Cancer Pathogenesis and Therapy 2 (2024) 164–172

Contents lists available at ScienceDirect

Cancer Pathogenesis and Therapy

journal homepage: www.journals.elsevier.com/cancer-pathogenesis-and-therapy

Review article

Common endocrine system adverse events associated with immune checkpoint inhibitors☆

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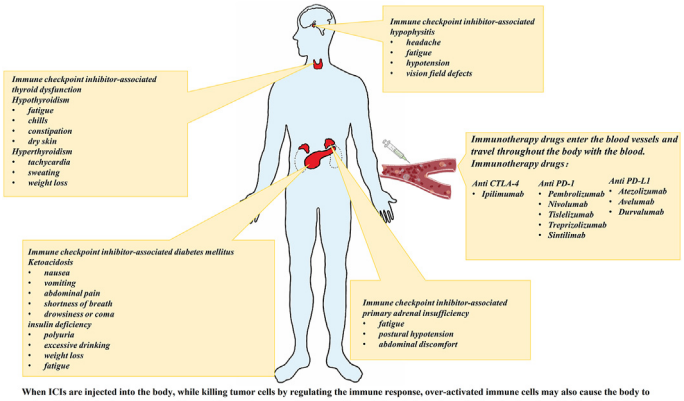
HIGHLIGHTS

- This review summarizes common endocrine immune-related adverse events (irAEs) after immunotherapy by endocrine organs.
- The mechanisms underlying irAEs in each endocrine organ were analyzed.
- Timely detection and treatment of immunotherapy-associated endocrine irAEs is essential to improve immunotherapy efficacy.

GRAPHICAL ABSTRACT



When ICIs are injected into the body, while killing tumor cells by regulating the immune response, over-activated immune cells may also cause the body to produce irAEs. Endocrine adverse reactions are the most common adverse reactions, which mainly involve endocrine glands such as the thyroid, pituitary, pancreas, adrenal glands, and other endocrine glands, and cause corresponding endocrine dysfunctions. CTLA-4: Cytotoxic T-lymphocyte antigen 4; ICIs: Immune checkpoint inhibitors; irAEs: immune-related adverse events; PD-1: Programmed cell death-1; PD-L1: Programmed cell death-ligand 1.

ARTICLE INFO

Edited by: LiLi Wang and Peng Lyu
Managing Editor: Peng Lyu

ABSTRACT

Immune checkpoint inhibitors (ICIs), a novel anti-tumor therapeutic modality, are monoclonal antibodies targeting certain immune checkpoints (ICs) that reactivate T cells to achieve anti-tumor immunity by targeting, binding, and blocking ICs. Targeted inhibitory antibodies against the ICs cytotoxic T-lymphocyte antigen and

☆ Given his role as Guest Editor of the special issue on Current Landscape and Latest Advances of Lung Cancer Research, Prof. Yintao Li had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Managing Editor, Peng Lyu.

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https://doi.org/10.1016/j.cpt.2023.11.005
Received 1 August 2023; Received in revised form 23 November 2023; Accepted 28 November 2023

Keywords:
Immune checkpoint inhibitors
Immune checkpoints
Cytotoxic T-lymphocyte antigen 4
Programmed cell death-1
Programmed cell death-ligand 1
Endocrine autoimmune-related adverse reactions

programmed death receptor-1 have demonstrated efficacy and durable anti-tumor activity in patients with cancer. ICs may prevent autoimmune reactions. However, ICIs may disrupt ICs properties and trigger autoimmune-related adverse reactions involving various organ systems including the cardiovascular, pulmonary, gastrointestinal, renal, musculoskeletal, dermal, and endocrine systems. Approximately 10% of patients with damage to target organs such as the thyroid, pituitary, pancreas, and adrenal glands develop endocrine system immune-related adverse events (irAEs) such as thyroid dysfunction, pituitary gland inflammation, diabetes mellitus, and primary adrenal insufficiency. However, the symptoms of immunotherapy-associated endocrine system irAEs may be nonspecific and similar to those of other treatment-related adverse reactions, and failure to recognize them early may lead to death. Timely detection and treatment of immunotherapy-associated endocrine irAEs is essential to improve the efficacy of immunotherapy, prognosis, and the quality of life of patients. This study aimed to review the mechanisms by which ICIs cause endocrine irAEs providing guidance for the development of appropriate management protocols. Here, we discuss (1) the biological mechanisms of ICs in tumorigenesis and progression, focusing on cytotoxic T-lymphocyte antigen and programmed cell death-1/programmed cell death-ligand 1; and (2) the epidemiology, clinical symptoms, diagnosis, and treatment of four immunotherapy-related endocrine complications.

Introduction

The immune system utilizes a complex array of mechanisms to monitor and attack tumor cells; these pathways not only prevent the development of malignant tumors but also prevent the host from developing an autoimmune response.[1] Immune checkpoints (ICs) are small molecules expressed by immune cells, such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death-1 (PD-1), which are expressed on the surface of activated T cells and play important roles in maintaining immune homeostasis and regulating physiological immune responses [Figure 1A].[2–5] However, tumor cells can take advantage of this feature to evade the immune system by promoting the binding of ICs to specific ligands (e.g., programmed cell death-ligand 1 [PD-L1]) to inhibit T-cell responses.[6] Cancer immunotherapy is broadly defined as a therapy that directly or indirectly targets any component of the immune system involved in the anti-cancer immune response, including stimulation, enhancement, inhibitions, or desensitization of the immune system.[7] Among them, immune checkpoint inhibitors (ICIs) are used to induce anti-tumor ICs by blocking ICs. ICIs are specific for ICs proteins, and their combination overcomes tumor-mediated suppression of T-cell function.

Since the approval of the first ICIs by the Food and Drug Administration (FDA) in 2011, immunotherapy has become a new treatment for a variety of tumors, supplementing surgery, radiation, chemotherapy, and targeted therapy.[8] These novel drugs have significantly improved the survival rates of patients with cancer. However, they can also induce a series of immune-related adverse events (irAEs), of which, ICI-induced endocrinopathy is the most common. Prompt recognition and timely treatment are essential to improve the quality of life of affected patients.

In this review, we discuss the biological mechanisms of action of ICs and provide an update on the currently available ICIs. Moreover, we

