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Endocrine Dysfunctions Associated with the Use of Immune Checkpoint Inhibitors – A Brief Review

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Abstract

Immune checkpoint inhibitors (ICIs) are regarded as a break-through discovery and are used in regimens for treating patients with various malignancies, inducing activated T-cells to kill cancer cells; however, the safeguard autoimmune systems that are "checked and halted" in function before the use of ICIs, are re-activated after terminating the treatment. Thus, during the treatment course ICIs may stimulate and activate the development of various autoimmune disorders, mostly related to endocrine organs including the pituitary gland, thyroid gland, adrenal gland, and endocrine pancreas. The endocrine dysfunctions induced by ICI treatment include central adrenal insufficiency (AI) and central hypothyroidism related to hypophysitis of the adenohypophysis, primary hypothyroidism related to thyroiditis, and insulin-dependent diabetes mellitus (IDDM) caused by *β*-cell destruction in the endocrine pancreas. With the increasing use of ICIs, these immune-related adverse events have been observed as a prominent clinical entity that deserves clinical vigilance with respect to timely diagnosis and optimal treatment in addition to treating the underlying malignancies. These endocrine dysfunctions may not be readily diagnosed because of the insignificant clinical symptoms and signs presented. However, with such cases being increasingly recognized and reported, it would be prudent for physicians to regard these potential endocrine disorders as important in their daily practice when ICI-containing regimens are used. At any suspicion from vague clinical presentations, laboratory tests relevant to endocrine functions must be promptly performed to confirm a diagnosis. Treatment including measures of either replacement or suppression of disease characteristics should then be initiated and monitored regularly.

Key Words: Immune checkpoint inhibitors, hypophysitis, adrenal insufficiency, thyroiditis, insulin-dependent diabetes mellitus

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Introduction

Immune checkpoint inhibitors (ICIs) have been described as a breakthrough discovery in the treatment of solid organ malignancies since their approval by the US FDA in 2011. Their continuous triumph over previous anti-cancer regimens in the following years resulted in the two distinguished investigators, professors Tasuku Honjo and James Allison being awarded the 2018 Nobel Prize in Physiology or Medicine[1]. The mechanisms underlying this breakthrough success in the management of malignant diseases mainly involves the inhibition of checkpoint molecules on the surface of T-cells and, with such re-activation of the T-cell function, unleashing the apoptotic power of immune systems that were primarily meant to function as a normal defense system when in a checked status[2]. So far, the most intensely investigated molecules that function as immune checkpoints are cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed death-ligand 1 (PD-L1), among many different receptors on T-cells. For instance, PD-1 (or CD279) is a determinant in downregulating the immune system and promoting self-tolerance through suppression of T-cell inflammatory activity, thus acting to prevent autoimmune reactions. However, cancer cells can exploit these immune checkpoints to evade immune detection and thus escape elimination. By blocking these immune checkpoint molecules using monoclonal antibodies, the immune system can regain its anti-tumor immune responses by overcoming the ability of cancer cells to evade immune functions[3]. Currently, several ICIs have been approved by the US FDA, and these have revolutionized the management of solid organ malignancies including melanoma, non-small cell lung cancer, and renal cell carcinoma, with the gradual extension of clinical application to other systems including gastrointestinal tumors[4-8]. Although the outcomes of this new category of anticancer drugs are promising, ICIs target certain cellular molecules that regulate immune response as antitumor activity, requiring the use of these new immunity-modifying agents to be carefully monitored. This is because ICIs have been noted to accompany a new spectrum of adverse events caused by toxicities related to their mechanism of action, collectively referred as immune-related adverse events (irAEs), among which autoimmune endocrine dysfunction is rather prominent[9-11]. Cases have been increasingly recorded and analyzed systematically by attentive investigators who have observed the clinical presentations and performed relevant laboratory tests to confirm these diagnoses. Compared with a systematic review of case reports of ICI-related irAEs published in 2016 (data collected up to 2015) that included 84 cases of endocrine irAEs, a more recent study published in 2019 (data collected up to 2017) showed a five-fold increase in the case reports of endocrine irAEs (from 84 to 451)[12,13]. The pituitary and thyroid glands are the most common endocrine organs involved in both reports, with the incidence of dysfunction in both glands on the rise in the more recent report (hypophysitis: 49.1%, thyroid dysfunction: 33.7% in the 2019 report, with corresponding figures of 29.1% and 3.4%, respectively, in the 2016 report)[12,13]. The increased incidence of ICI-related endocrinopathies with time most likely reflects the wider use of ICI therapy in patients with cancer (e.g., more melanoma patients are now being treated with both classes of ICIs), especially as more cases of anti-PD-1-induced endocrinopathies have been reported after their approval in 2014. Notably, hypophysitis is the most frequent anti-CTLA-4-related irAE, whereas thyroid abnormalities are more frequently associated with anti-PD-1 therapy[14]. With the introduction of anti-PD-L1 drugs in 2016 and 2017, more cases of ICI-induced endocrinopathies are expected to be reported in the next few years[15].

