroidism which is characterized by low or inappropriately normal PTH levels. Treatment typically involves calcium supplementation along with calcitriol administration to maintain normal serum calcium levels.

SCREENING RECOMMENDATIONS

Patients, family members, and physicians should receive thorough education regarding potential endocrine complications of ICPIs before starting treatment and continuously throughout the process. This education should be provided by a team comprising of endocrinologist and an oncologist. Individuals should be able to recognize and promptly report various symptoms or signs, such as severe

Table 1: Evaluation for patients for possible ICPI-induced endocrinopathy.

At baseline	Clinical evaluation for symptoms such as severe weakness, vision changes headache palpitation, weight loss or weight gain, diarrhea or constipation, mood changes, polyuria, polydipsia, polyphagia, low appetite, nausea, vomiting, pain abdomen Laboratory evaluation for TSH, FT4, morning cortisol, plasma glucose, and serum electrolytes
Every 4–6 weeks and 4–6 weeks after the last treatment cycle	Clinical evaluation for symptoms and laboratory evaluation for TSH, FT4, morning cortisol, plasma glucose, and serum electrolytes
Additional Tests	
Hypothyroidism	Anti-TPO (antibody)
Hyperthyroidism	TSH, FT4, T3 every 2–3 weeks, TRAb
Low Cortisol	ACTH, ACTH stimulation test adrenal CT (in case of suspected primary adrenal insufficiency)
Hypophysitis	ACTH, LH, FSH, and testosterone in male or estradiol in female pituitary MRI
Hyperglycemia	Arterial blood gas analysis for metabolic acidosis, urine for ketone body. Autoantibodies such as GAD Islet autoantibodies, insulin autoantibodies, anti-ZnT8 (zinc transporter), serum fasting, and post-mixed meal C-peptide level

ICPI: Immune checkpoint inhibitor, TSH: Thyroid-stimulating hormone, FT4: Free thyroxine, T3: Triiodothyronine, ACTH: Adrenocorticotropic hormone, CT: Computed tomography, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, MRI: Magnetic resonance imaging, TRAb: TSH receptor antibody, GAD: Glutamic acid decarboxylase, Anti-TPO: Anti-thyroid peroxidase

weakness, unusual headache patterns, excessive sweating, palpitation, mood changes, constipation, diarrhea, polyuria, polydipsia, polyphagia, low appetite, nausea, vomiting, and abdominal pain.^[47] Baseline assessment should include TSH, FT4, morning cortisol, glucose, and electrolyte levels. These tests should be repeated every 4–6 weeks interval during treatment, with another round of testing 4–6 weeks after the final cycle of immunotherapy to detect late-onset complications. [Table 1] outlines the appropriate clinical and laboratory evaluation for patients receiving ICPIs for potential endocrinopathies.

CONCLUSION

ICPI therapy has transformed cancer treatment, but it comes with a range of irAEs that differ significantly from the side effects of traditional radiation therapy, chemotherapy, and other cancer treatments. Common irAEs include ICPI-induced thyroid and pituitary dysfunction, while

ICPI-related DM, PAI, and other rare endocrinopathies can also occur. If these endocrinopathies are not promptly identified and treated, they can be life-threatening. Educating patients, their family members, and caregivers about the signs and symptoms of ICPI-related endocrinopathies is crucial. Ideally, managing these cases should involve both oncology and endocrinology collaboration. Several challenges remain while diagnosing and managing irAEs, including identifying potential risk factors which could influence ICPI therapy selection, clinical monitoring, and screening approaches. Although hormone deficiencies due to ICPI-related endocrinopathies may be permanent, hormone replacement therapy is effective in most cases.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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