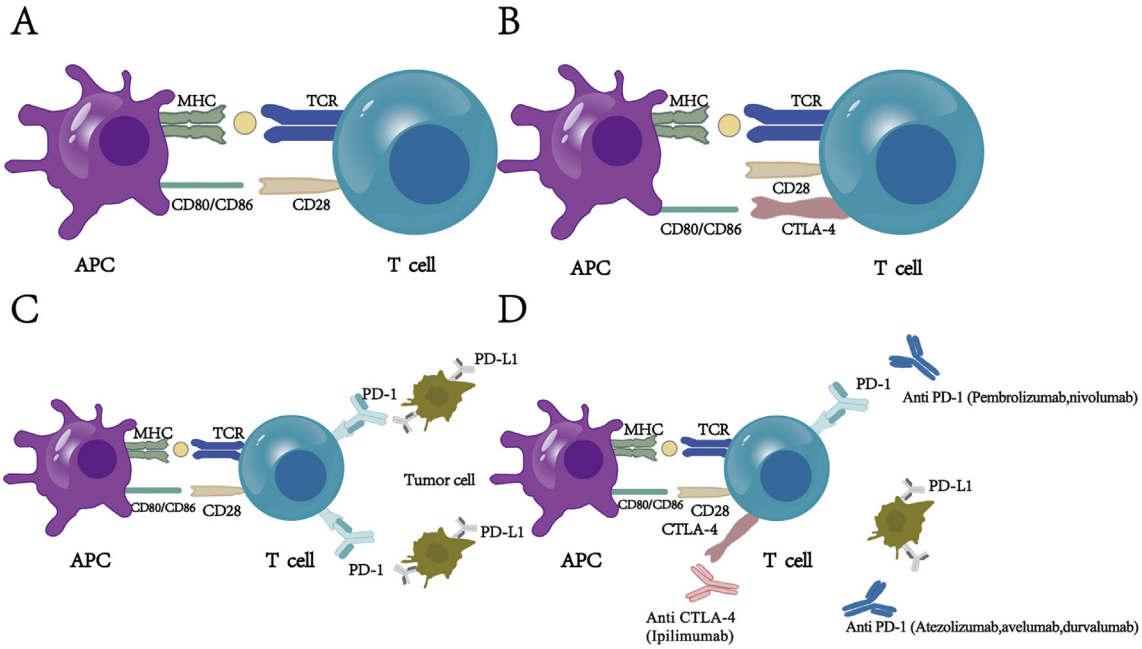

Figure 1. Role of immune checkpoint inhibitors in immune escape. (A) Tumor antigen is recognized and captured by the APC and presented to T cells via the antigen class II MHC-TCR, the first signal for T-cell activation; CD28 on the T-cell surface interacts with CD80 and CD86 molecules on the professional APC to generate the second signal required for T-cell activation, resulting in full T-cell activation.[6,7,9] (B) CTLA-4 is highly homologous to CD28 and competitively inhibits CD28 at the cell surface, resulting in the inability to form a second signal for T-cell activation and the inability of T cells to fully activate. (C) PD-1 and PD-L1 do not affect the formation of first and second signals, but their binding triggers a cascade of T-cell suppression processes that inhibit the function of effector T cells. (D) The mechanism of action of the corresponding inhibitors against these ICs. APC: Antigen-presenting cell; CTLA-4: Cytotoxic T lymphocyte-associated protein 4; IC: Immune checkpoint; MHC: Major histocompatibility complex; PD-1: Programmed cell death-1; PD-L1: Programmed cell death-ligand 1; TCR: T-cell receptor.

highlight endocrine-related adverse events during immune therapy and treatment strategies.

Biological mechanisms of immune checkpoints

A variety of ICs already exist in the human body, among which, CTLA-4 and PD-1/PD-L1 are the main members of the ICs family, and the ICIs currently used in clinical practice are mainly focused on these three ICs.

Cytotoxic T lymphocyte-associated protein 4

CTLA-4, a negative co-stimulatory receptor, normally resides in the cytoplasm of CD4+ and CD8+ T lymphocytes.[4,9] It shares high homology with CD28 but exhibits 20 times greater affinity for key co-stimulatory molecules (CD80 and CD86) than CD28. While resting, CTLA-4 remains an intracellular protein, but it translocates to the cell surface when inhibitory signals are triggered by T-cell receptors through CD28.[10,11] It can competitively inhibit the action of CD28 and bind to CD80 or CD86, delivering inhibitory signals to T cells, limiting interleukin-2 production, and causing excessive activation and proliferation of T lymphocytes [Figure 1B].[2,12,13] CTLA-4 inhibitors block the binding of ICs B7 (One is the B7 family of proteins expressed on the surface of antigen-presenting cells, i.e., the CD80 and CD86 proteins) to CTLA-4, thereby enhancing tumor-specific T-cell activation.

Leach et al.[14] first demonstrated that blocking antibodies targeting CTLA-4 in mice prevented tumorigenesis and induced the rejection of preestablished tumors. These findings have accelerated the development of ICs blockade. Ipilimumab anti-tumor interactions beyond merely blocking CTLA-4/CD80. It effectively eliminates tumor-localized regulatory T cells (Tregs) with high CTLA-4 expression through Fc (The Fc receptor is a receptor for IgG antibodies located on the cell membrane surface of certain immune cells, which can be involved in antigen recognition) receptor-mediated antibody-dependent cellular cytotoxicity, thereby alleviating Treg-induced immunosuppression and achieving anti-tumor effects.[15] However, there is limited understanding of the mechanism of action of CTLA-4 antibodies.

Programmed cell death-1/programmed cell death-ligand 1

PD-1 glycoprotein is a second inhibitory receptor that belongs to the immunoglobulin superfamily.[9,10,16,17] It is expressed on the surface of activated T lymphocytes, B lymphocytes, and monocytes/macrophages. CTLA-4 is molecularly linked to B7 (CD80/CD86), whereas PD-1 has specific ligands, PD-L1 and PD-L2 [Figure 1C].[2,18] PD-1 binds to PD-L1 and phosphorylates tyrosine in the ITSM (immunoreceptor tyrosine-based switch motif) domain of PD-1, which in turn causes dephosphorylation of the downstream protein kinases Syk (Spleen tyrosine kinase) and PI3K(phosphoinositide 3-kinase), inhibiting the activation of downstream AKT, ERK and other pathways, and ultimately inhibiting the transcription and translation of the genes and cytokines required for T-cell activation, thus exerting a role in negatively regulating the activity of T cells.[19,20] PD-1 inhibits transcription and translation during T-cell activation, thereby negatively regulating T-cell activity.[12,21] The activation of T lymphocytes is inhibited, and this promotes immune tolerance, thereby preventing the immune system from rejecting the tumor.[22,23]

The PD-1/PD-L1 signaling pathway not only converts T helper cells into Treg cells (previously known as suppressor lymphocytes), which play an important role in the immune response, particularly in immune tolerance but also activates pro-survival signaling pathways in cancer cells after binding to PD-1, causing cancer cells to develop antibodies against T cell-mediated cytotoxicity.[9]

The remarkable success of cancer immunotherapies targeting CTLA-4 and PD-1/PD-L1 has stimulated great interest in new regeneration of ICIs [Figure 1D]. The emerging targets of IC blockade for cancer immunotherapy include *lymphocyte activation gene-3* (*LAG3*),[24] T-cell immunoglobulin mucin domain 3,[25] B and T lymphocyte attenuator, V-domain immunoglobulin suppressor of T-cell activation, T-cell immunoglobulin, and the immunoreceptor tyrosine-based inhibition motif domain.[26]

Update on available immune checkpoint inhibitors

ICIs are monoclonal antibodies specific for IC molecules that are widely used in tumor treatment. The main mechanisms underlying ICI function involve two key signaling pathways related to T-cell activation and exhaustion. In 2011, the U.S. FDA and the European Medicines Agency approved the first anti-CTLA-4 monoclonal antibody, ipilimumab for the treatment of metastatic melanoma.[23,27,28] In patients with melanoma, treatment with ipilimumab was associated with a response rate of 15%–20% and a 5-year survival rate of 20%.[29] The clinical activity of ipilimumab provides important evidence of the application of immunotherapy in cancer. In 2015, the FDA approved the use of two anti-PD-1 antibodies, pembrolizumab, and nivolumab, for the treatment of advanced melanoma. Nivolumab was also approved for the treatment of non-small cell lung cancer in 2015. To date, agents targeting PD-1 (nivolumab, pembrolizumab, and cemiplimab) and PD-L1 (atezolizumab, avelumab, and durvalumab) have demonstrated widespread efficacy and have been approved for multiple types of cancer including skin, kidney, lung, head and neck, and bladder cancer.[22,30]