The consequences of hypophysitis associ-

ated with ICIs include central adrenal insufficiency (AI), central hypothyroidism, and rarely, central hypogonadism. Diabetes insipidus (DI) is an entity that is even rare[16-17]. Autoimmune thyroiditis may mostly present as hypothyroidism in the long run[18]. Autoimmune injury to the endocrine pancreas has been reported to cause insulin-dependent diabetes mellitus (IDDM), with or without the presence of autoantibodies on diagnosis, and many cases of ketoacidosis as initial presentation[19]. These findings regarding the side effects of this novel class of anti-cancer regimens are worthy of clinical attention both from the aspects of investigational interest and clinical practice as the application of these regimens is expected to increase and to extend to various oncology fields over time. It would thus be prudent for clinicians to learn about the facts and clinical features of this emerging clinical entity to make a timely diagnosis and to design the optimal strategy of management for ameliorating any of the negative impacts on the general health of the patients by any potential endocrinopathy[11].

1. Epidemiology of endocrine dysfunctions associated with ICI therapy

To date, the incidence and prevalence of ICI-related endocrine dysfunction have been derived mostly from case series reports or retrospective reviews of medical records for subjects recruited in studies involving ICIs. There is a paucity of studies designed prospectively for this purpose[13,16,19,20-25].

The prevalence of endocrine dysfunctions caused by the use of ICIs differs according to the type of ICI used because of the different susceptibility of the endocrine glands targeted. For anti-CTLA-4, the respective prevalence of endocrine disorders is as follows: hypophysitis: 0-17% with ipilimumab, and 0.4-5% with tremelimumab; regardless of the type of anti-CTLA-4 used, secondary hypothyroidism: 4.3-11.0%, primary hypothyroidism: 5.2-5.9%; hyperthyroidism: 2%, and adrenalitis: < 2%. For anti-PD-1/anti PD-L1 the respective prevalence of endocrine disorders is as follows: hypophysitis: < 1%; hypothyroidism: 5.9%; hyperthyroidism 1.0-4.7%; adrenalitis: < 2%; and DM: 0-1%. Higher rates of secondary hypothyroidism, primary hypothyroidism, and hyperthyroidism have been registered in combination therapy compared to those in monotherapy[24].

2. Types of endocrine dysfunctions associated with ICI therapy

In a review article regarding the spectrum of ICI-induced endocrinopathies in patients with cancer, the authors summarized the available data obtained from 179 articles into five endocrine glands that are affected by 12 endocrinopathies as follows: (1) pituitary (hypopituitarism with multiple or isolated hormone deficiency, DI, and adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome); (2) thyroid (thyrotoxicosis due to Graves' disease or thyroiditis, and hypothyroidism due to primary hypothyroidism or preceded by thyrotoxicosis); (3) adrenal (primary AI); (4) pancreas (type 1 or rarely type 2 DM); and (5) parathyroid glands (primary hypoparathyroidism)[13].