There is increasing evidence that the combination of nivolumab and ipilimumab in patients with melanoma may produce significant anti-tumor effects. Based on the remarkable activity of ICIs, combinations of different ICIs and the combination of ICIs with chemotherapy or radiotherapy, have been explored for different types of solid and hematologic tumors in several clinical trials.[9,23]

Immune-associated endocrine irAEs

Despite the promising clinical efficacy of combination immunotherapy, the occurrence of irAEs should be considered. ICIs can kill tumors by modulating the immune response; however, over-activated immune cells may also lead to autoimmune damage, resulting in irAEs. The presence of ICs can contribute significantly to preventing autoimmune reactions, and the use of ICIs can disrupt the balance of the body's immune system, leading to the occurrence of irAEs.[20] ICI-induced irAEs such as imbalance of immune tolerance, cross-antigen presentation,[31] production of multiple cytokines, off-target effects, and altered microbiota involve multiple mechanisms, the specifics of which remain unclear.[32] Endocrine glands are one of the most frequently affected organs by ICI therapy-related irAEs and this may be explained by the fact that they have a rich blood supply, which may increase their sensitivity to the mechanisms described above.[11]

A significant percentage of patients with cancer treated with ICIs present with endocrine irAEs. Endocrine irAEs may occur in 5%–10% of patients treated with ICIs[33] and the incidence varies depending on the type of ICIs used. The common endocrine complications associated with ICIs include thyroid dysfunction, hypophysitis, insulin-deficient diabetes (IDD), and primary adrenal insufficiency (PAI).[12,34–36] Thyroid dysfunction and hypophysitis are the most common events, IDD and PAI are relatively rare. Symptoms usually occur within 6 months of treatment with ICIs, but the onset is unpredictable. It can occur at any time during treatment, even months after discontinuation.[16] Although prompt recognition and treatment are essential for the typical symptoms, non-specific manifestations may overlap with cancer- or therapy-related complications. Therefore, regular monitoring of patient hormone levels is important and collaboration between oncologists and endocrinologists for the implementation of symptomatic treatment should be promoted.

Immune checkpoint inhibitor-associated thyroid dysfunction

Abnormal thyroid function is the most common endocrine irAE after treatment with ICIs.[37,38] The specific pathogenesis of thyroid dysfunction remains unclear but it has been associated with underlying thyroid dysfunction, thyroid autoantibodies, baseline levels of thyrotropin, the tumor microenvironment, the homology of tumor antigens to antigens of the thyroid tissues, specific types and doses of medication, and body mass index.[39–41] The incidence and prevalence of immunotherapy-induced thyroid function abnormalities depend on the type of antibody used and the mode of administration (monotherapy or combination therapy).[42] As PD-1/PD-L1 is abundantly expressed in the thyroid, patients treated with anti-PD-1/PD-L1 have a higher incidence of abnormal thyroid function than that in patients treated with CTLA-4 inhibitors.[43–45] Torimoto et al.[46] suggested that ICIs induce hypothyroidism by inhibiting the PD-1 pathway and increasing the proliferation of follicular helper T cells. The incidence of hypothyroidism ranges from 6% to 11% in patients treated with anti-PD-L1, with an incidence of up to 40% in patients treated with anti-PD-1 therapy and 1%–6% in patients treated with ipilimumab.[4,23,47] The risk of thyroid dysfunction is higher in patients undergoing anti-CTLA-4 and anti-PD-1 combination therapy than that in patients undergoing immune monotherapy, with an incidence of 15%–20%.[3] Thyroid dysfunction is classified into hyperthyroidism (incidence 3%–16%, simple <2.5%, subclinical 15.9%) and hypothyroidism (incidence 6%–13%, simple 1%–6%, subclinical 6.4%), and this determines the type of treatment and treatment regimen required and whether mild or subclinical forms are considered.[16,23,48] Previous studies have shown that thyroid function abnormalities appear within 6–12 weeks after the initiation of ICI treatment and that the onset of thyroid dysfunction associated with irAEs appears to be dose-dependent, usually occurring after the second to fourth dose of immunotherapeutic agents.[39,49]

Symptoms and signs of thyroid dysfunction associated with ICIs are nonspecific, with most patients exhibiting no obvious symptoms in the early stage and the most common clinical manifestations including weakness and fatigue.[50] Nearly half of the patients treated with anti-PD-1 or anti-PD-L1 therapy present with destructive thyroiditis characterized by destruction of the thyroid follicular cells and excessive release of preformed thyroid hormones and thyrotoxicosis; however, the clinical symptoms are often mild or even negligible.[16,51] Thyrotoxicosis is usually transient and can spontaneously progress to hypothyroidism.[10,52,53] The clinical symptoms of hyperthyroidism may include tachycardia, sweating, and weight loss, whereas fatigue, chills, constipation, and dry skin are most likely to indicate the presence of hypothyroidism.[54]

The severity of hyperthyroidism is determined by the clinical symptoms and elevated free thyroxine (FT4) levels; hypothyroidism may decrease FT4 levels. A diagnosis of primary hypothyroidism is made if FT4 is decreased and thyroid-stimulating hormone (TSH) is increased; hypothyroidism is diagnosed if FT4 is increased and TSH is decreased; and central hypothyroidism should be considered if FT4 is decreased and TSH is decreased or within normal limits. It is important to carefully differentiate between primary and secondary hypothyroidism. Furthermore, pituitary function should be further evaluated to clarify whether pituitary inflammation is due to ICIs. When initial tests suggest hypothyroidism, thyroid autoantibodies, namely, anti-thyroid peroxidase and anti-thyroglobulin antibodies, are preferred. These autoantibodies are elevated in some but not all patients. Positive thyrotropin receptor autoantibodies (auto-antibody-stimulated TSH receptors) are also helpful in the diagnosis of hyperthyroidism.[46] The measurement of blood TSH concentration is preferred and is more sensitive. Primary hypothyroidism is characterized by elevated levels of TSH, whereas secondary hypothyroidism is characterized by low levels of TSH and free T4. The pituitary function should be further examined when considering secondary hypothyroidism.[55]

Patients with hyperthyroidism and symptoms of tachycardia may be considered for β-blockers if not contraindicated, and corticosteroid therapy may be considered for patients who exhibit a hyperthyroid crisis

Table 1
Clinical protocols for thyroid dysfunction associated with ICIs therapy.