2.1 Hypophysitis

Defined as inflammation of the pituitary gland and/or stalk, hypophysitis is a rare disorder in the general population with an estimated annual incidence of 1 in 7-9 million, accounting for approximately 0.4 % of the cases collected during pituitary surgeries[26]. With the expanding use of ICIs in cancer therapy, hypophysitis associated with these immune-modifying agents has gained wider and increasing clinical attention regarding its epidemiology, underlying pathophysiology, and management. Acute hypophysitis caused by ICIs may result in hypopituitarism that presents with central AI, central hypothyroidism, and hypogonadotropic hypogonadism. The incidence of hypophysitis associated with the

use of ICIs varies with the category used. For ipilimumab (a CTLA-4 inhibitor), it has been observed to be as high as 17%, whereas for nivolumab or pembrolizumab (PD-1 inhibitors), the figure was significantly lower at < 1% for both drugs. Combination of ICI regimens (specifically ipilimumab and nivolumab) increases the risk of hypophysitis[23]. The risk factors for ipilimumab-induced hypophysitis include older age and male sex, with the latter being at 2-5 times higher risk compared to their female counterparts. ICI-related hypophysitis can develop soon after treatment initiation or as late as 6 months after immunotherapy is stopped[20,27].

In the aforementioned review article on the spectrum of ICI-induced endocrinopathies, patients suffering from hypophysitis with anterior hypopituitarism had a median onset of clinical presentation of 12 weeks (range: 3-76 weeks) after the initiation of ICIs. The symptoms reflected deficiency of the relevant hormone(s), with or without the mass effect caused by pituitary enlargement (e.g., headache). Among the 222 cases of hypopituitarism identified among the total cohort including 451 cases of ICI-induced endocrinopathies, hormonal profiles revealed that 82% (183/222) showed low ACTH/cortisol levels; 77% (172/222) had low thyroid-stimulating hormone (TSH)/free thyroxine (FT4)/free triiodothyronine (FT3); 62% (137/222) had low luteinizing hormone (LH)/follicular stimulating hormone (FSH)/testosterone (T)/estradiol; 10% (22/222) showed hypoprolactinemia; 10% (22/222) showed low growth hormone/insulin-like growth factor-1 (IGF-1); and 1% (2/222) showed higher TSH but lower FT4/FT3 levels. These profiles implied that the deficiency of hormones may be multiple and not limited to an isolated hormone [13]. However, hyperprolactinemia and central DI have been rarely reported.

In ICI-induced central hypothyroidism, characteristic findings on thyroid function profile include low FT4 levels and low or inappropriately normal TSH levels compared to the pre-treatment levels[28].

The occurrence of hypogonadotropic hypogonadism induced by ICIs has rarely been comprehensively assessed in clinical trials. However, the assessment of gonadal function in reproductive-age subjects undergoing ICI therapy should not be overlooked because cancer incidence in young adults has also been increasing; thus, more individuals of reproductive age will be exposed to ICIs, and need to be informed about the potential of gonadal toxicity, and the relevant strategies needed to be considered in advance when fertility is a concern[29].

Causes of hyperprolactinemia may include pituitary stalk inflammation or compression with the disruption of inhibitory hypothalamic signals, or a concomitant hypothalamic inflammation that leads to reduced dopamine synthesis. A prolactin level test should thus be performed for the differential diagnosis of central hypogonadism[30].

ICI-induced central DI was rarely found in the cases reported[17,28,31]. The clinical symptoms of DI include nocturia, polydipsia, polyuria, and lethargy and its diagnosis can be aided by laboratory findings including hypernatremia and diluted urine, and can be further confirmed by a water deprivation test when the patient's general health condition allows. However, as metastases to the pituitary gland are found to have a predilection for the posterior pituitary, a differential diagnosis must be made against ICI-induced DI; therefore, the presence of DI may help differentiate hypophysitis from metastatic lesions[32].

In a case series collected from a single tertiary medical center reported in Taiwan, seven cases of immune-mediated hypophysitis were retrospectively identified in patients who were diagnosed with various types of advanced and/or metastatic cancers (lung adenocarcinoma, urothelial carcinoma, melanoma, peri-ampullary adenocarcinoma of the common bile duct, cervical squamous cell carcinoma, and lung sarcomatoid carcinoma) and

had received different regimens of ICIs (including anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-1-based combination therapies). All seven patients were diagnosed with central AI, and four of them had additional primary hypothyroidism. Hormone replacements were prescribed according to the respective pituitary dysfunction immediately after diagnosis, except in one patient who was diagnosed with subclinical hypothyroidism and no supplement was prescribed. The time of onset after initiation of immunotherapy ranged from 5 to 36 weeks. Clinically, only one patient presented with headache as the initial symptom, whereas the others had nonspecific symptoms at the time of diagnosis (poor appetite, general fatigue, or weight loss). No hormonal recovery was documented after the diagnosis of hypophysitis during follow-up, and all patients had to be kept on hormonal replacement therapy, except for one patient with AI who had discontinued hormonal replacement after 3 months but unfortunately died 3 months later; this occurrence may thus make the evaluation of hormone recovery inconclusive in this case series[25]. In a nationwide retrospective study that described the characteristics of hypophysitis reported in the French Pharmacovigilance database, all cases of ICI-related hypophysitis that were requested to be registered in the database before May 2018 were analyzed. Among the 249 cases identified as endocrine disorders associated with ipilimumab, nivolumab, or pembrolizumab, a total of 94 cases (F/M = 49/45) with pituitary gland involvement were selected for further analysis. Among this cohort, ipilimumab alone or in combination was the most prescribed ICI (56%). The mean time of onset was significantly shorter with ipilimumab or in combination with nivolumab (83 days; 14-506 days) than that with nivolumab or pembrolizumab treatment alone (165 days; 5-686 days; p = 0.0001). Clinical symptoms were present in most of the study subjects (88%), mainly with fatigue and headache. The majority of pituitary dysfunction (90%) was diagnosed as corticotropic deficiency, whereas thyroid and/or gonadotropin deficiency was diagnosed in 21% and 1%, respectively. Five patients (8%) had pan-hypopituitarism. None of the patients were diagnosed with DI. Hydrocortisone supplementation was administered to 85 patients (90.4%) and levothyroxine was administered to 20 patients (21.3%). None of the patients were weaned from hormonal supplementation according to the last available information, except for one male patient who had received short-term hydrocortisone treatment and thereafter displayed a normal ACTH stimulation test result. Pituitary MRI was available for 40 patients and showed features of hypophysitis in 50% of the cases. From the medical records reviewed, none of the patients in this large study cohort had a history of previous immune disease; the authors thus concluded that the development of hypophysitis is not triggered by a pre-existing immune condition[16].

The clinical symptoms of hypophysitis are mostly subtle and nonspecific, as has been stated in the aforementioned case series, with fatigue (59%-73%) and headache (32%-87%) being most commonly encountered symptoms among others including hypotension, nausea, confusion, amenorrhea, and sexual dysfunction, depending on the impaired endocrine function. Headache is caused by the mass effect from inflamed and enlarged glands, whereas fatigue may be caused by endocrine dysfunction, especially from AI. As the degree of pituitary enlargement is typically mild, compression of the optic apparatus with impaired visual field, as encountered in conventional hypophysitis, is very rare. DI is rare compared to that with anterior pituitary dysfunction, but symptoms suggesting this serious endocrine disorder (nocturia, polydipsia, and polyuria) should prompt suspicion for timely treatment[17, 31]. The mechanisms by which anti-CTLA-4 causes hypophysitis have been studied in murine models and in autopsy specimens from human

pituitary glands. In the human pituitary, CTLA-4 antigen is expressed by pituitary endocrine cells in all patients, although at different levels. Higher levels were found in patients showing clinical and pathological evidence of severe hypophysitis. This high pituitary CTLA-4 expression was associated with T-cell infiltration and IgG-dependent complement fixation, phagocytosis, and immune reactions that induced extensive destruction of the adenohypophyseal architecture. These findings suggest that administration of CTLA-4 blocking antibodies to patients who express high levels of CTLA-4 antigen in the pituitary can cause an aggressive (necrotizing) form of hypophysitis through type IV (T-cell-dependent) and type II (IgG-dependent) immune mechanisms[21, 22].