Hyperthyroidism grade	Description	Treatments	Whether or not to discontinue ICIs	Detection of TSH, FT4	Hypothyroidism grade	Description	Treatments	Whether or not to discontinue ICIs	Detection of TSH, FT4
G1	Asymptomatic: clinical or diagnostic tests only.	–	Not	Usually 4–6 weeks. When hypothyroidism is imminent, monitor every 2–3 weeks.	G1	Asymptomatic: clinical or diagnostic tests only.	–	Not	4–6 weeks
G2	Symptomatic: no restrictions on daily activities.	Application of antithyroid drugs in patients with Graves' disease (MMI or PTU); β-blockers are taken orally to relieve symptoms.	Suspension of ICIs until after symptom resolution.	4–6 weeks	G2	Symptomatic: no restrictions on daily activities.	Continuation of ICIs; elevated TSH (>10 IU/mL), thyroxine supplementation.	Suspension of ICIs until after symptom resolution.	4–6 weeks
G3	Severe symptoms: impaired personal autonomy; hospitalization required.	Application of antithyroid drugs in patients with Graves' disease (MMI or PTU); β-blockers are taken orally to relieve symptoms; apply glucocorticoids as appropriate.	Suspension of ICIs until after symptom resolution.	4–6 weeks	G3	Severe symptoms: impaired personal autonomy; hospitalization required.		Suspension of ICIs until after symptom resolution.	4–6 weeks
G4	Threatens life: requires urgent intervention.	Principles of management of hyperthyroid crisis; β-blockers are taken orally to relieve symptoms; prednisone 1–2 mg kg^{-1}·day^{-1} to start, reduce every 1–2 weeks according to condition.	Permanent deactivation of ICIs.	4–6 weeks	G4	Threatens life: requires urgent intervention.	Principles of mucous edema management; prednisone 1–2 mg kg^{-1}·day^{-1} to start, reduce every 1–2 weeks according to condition.	Permanent deactivation of ICIs.	4–6 weeks

FT4: Free thyroxine; ICI: Immune checkpoint inhibitor; IU: International unit; MMI: Methimazole; PTU: Propylthiouracil; TSH: Thyroid stimulating hormone.

[Table 1].[2,50] Hyperthyroidism is usually temporary and can progress to hypothyroidism. TSH levels >10 mIU/L or moderately elevated TSH and reduced free T4 can be diagnosed as primary hypothyroidism without further testing and levothyroxine replacement therapy can be directly administered. Levothyroxine can be started at an initial dose of 1–1.6 μg/kg daily with retesting every 6 weeks for dose adjustment. It must be adjusted according to age, comorbidities, and patient survival prognosis in the same way as in other hypothyroid patients.[12] TSH level testing is required every 3 months during levothyroxine therapy. To avoid adrenal crises, it is important to rule out cortisol deficiency before starting levothyroxine therapy to avoid adrenal crisis.[12] In rare cases, mucinous edema (tachycardia or hypothermia) may occur and require intravenous treatment.[2]

The presence of previously treated dysfunction or thyroid abnormalities is not a contraindication to ICIs, nor is the presence of developing thyroid dysfunction. In cases of thyrotoxicosis or severe hypothyroidism, treatment with ICIs can be delayed and should not be explicitly contraindicated in any case.[16]

Immune checkpoint inhibitor-associated hypophysitis

ICI-associated hypophysitis (IH) is a rare condition outside the context of ICI treatment, but a common endocrine complication in patients treated with immunotherapy.[3,18] Iwama et al.[56] demonstrated that the CTLA-4 antigen was expressed in the pituitary tissue of mice with CTLA-4 inhibitor-induced pituitary inflammation. Furthermore, autopsies of patients treated with CTLA-4 inhibitors who developed IH revealed that CTLA-4 was also expressed in the pituitary tissues, suggesting that CTLA-4 inhibitors can directly bind to CTLA-4 on pituitary cells and present it as an antigen on CD8+ cells, inducing IH via a type IV hypersensitivity reaction.[57,58] The population susceptible to IH mostly comprises men over 60 years of age, and the risk of developing the IH is two to five times higher in men than in women. The incidence of IH is higher in patients undergoing treatment with CTLA-4 inhibitors (5%–10%) than in those undergoing PD-1/PD-L1 blockade therapy (0.5%–1%).[16,38,59] CTLA-4 is expressed in a subset of secreting cells in the pituitary gland, which bind to the anti-CTLA-4 antibody, resulting in IH. The prevalence of IH also depends on whether monotherapy or combination therapy is administered, ranging from 4% to 20% for ipilimumab, 8% for the combination of ipilimumab and nivolumab, 0.6% for nivolumab, and 0.7% for pembrolizumab.[60] The time-to-onset of IH with anti-CTLA-4 and anti-PD-1 inhibitors varies depending on the ICI dose. IH can occur early (median time, 30 days) during combination therapy, usually at 2–3 months after commencing anti-CTLA-4 therapy, and 3–5 months after commencing anti-PD-1/PD-L1 therapy.

The clinical symptoms of IH in most patients undergoing immunotherapy are non-specific. The most common symptoms include headache, fatigue, hypotension, and vision field defects.[50] Mental confusion, memory loss, anorexia, hyponatremia, decreased sexual function, amenorrhea, and enuresis were less common. Typically, IH caused by ICI treatment affects only one axis, which differs from conventional cases of pituitary hypofunction. The most common causes are central hypothyroidism (TSH deficiency), central adrenal insufficiency (adrenocorticotropic hormone [ACTH] deficiency), and hypogonadism (follicle-stimulating hormone [FSH] and luteinizing hormone [LH] deficiency).

Approximately 80% of patients with IH exhibit one or more of these three defects.[2,27]

Low morning cortisol concentrations (<5 μg/dL) and low serum levels of ACTH indicate secondary adrenal insufficiency, which has been reported to be triggered by IH and may be life-threatening.[3] Low TSH and FT4 levels indicate secondary hypothyroidism, whereas low testosterone, FSH, and LH levels indicate secondary hypogonadism.[3] If the morning cortisol concentration is mildly low (5–10 μg/dL), cosyntropin stimulation testing should be performed, which may be helpful for the diagnosis of either primary or secondary adrenal insufficiency.

Brain magnetic resonance imaging (MRI) with a pituitary window is the most sensitive imaging tool for the diagnosis of pituitary inflammation caused by ICI treatment; IH is characterized by immune cell infiltration and typical MRI findings are present in most patients with an enlarged pituitary gland.[59,61] MRI abnormalities suggest pituitary IH but no pituitary insufficiency in the diaphysis. Close monitoring of the hormone levels is required because symptoms related to pituitary insufficiency may occur during the second stage of IH. In this case, routine measurement of the 8-am cortisol level is recommended (once a week for 1 month and then once a month for monitoring), as well as monitoring of some clinical symptoms such as polyuria and irritable thirst.[21]

In the acute phase of IH, high-dose glucocorticoid therapy is neither therapeutically effective nor harmful and is therefore not recommended [Table 2].[62] It may only be recommended in the presence of headaches and visual disturbances for which conventional analgesics are ineffective. If an ICI-treated patient is suspected of having acute ACTH deficiency, random plasma cortisol measurements should be performed immediately, and 100 mg of hydrocortisone succinate should be promptly administered by intravenous, intramuscular, or subcutaneous injection, followed by a 24-h continuous dosing of 100 mg (similar to the management of non–ICI–induced ACTH deficiency). Following improvement in the clinical symptoms and biochemical parameters, hydrocortisone 60 mg/24 h may be administered orally in three divided doses and gradually reduced until the replacement dose is achieved. In patients with chronic

Table 2
Clinical recommendations for the management of hypophysitis caused by ICIs.

ICI-associated hypophysitis					
Grade	Description	Treatment	Whether or not to discontinue ICIs	Hormone testing	MRI of the pituitary gland
G1	Asymptomatic or mildly symptomatic.	Observation of changes in clinical symptoms, no intervention required.	Not	One per month for the first 6 months; every 3 months for the second 6 months; reviews every 2 years thereafter.	Once every 3 months.
G2	Mild to moderate with mild localized symptoms; non-invasive treatment; impaired self-care.	Glucocorticoid and thyroxine replacement therapy is given in conjunction with hormone levels.	Not		
G3	Serious or clinically important, but not life-threatening for the time being.		Acute phase pause, assessed after symptomatic improvement with hormone replacement therapy.		
G4	Life-threatening, requiring urgent intervention.	Hydrocortisone 100 mg IV every 8 h; supplemental salt corticosteroids if necessary; treatment of the primary disease and removal of the causative agent; gradual change to oral after stabilization.			
G5	Death				

ICI: Immune checkpoint inhibitor; IV: Intravenous drip; MRI: Magnetic resonance imaging.

ACTH deficiency treated with oncological ICIs, the daily dose of hydrocortisone should be 15–20 mg/day (two to three times daily) and adjusted according to clinical symptoms. TSH or gonadotropin deficiency often recovers within a few months and therefore does not require routine supplementation, only follow-up monitoring (monthly for TSH, 3 monthly for FSH and LH) and, depending on the circumstances, replacement therapy. Patients with diabetes insipidus should be treated systemically and growth hormone replacement should not be considered based on the oncological background.

Immunotherapy may be discontinued during the acute phase of pituitary inflammation. Pituitary inflammation secondary to the first ICI (anti-CTLA-4, anti-PD-1, or anti-PD-L1) is not a contraindication for the use of other ICIs. Immunotherapy is not contraindicated in patients with a history of pituitary disease and only requires adjustment of the antitumor regimen during treatment.[63,64] For patients presenting with pituitary inflammation, clinical and hormonal monitoring is recommended every 6 months, with specialist consultations every 3 months for 6 months, and every 2 years thereafter.[16]

Immune checkpoint inhibitor-associated diabetes mellitus

ICI-associated diabetes mellitus (ICI-DM) is a rare and potentially life-threatening endocrine complication,[10] characterized by severe and persistent insulin deficiency. ICI-DM may be a novel autoimmune disease associated with the activation of autoreactive T lymphocytes and the production of specific autoantigens. Studies have shown that the combination of PD-L1 expressed by pancreatic islet cells and PD-1 on the surface of activated T lymphocytes inhibits tissue damage and cytokine release mediated by pathologically autoreactive CD4+ T lymphocytes.[65] Ansari et al.[66] showed that mice treated with anti-PD-1 or anti-PD-L1 antibodies developed more severe islet inflammation compared to controls, accompanied by higher levels of cytokines such as interferon-gamma. This suggests that the binding of PD-1 to PD-L1 is important for the regulation of autoimmunity and that treatment with anti-PD-1 or anti-PD-L1 antibodies may lead to a disruption of this binding inhibition, similar to the inflammatory destruction of the pancreas in experimental mice, leading to ICI-DM.[67] This view is further supported by immunohistochemical analyses by Yoneda et al.[68] revealing a significantly increased T-cell infiltration in pancreatic islets in patients with ICI-DM. The incidence of ICI-DM is <1% in patients undergoing ICI treatment.[69] To date, 97% of the reported cases have occurred in patients undergoing anti-PD-1/PD-L1 monotherapy or combination therapy, whereas its occurrence in patients undergoing CTLA-4 inhibitor therapy is rare.[2,70] This may be due to the fact that PD-L1 is expressed in pancreatic β-cells.

Diabetes caused by ICI treatment develops as hyperglycemia and rapidly progresses to endogenous insulin deficiency until detection [Table 2]. If a physician does not suspect this condition and does not administer timely and appropriate insulin therapy, the patient is at high risk of developing diabetic ketoacidosis. In fact, the majority of patients (70%) present with nausea, vomiting, abdominal pain, shortness of breath or drowsiness, and coma.[2,10,18] Therefore, it is important to rigorously monitor blood glucose after starting treatment with ICIs; furthermore, when typical insulin deficiency symptoms occur during ICI treatment, such as polyuria, excessive drinking, weight loss, or fatigue, measurement of blood glucose and pH and urine ketone bodies is crucial to avoid diabetic ketoacidosis. The diagnostic criterion for ICI-DM is hyperglycemia. As most cases of hyperglycemia occur in the acute phase, Hemoglobin A1c may not be a good screening indicator. However, it can be used in patients with type 2 diabetes to assess their glucose status over the previous months. Glutamic acid decarboxylase, tyrosine phosphatase-like protein IA-2, autoantibodies against insulin, and zinc transporter 8 autoantibodies are highly specific for autoimmune diabetes, and insulin and C-peptide levels may also assist in the assessment of endogenous insulin secretion.[27]

Multiple insulin injections are recommended in patients with diabetic complications resulting from ICI therapy. ICI-DM is not a contraindication for continuing anti-PD-1 or PD-L1 therapy, and patients may undergo ICI treatment in combination with the initiation of insulin therapy and ICI-DM treatment.

Immune checkpoint inhibitor-associated primary adrenal insufficiency

PAI is a relatively rare complication of ICI administration. A higher incidence of PAI has been observed in male patients after treatment with ipilimumab, nivolumab, and pembrolizumab or a combination.[2] However, the mechanism by which ICIs cause adrenocortical hypoplasia remains unclear. Previous studies have suggested that this may be an autoimmune mechanism and that the blockade of CTLA-4 and PD-1/PD-L1 plays an important role in the development of adrenal inflammation.[37] Positivity for organ-specific antibodies (e.g., against the adrenal gland, thyroid, and pancreas) may also be associated with organ damage. The presence of adrenocortical autoantibodies and antibodies to 21-hydroxylase has been reported in more than 90% of patients with autoimmune adrenal inflammation, although this association has not been fully demonstrated. Tumor crossover with human leukocyte antigen epitopes may also contribute to adverse events in the immune-related endocrine system.[71] The incidence of PAI is <1% in patients treated with a single ICI and 4%–5% in patients treated with combination therapy.[47] To date, there is a paucity of studies on ICI treatment for PAI or of reported cases of definite PAI, and few clinical trials have investigated the causes of adrenal insufficiency. ICIs that induce PAI include ipilimumab, nivolumab, and pembrolizumab, although the underlying pathophysiological mechanisms remain unknown. The median time to the appearance of PAI is highly variable, ranging from 2.5 to 5 months, depending on the drug used. PAI can also occur after ICI discontinuation, for example with pembrolizumab discontinuation.[16] Adrenal insufficiency is usually characterized by the inability of the adrenal cortex to produce sufficient glucocorticoids. Untreated adrenal insufficiency associated with ICIs can be life-threatening.[3] The signs and symptoms of PAI are non-specific and include fatigue, postural hypotension, and abdominal discomfort. Hyponatremia and hyperkalemia are common, whereas hypoglycemia and hypercalcemia are less common. PAI is characterized by low cortisol levels, elevated ACTH concentrations, salt corticosteroid deficiency, low aldosterone levels, and elevated renin levels.[2] The use of ipilimumab alone or in combination with nivolumab may cause adrenal insufficiency, with a greater focus on potential dehydration, hypotension, and electrolyte imbalance events.