2.1.1 Treatment of hypophysitis

Management of ICI-induced hypophysitis primarily involves replacement of deficient hormones. In severe cases, treating hypophysitis with high-dose glucocorticoids with at least temporary discontinuation of ipilimumab may also be required. The use of high-dose systemic steroids in patients with severe forms (grade 3 or 4, according to toxicity grading of ICI-induced hypophysitis by Common Terminology Criteria for Adverse Events [CTCAE])[33] (Table) of ipilimumab-induced hypophysitis has been reported. A short course of high-dose steroids (prednisone at a dose of 1-2 mg/kg/day) per os may resolve acute symptoms and improve pituitary function. The dose can then be tapered to a physiological replacement dose of hydrocortisone or prednisolone[20,34,35]. Improvement of pituitary function has been observed in some patients following the resolution of hypophysitis, with thyroidal and gonadal axis normalization occurring more frequently compared to adrenal normalization[26,36]. However, there are no compelling data to support this management approach, as there is no prospective study comparing normal replacement versus high-dose glucocorticoids (HDG) in patients with ICI-induced hypophysitis; further, retrospective studies have shown that the use of high-dose steroids did not alter the disease course[37]. Furthermore, in a recent study conducted in 98 patients with ipilimumab-induced hypophysitis that had compared the outcomes between low-dose (LD, defined as a maximum average daily dose of 7.5 mg prednisone or equivalent during the initial 2 months after the diagnosis of hypophysitis) and high-dose (HD, prednisone doses above this average dose level) glucocorticoid administration, the radiologic and endocrine outcomes and symptom resolution did not differ between the two groups, whereas progression-free survival improved significantly in the LD group versus the HD group (hazard ratio, 0.36; 95% confidence interval [CI], 0.14-0.77; p = 0.007). The median progression-free survival was 35.0 months (95% CI, 14.4-77.8 months) and 4.9 months (95% CI, 3.4-9.1 months) in the LD and HD

Table. Common Terminology Criteria for Adverse Events* on hypophysitis**

Grading	Grade 1	Grade 2	Grade 3	Grade 4	Grade5
Description	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL***.	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL***.	Life-threatening consequences; urgent intervention indicated.	Death.

* CTCAE v5.0 – November 27, 2017 (ref. 33).
**Definition: A disorder characterized by inflammation and cellular infiltration of the pituitary gland.
*** activities of daily living.
(adopted and modified from ref. 33).

groups, respectively[38]. Hence, according to recent guidelines, it is recommended that treatment with HDG be reserved for cases with significant hyponatremia, severe headaches, visual aberrations, or other autoimmune side effects that justify its use[39,40]. When doing so, ICI therapy may be discontinued first, followed by administration of high-dose glucocorticoids therapy[27].