In patients treated with ICIs, plasma cortisol and ACTH tests should be conducted immediately in cases of fatigue, weight loss, dehydration, hypotension, fever, abdominal pain, nausea, vomiting, diarrhea, muscle pain, and cramps suggesting acute adrenal insufficiency. Furthermore, hydrocortisone supplementation should be promptly initiated without waiting for test results [Table 3].[16,36] A plasma cortisol level >500 nmol/L excludes the diagnosis of adrenal insufficiency. In non-emergency situations, elevated plasma ACTH and plasma cortisol <138 nmol/L (5 μg/dL) at 8 am confirms the diagnosis of PAI. If cortisol is between 138 and 500 nmol/L (5–18 μg/dL), an ACTH stimulation test, such as the synacthen 250 μg stimulation test, should be performed as a secondary diagnostic criterion for “latent” PAI. Cortisol levels <500 nmol/L (18 μg/dL) confirm a diagnosis of PAI [Table 4].[16]

In acute PAI, 100 mg hydrocortisone succinate may be administered intravenously (intramuscularly or subcutaneously), followed by a continuous infusion of 100 mg hydrocortisone succinate over 24 h.[36] When clinical symptoms and electrolyte parameters improve, oral administration of 60 mg/24 h hydrocortisone should be continued. After stabilization, the dose can be reduced to 15–30 mg/24 h. Treatment with

Table 3
Clinical recommendations for the management of diabetes mellitus caused by ICIs.

ICI-associated diabetes mellitus				
Grade	Description	Fasting blood sugar	Treatment	Discontinuation ICIs
G1	Asymptomatic or mildly symptomatic with no evidence of ketosis or autoimmune diabetes mellitus.	Greater than ≥7.0 mmol/L, but <8.9 mmol/L.	Oral medication or insulin (to be administered promptly if there is an acute increase in blood glucose or ketosis).	No
G2	Moderate symptoms, ability to perform daily activities, evidence of ketosis or autoimmune diabetes mellitus.	8.9–13.9 mmol/L	Endocrine clinic evaluation with dose adjustment of oral medications or addition of insulin therapy; prioritize insulin if regular outpatient evaluation is not possible or if signs of DKA are present.	ICI discontinuation until glycemic control is achieved.
G3	Severe symptoms, medically significant or life-threatening consequences, inability to perform daily activities.	13.9–27.8 mmol/L	Prompt activation of insulin, requiring hospitalization for endocrinology consultation.	ICI discontinuation until glycemic control is achieved.
G4	Severe symptoms, medically significant or life-threatening consequences, inability to perform daily activities, life-threatening.	>27.8 mmol/L	Prompt activation of insulin, hospitalization, and urgent endocrinology consultation.	ICI discontinuation until glycemic control is achieved.

DKA: Diabetic ketoacidosis; ICI: Immune checkpoint inhibitor.

Table 4
Clinical recommendations for the management of PAI caused by ICIs.

ICI-associated PAI				
Grade	Description	Treatment	Whether or not to discontinue ICIs	Blood cortisol, ACTH (AM), and biochemical markers
G1	Symptomatic: no restrictions on daily activities.	Prednisone 5–10 mg/day, or hydrocortisone 10–20 mg orally in the early morning and 5–10 mg orally in the afternoon daily; some patients with PAI may require saline corticosteroid replacement therapy: fludrocortisone 0.05–0.2 mg/day; adjustments may be made based on blood pressure, blood potassium, and blood renin levels.	Consider suspending ICIs until hormone replacement stabilizes the disease.	Review every 2–3 weeks, follow-up every 6–12 weeks.
G2	Symptomatic: no restrictions on daily activities.	Two to three episodes requiring outpatient treatment to control acute symptoms: prednisone 20 mg/day or hydrocortisone 20–30 mg/day orally early each morning, 10–20 mg orally in the afternoon; gradually controlled reduction of hormones from stress dose to maintenance dose over 5–10 days after symptom control (same as level 1); some patients with PAI may require saline corticosteroid (corticosteroid hormone secreted by the brain) replacement therapy： fludrocortisone 0.05–0.2 mg/day; adjustments can be made based on blood pressure, blood potassium, and blood renin levels.	Consider suspending ICIs until hormone replacement stabilizes the disease.	Review every 2–3 weeks, follow-up every 6–12 weeks.
G3	Severe symptom: impaired personal autonomy; hospitalization required.	Intravenous glucocorticoid supplementation when an adrenal crisis is considered: hydrocortisone 100 mg or dexamethasone 4 mg with copious fluid replacement (saline at least 2000 mL): gradual reduction of hormones from stress dose to maintenance dose over 7–14 days after hospital discharge (same as level 1); when an adrenal crisis is considered, supplementation of glucocorticoid agonists is followed by supplementation of saline corticosteroids as required: fludrocortisone 0.05–0.2 mg/day; adjustments were made based on blood pressure, and potassium and plasma renin levels.	Consider suspending ICIs until hormone replacement stabilizes the disease.	Urgently check blood cortisol, ACTH and serum electrolytes, blood glucose when considering an adrenal crisis.
G4	Life-threatening: requires urgent intervention.	Same as level 3.	Same as level 3.	Same as level 3.

ACTH: Adrenocorticotropic hormone; AM: Ante meridiem; ICI: Immune checkpoint inhibitor; PAI: Primary adrenal insufficiency.

fludrocortisone is then started at 50 μg per day, and the dose is adjusted by an endocrinologist.

ICIs can be discontinued in the event of acute adrenal insufficiency but there is no absolute contraindication to their use. When hydrocortisone is correctly administered as a replacement therapy and the patient is clinically and biochemically (blood electrolytes) stable, ICIs can be reintroduced at normal doses.

Conclusions

Immunotherapy has revolutionized tumor treatment in recent years and has the potential to become a major treatment modality. However, because ICIs disrupt autoimmune tolerance, these may cause reversible or irreversible functional damage to endocrine organs, leading to endocrine dysfunction and its associated symptoms. Although most irAEs are not serious, acute severe reactions may be life-threatening and require prompt diagnosis and treatment. Therefore, close collaboration between oncologists and endocrinologists is recommended for early detection and timely intervention of irAEs to reduce the toxic side effects of immunotherapy and ensure patient safety, reduce mortality, and improve prognosis.

Funding

This study was supported by the National Natural Science Foundation of China (No. 82373044) and the Natural Science Foundation of Shandong Province (No. ZR2022LSW001).

Authors contribution

Ying Li, Junfeng Zhao and Yue Wang: conceptualization, investigation, methodology, and writing – original draft; Yali Xu, Ruyue Li, and Ying Zhao: methodology, investigation; Xue Dong and Xiujing Yao: investigation; Yintao Li: conceptualization, writing, reviewing, and editing. All the authors have read and approved the final draft of this manuscript.

Ethics statement

None.

Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

References

1. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. *CA Cancer J Clin*. 2020;70:86–104. https://doi.org/10.3322/caac.21596.
2. Paschou SA, Stefanaki K, Psaltopoulou T, et al. How we treat endocrine complications of immune checkpoint. *ESMO Open*. 2021;6:100011. https://doi.org/10.1016/j.esmoop.2020.100011.
3. Wright JJ, Powers AC, Johnson DB. Endocrine toxicities of immune checkpoint inhibitors. *Nat Rev Endocrinol*. 2021;17:389–399. https://doi.org/10.1038/s41574-021-00484-3.
4. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. *Endocr Rev*. 2019;40:17–65. https://doi.org/10.1210/er.2018-00006.
5. Carlino MS, Larkin J, Long GV. Immune checkpoint inhibitors in melanoma. *Lancet*. 2021;398:1002–1014. https://doi.org/10.1016/S0140-6736(21)01206-X.
6. Ahmed H, Mahmud AR, Siddiquee MFR, et al. Role of T cells in cancer immunotherapy: opportunities and challenges. *Cancer Pathog Ther*. 2023;1:116–126. https://doi.org/10.1016/j.cpt.2022.12.002.
7. Ramos-Casals M, Brahmer JR, Callahan MK, et al. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Prim*. 2020;6:38. https://doi.org/10.1038/s41572-020-0160-6.
8. Vaddepally RK, Kharel P, Pandey R, Garje R, Chandra AB. Review of indications of FDA-approved immune checkpoint inhibitors per NCCN guidelines with the level of evidence. *Cancers*. 2020;12:738. https://doi.org/10.3390/cancers12030738.
9. Elia G, Ferrari SM, Galdiero MR, et al. New insight in endocrine-related adverse events associated to immune checkpoint blockade. *Best Pract Res Clin Endocrinol Metabol*. 2020;34:101370. https://doi.org/10.1016/j.beem.2019.101370.
10. Chiloiro S, Bianchi A, Giampietro A, Milardi D, De Marinis L, Pontecorvi A. The changing clinical spectrum of endocrine adverse events in cancer immunotherapy. *Trends Endocrinol Metabol*. 2022;33:87–104. https://doi.org/10.1016/j.tem.2021.10.009.
11. Joshi MN, Whitelaw BC, Palomar MT, Wu Y, Carroll PV. Immune checkpoint inhibitor-related hypophysitis and endocrine dysfunction: clinical review. *Clin Endocrinol*. 2016;85:331–339. https://doi.org/10.1111/cen.13063.
12. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science*. 2018;359:1350–1355. https://doi.org/10.1126/science.aar4060.
13. Liu Y, Zheng P. Preserving the CTLA-4 checkpoint for safer and more effective cancer immunotherapy. *Trends Pharmacol Sci*. 2020;41:4–12. https://doi.org/10.1016/j.tips.2019.11.003.
14. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science*. 1996;271:1734–1736. https://doi.org/10.1126/science.271.5256.1734.
15. Tang F, Du X, Liu M, Zheng P, Liu Y. Anti-CTLA-4 antibodies in cancer immunotherapy: selective depletion of intratumoral regulatory T cells or checkpoint blockade? *Cell Biosci*. 2018;8:30. https://doi.org/10.1186/s13578-018-0229-z.
16. Castinetti F, Albarel F, Archambeaud F, et al. French Endocrine Society Guidance on endocrine side effects of immunotherapy. *Endocr Relat Cancer*. 2019;26:G1–G18. https://doi.org/10.1530/ERC-18-0320.
17. Król A, Gawlik T, Jarząb B. Endocrine complications of cancer immunotherapy. *Endokrynol Pol*. 2018;69:722–733. https://doi.org/10.5603/EP.a2018.0073.
18. Byun DJ, Wolchok JD, Rosenberg LM, Girotra M. Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies. *Nat Rev Endocrinol*. 2017;13:195–207. https://doi.org/10.1038/nrendo.2016.205.
19. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol*. 2008;26:677–704. https://doi.org/10.1146/annurev.immunol.26.021607.090331.
20. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. *N Engl J Med*. 2016;375:1767–1778. https://doi.org/10.1056/NEJMra1514296.
21. Albarel F, Gaudy C, Castinetti F, et al. Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. *Eur J Endocrinol*. 2015;172:195–204. https://doi.org/10.1530/EJE-14-0845.
22. Ott PA, Hodi FS, Robert C. CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. *Clin Cancer Res*. 2013;19:5300–5309. https://doi.org/10.1158/1078-0432.CCR-13-0143.
23. Iglesias P. Cancer immunotherapy-induced endocrinopathies: clinical behavior and therapeutic approach. *Eur J Intern Med*. 2018;47:6–13. https://doi.org/10.1016/j.ejim.2017.08.019.
24. Shen R, Postow MA, Adamow M, et al. LAG-3 expression on peripheral blood cells identifies patients with poorer outcomes after immune checkpoint blockade. *Sci Transl Med*. 2021;13:eabf5107. https://doi.org/10.1126/scitranslmed.abf5107.
25. Zhao L, Cheng S, Fan L, Zhang B, Xu S. TIM-3: an update on immunotherapy. *Int Immunopharm*. 2021;99:107933. https://doi.org/10.1016/j.intimp.2021.107933.
26. Melaiu O, Lucarini V, Giovannoni R, Fruci D, Gemignani F. News on immune checkpoint inhibitors as immunotherapy strategies in adult and pediatric solid tumors. *Semin Cancer Biol*. 2022;79:18–43. https://doi.org/10.1016/j.semcancer.2020.07.001.
27. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the society for immunotherapy of cancer (SITC) toxicity management working group. *J Immunother Cancer*. 2017;5:95. https://doi.org/10.1186/s40425-017-0300-z.
28. Llovet JM, Castet F, Heikenwalder M, et al. Immunotherapies for hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2022;19:151–172. https://doi.org/10.1038/s41571-021-00573-2.
29. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711–723. https://doi.org/10.1056/NEJMoa1003466.
30. Kyi C, Postow MA. Immune checkpoint inhibitor combinations in solid tumors: opportunities and challenges. *Immunotherapy*. 2016;8:821–837. https://doi.org/10.2217/imt-2016-0002.
31. Jhunjhunwala S, Hammer C, Delamarre L. Antigen presentation in cancer: insights into tumour immunogenicity and immune evasion. *Nat Rev Cancer*. 2021;21:298–312. https://doi.org/10.1038/s41568-021-00339-z.
32. Esfahani K, Elkrief A, Calabrese C, et al. Moving towards personalized treatments of immune-related adverse events. *Nat Rev Clin Oncol*. 2020;17:504–515. https://doi.org/10.1038/s41571-020-0352-8.
33. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer*. 2016;54:139–148. https://doi.org/10.1016/j.ejca.2015.11.016.
34. Parlati L, Vallet-Pichard A, Batista R, et al. Incidence of grade 3–4 liver injury under immune checkpoints inhibitors: a retrospective study. *J Hepatol*. 2018;69:1396–1397. https://doi.org/10.1016/j.jhep.2018.08.014.
35. Ferrari SM, Fallahi P, Galetta F, Citi E, Benvenga S, Antonelli A. Thyroid disorders induced by checkpoint inhibitors. *Rev Endocr Metab Disord*. 2018;19:325–333. https://doi.org/10.1007/s11154-018-9463-2.
36. Atkinson M, Lansdown AJ. Endocrine immune-related adverse events: adrenal, parathyroid, diabetes insipidus, and lipoatrophy. *Best Pract Res Clin Endocrinol Metabol*. 2022;36:101635. https://doi.org/10.1016/j.beem.2022.101635.
37. 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;4:173–182. https://doi.org/10.1001/jamaoncol.2017.3064.
38. Chan KK, Bass AR. Autoimmune complications of immunotherapy: pathophysiology and management. *BMJ*. 2020;369:m736. https://doi.org/10.1136/bmj.m736.
39. Agrawal L, Bacal A, Jain S, et al. Immune checkpoint inhibitors and endocrine side effects, a narrative review. *Postgrad Med*. 2020;132:206–214. https://doi.org/10.1080/00325481.2019.1709344.
40. Presotto EM, Rastrelli G, Desideri I, et al. Endocrine toxicity in cancer patients treated with nivolumab or pembrolizumab: results of a large multicentre study. *J Endocrinol Invest*. 2020;43:337–345. https://doi.org/10.1007/s40618-019-01112-8.
41. Delivanis DA, Gustafson MP, Bornschlegl S, et al. Pembrolizumab-induced thyroiditis: comprehensive clinical review and insights into underlying involved mechanisms. *J Clin Endocrinol Metab*. 2017;102:2770–2780. https://doi.org/10.1210/jc.2017-00448.
42. Cukier P, Santini FC, Scaranti M, Hoff AO. Endocrine side effects of cancer immunotherapy. *Endocr Relat Cancer*. 2017;24:T331–T347. https://doi.org/10.1530/ERC-17-0358.
43. Orlov S, Salari F, Kashat L, Walfish PG. Induction of painless thyroiditis in patients receiving programmed death 1 receptor immunotherapy for metastatic malignancies.