2.1.2 Diagnosis and treatment of adrenal insufficiency associated with hypophysitis

Clinical features presenting with hypotension, postural hypotension, vomiting, fever, confusion/delirium, hyponatremia/hyperkalemia/hypoglycemia, acute kidney injury, and hypovolemic shock should raise concerns of adrenal crisis, which requires emergent management[41]. In addition to a hormonal profile consisting of both low serum cortisol and ACTH levels in hypophysitis-related AI, the diagnosis could be further confirmed by a standard corticotropin 1-24 (0.25 mg, intravenously) stimulation test[42]. Further dynamic tests with corticotropin-releasing hormone would show the absence of ACTH and cortisol response[43,44]. In a retrospective study carried out in a cohort of 168 patients who had received anti-PD-1 therapy alone or in combination with anti-CTLA-4, 3% (5/168) of the patients who had developed AI had all received PD-1 inhibitors. The investigators observed that the presence of eosinophilia in peripheral blood could be considered an early indicator of ACTH deficiency during PD-1 inhibitor treatment. Eosinophilia (> 500/μL) was present in four cases at the onset of symptoms, and in three of them, it was observed even more than a month before the onset of symptoms. As no specific symptoms exist for AI, and frequent assessment of ACTH and cortisol levels is not as feasible as a routine test for peripheral blood cell counts and its differentiation in daily clinical practice, the authors concluded that eosinophilia, which appeared prior to the onset of clinical symptoms, may be used as an early predictive marker of AI[45]. There were also cases of late development of central AI after discontinuation of nivolumab for 4-6 months, presenting with clinical features of fatigue, appetite loss, and diarrhea, as well as laboratory findings of eosinophilia. The ratio of eosinophil counts dropped significantly after the introduction of hydrocortisone therapy[46]. Previous studies have shown an inverse relationship between adrenal activity and the level of circulating eosinophil counts[47]; treatment with dexamethasone could induce eosinophil apoptosis and, potently inhibit neutrophil apoptosis[48].

Early recognition of hypophysitis and subsequent ACTH deficiency is crucial because it is a potentially life-threatening but remediable disorder caused by steroid replacement therapy when administered promptly. However, most cases of AI do not recover and require continual supplementation of steroid hormone even after the ICIs are discontinued[20,49]. Nevertheless, rare cases have reported a gradual recovery from AI that developed after either single use of ipilimumab, or after combination therapy with nivolumab. In such cases, steroid supplementation was required for the first diagnosis of hypophysitis and AI. Periodic and regular follow-up (every 3 months) for up to one year is thus recommended to confirm the hormonal status, with a decision regarding whether the supplement therapy should be administered continuously[20,50,51].

Management of ICI-induced hypophysitis with AI can be currently found in the US prescribing information for ipilimumab. For patients with symptoms of AI, it is recommended that CTLA-4 inhibitor treatment be withheld and glucocorticoid therapy be started at a dose of 1-2 mg/kg of prednisone or equivalent. The ICI can be resumed in patients with complete or partial resolution of adverse reactions (grade 0 to 1, according to the toxicity grade of ICI-induced hypophysitis based on the Common Terminology Criteria for Adverse Events)[33] and in those receiving less than 7.5 mg prednisone or equiva-

lent per day. However, if the symptoms persist for 6 weeks or longer, or if the dose cannot be reduced to 7.5 mg prednisone or equivalent per day, the ICI should be discontinued permanently[52].

2.2 Primary adrenal insufficiency

Primary AI associated with the use of ICIs is encountered infrequently and has only appeared in case reports or case series. Nevertheless, due to its severity and mortality if not promptly recognized and treated, primary AI is a clinical entity that needs to be studied based on its rare case reports[53]. Both anti-CTLA-4 and anti-PD-1/PD-L1 agents have been implicated in the development of primary AI, and most of the reported cases were from melanoma patients treated with nivolumab, ipilimumab, or pembrolizumab[54-56]. In a study conducted using data obtained from VigiBase (the World Health Organization's pharmacovigilance database of individual case safety reports) to identify and characterize the main features of primary AI among irAEs, the results showed that, from a total of 50,108 irAEs reported during September 2008-October 2018, 451 cases of primary AI were identified. Among these, 45 cases were diagnosed as "definite primary AI" and 406 were "possible primary AI." No differences in clinical or demographic characteristics and outcomes could be identified between the "definite" versus "possible" group. The patients were mainly male (58.1%) with a median age of 66 years (range: 30-95). The indications of ICI were predominantly for melanoma (41.2%) and lung cancer (28.6%). Most patients were treated with ICI monotherapy (nivolumab, 44.3%; pembrolizumab, 11.7%; ipilimumab, 23.6%), whereas 17.9% received ICI combination therapy. The onset of events occurred with a median time of 120 days (range: 6-576). A notable finding from this database is that ICI-associated primary AI was associated with significant morbidity (≥ 90% severe) and even mortality (7.3%). Although ICI-associated primary AI is a rare adverse event from this largest report, early recognition is still critical to implement corticosteroid treatment for minimizing the potential poor outcomes of morbidity and mortality[57].