J Clin Endocrinol Metab. 2015;100:1738–1741. https://doi.org/10.1210/jc.2014-4560.
44. Kotwal A, Kottschade L, Ryder M. PD-L1 inhibitor-induced thyroiditis is associated with better overall survival in cancer patients. *Thyroid*. 2020;30:177–184. https://doi.org/10.1089/thy.2019.0250.
45. Muir CA, Clifton-Bligh RJ, Long GV, et al. Thyroid immune-related adverse events following immune checkpoint inhibitor treatment. *J Clin Endocrinol Metab*. 2021;106:e3704–e3713. https://doi.org/10.1210/clinem/dgab263.
46. Torimoto K, Okada Y, Nakayamada S, Kubo S, Tanaka Y. Anti-PD-1 antibody therapy induces Hashimoto's disease with an increase in peripheral blood follicular helper T cells. *Thyroid*. 2017;27:1335–1336. https://doi.org/10.1089/thy.2017.0062.
47. de Filette J, Andreescu CE, Cools F, Bravenboer B, Velkeniers B. A systematic review and meta-analysis of endocrine-related adverse events associated with immune checkpoint inhibitors. *Horm Metab Res*. 2019;51:145–156. https://doi.org/10.1055/a-0843-3366.
48. Illouz F, Briet C, Cloix L, et al. Endocrine toxicity of immune checkpoint inhibitors: essential crosstalk between endocrinologists and oncologists. *Cancer Med*. 2017;6:1923–1929. https://doi.org/10.1002/cam4.1145.
49. Castinetti F. Thyroiditis and immune check point inhibitors: the post-marketing experience using the French National pharmacovigilance database. *Fundam Clin Pharmacol*. 2019;33:239–240. https://doi.org/10.1111/fcp.12453.
50. Mantia CM, Buchbinder EI. Immunotherapy toxicity. *Hematol Oncol Clin N Am*. 2019;33:275–290. https://doi.org/10.1016/j.hoc.2018.12.008.
51. Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol*. 2022;19:254–267. https://doi.org/10.1038/s41571-022-00600-w.
52. Chhabra N, Kennedy J. A review of cancer immunotherapy toxicity: immune checkpoint inhibitors. *J Med Toxicol*. 2021;17:411–424. https://doi.org/10.1007/s13181-021-00833-8.
53. Lee H, Hodi FS, Giobbie-Hurder A, et al. Characterization of thyroid disorders in patients receiving immune Checkpointm inhibition therapy. *Cancer Immunol Res*. 2017;5:1133–1140. https://doi.org/10.1158/2326-6066.CIR-17-0208.
54. Olsson-Brown A, Lord R, Sacco J, Wagg J, Coles M, Pirmohamed M. Two distinct clinical patterns of checkpoint inhibitor-induced thyroid dysfunction. *Endocr Connect*. 2020;9:318–325. https://doi.org/10.1530/EC-19-0473.
55. Kroiß M, Schilling B, Deutschbein T. Endocrine side effects of cancer immunotherapy (in German) *Dtsch Med Wochenschr*. 2020;145:1736–1741. https://doi.org/10.1055/a-1140-2920.
56. Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. *Sci Transl Med*. 2014;6:230ra45. https://doi.org/10.1126/scitranslmed.3008002.
57. Caturegli P, Di Dalmazi G, Lombardi M, et al. Hypophysitis secondary to cytotoxic T-lymphocyte-associated protein 4 blockade: insights into pathogenesis from an autopsy series. *Am J Pathol*. 2016;186:3225–3235. https://doi.org/10.1016/j.ajpath.2016.08.020.
58. Di Dalmazi G, Ippolito S, Lupi I, Caturegli P. Hypophysitis induced by immune checkpoint inhibitors: a 10-year assessment. *Expet Rev Endocrinol Metabol*. 2019;14:381–398. https://doi.org/10.1080/17446651.2019.1701434.
59. Lasocki A, Iravani A, Galligan A. The imaging of immunotherapy-related hypophysitis and other pituitary lesions in oncology patients. *Clin Radiol*. 2021;76:325–332. https://doi.org/10.1016/j.crad.2020.12.028.
60. Ferrari SM, Fallahi P, Elia G, et al. Autoimmune endocrine dysfunctions associated with cancer immunotherapies. *Int J Mol Sci*. 2019;20:2560. https://doi.org/10.3390/ijms20102560.
61. Bronstein Y, Ng CS, Hwu P, Hwu WJ. Radiologic manifestations of immune-related adverse events in patients with metastatic melanoma undergoing anti-CTLA-4 antibody therapy. *AJR Am J Roentgenol*. 2011;197:W992–W1000. https://doi.org/10.2214/AJR.10.6198.
62. Faje A. Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights. *Pituitary*. 2016;19:82–92. https://doi.org/10.1007/s11102-015-0671-4.
63. Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study. *J Clin Oncol*. 2017;35:2117–2124. https://doi.org/10.1200/JCO.2016.71.6795.
64. Massard C, Gordon MS, Sharma S, et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. *J Clin Oncol*. 2016;34:3119–3125. https://doi.org/10.1200/JCO.2016.67.9761.
65. Keir ME, Liang SC, Guleria I, et al. Tissue expression of PD-L1 mediates peripheral T cell tolerance. *J Exp Med*. 2006;203:883–895. https://doi.org/10.1084/jem.20051776.
66. Ansari MJ, Salama AD, Chitnis T, et al. The programmed death-1 (PD-1) pathway regulates autoimmune diabetes in nonobese diabetic (NOD) mice. *J Exp Med*. 2003;198:63–69. https://doi.org/10.1084/jem.20022125.
67. Tan CL, Kuchroo JR, Sage PT, et al. PD-1 restraint of regulatory T cell suppressive activity is critical for immune tolerance. *J Exp Med*. 2021;218:e20182232. https://doi.org/10.1084/jem.20182232.
68. Yoneda S, Imagawa A, Hosokawa Y, et al. T-lymphocyte infiltration to islets in the pancreas of a patient who developed type 1 diabetes after administration of immune checkpoint inhibitors. *Diabetes Care*. 2019;42:e116–e118. https://doi.org/10.2337/dc18-2518.
69. Wright JJ, Salem JE, Johnson DB, et al. Increased reporting of immune checkpoint inhibitor-associated diabetes. *Diabetes Care*. 2018;41:e150–e151. https://doi.org/10.2337/dc18-1465.
70. Stamatouli AM, Quandt Z, Perdigoto AL, et al. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. *Diabetes*. 2018;67:1471–1480. https://doi.org/10.2337/dbi18-0002.
71. Shiba M, Inaba H, Ariyasu H, et al. Fulminant type 1 diabetes mellitus accompanied by positive conversion of anti-insulin antibody after the administration of anti-CTLA-4 antibody following the discontinuation of anti-PD-1 antibody. *Intern Med*. 2018;57:2029–2034. https://doi.org/10.2169/internalmedicine.9518-17.