The clinical signs and symptoms of primary AI may manifest as fatigue, weight loss, orthostatic hypotension, and anorexia in mild cases, and as syncope, hypotension, and impaired consciousness in severe cases. Laboratory tests are required for a definite diagnosis when low morning cortisol levels and concomitantly high ACTH levels are found. Hyponatremia and hyperkalemia may add to the strength of the diagnosis when clinical features are strongly suggestive. The ACTH stimulation test can help confirm the diagnosis[58].

The clinical presentations of central AI would not differ much from those in primary AI, but laboratory tests may show normal serum potassium levels that may differ from the hypokalemia encountered in 50% of the patients with primary AI, as the aldosterone level in patients with central AI is preserved and does not cause loss of potassium. This is also true for the need of additional mineralocorticoid replacement in patients with primary AI to restore normal electrolyte balance between sodium and potassium[59].

2.3 Thyroid dysfunctions

Among the dysfunctions of a solitary endocrine gland, thyroid dysfunction ranks second to hypophysitis-associated hypopituitarism related to the use of ICIs, with decreasing frequency in clinical presentations from thyroiditis, transition from thyrotoxicosis to hypothyroidism, primary hypothyroidism, and Graves' hyperthyroidism. Based on multiple studies, the rates of hypothyroidism vary between 3-22%, and those for thyrotoxicosis vary between 1-11%[60]. However, when subclinical forms of dysfunction (hypothyroidism or hyperthyroidism) are included in the analysis, the rate can reach 28% and 22%, respectively, totaling as high as 50%

[61]. The frequency of thyroid dysfunction has been noted to be higher in more recent reports, implying an improvement in screening of hormonal profiles during anti-cancer therapy[62-66].

The risk of hypothyroidism was found to be higher with anti-PD-1 treatments than with anti-CTLA-4, and was even higher when both agents were used in combination[67]. In a recent meta-analysis of 38 randomized trials that included 7,551 patients, the risk was verified to be higher for anti-PD-1 treatments than for anti-CTLA-4, independent of the tumor type. Furthermore, the risk of thyroid dysfunction was also found to be higher in regimens combining anti-PD-1 and anti-CTLA-4 than in either monotherapy, a phenomenon that is also true for hypophysitis. On the contrary, no statistical inferences could be made from primary AI and IDDM because of the small number of events included in this meta-analysis[68].

The pathophysiology of thyroid dysfunction under ICI treatments is not fully understood, but has been considered to mainly involve silent inflammatory thyroiditis, which in turn involves T-cell cytotoxicity. Thyroiditis is often diagnosed in the phase of thyrotoxicosis, which is often transient, or during phases of subclinical or clinical hypothyroidism, with characteristics closer to those of postpartum silent thyroiditis rather than those of the more common autoimmune thyroiditis, which involves cytotoxicity caused by the presence of anti-thyroid antibodies (e.g., Hashimoto thyroiditis)[69,70].

In a study that analyzed five consecutive patients who were diagnosed with thyroid dysfunction, associated with nivolumab therapy, further examination of PD-L1 and PD-L2 mRNA and protein expression using reverse transcription polymerase chain reaction and western blotting methods, respectively revealed their presence in normal thyroid tissue[71]. These findings may also explain the higher rates of thyroid dysfunction induced by the anti-PD-1 regimen[60].

A recent study with data obtained from a retrospective review of electronic medical records with the aim of finding the incidence of and mechanisms underlying thyroiditis induced by ICI (pembrolizumab, a PD-1 inhibitor, in this study) found that among the cohort of 93 patients with advanced cancer (ages 24 to 82 years; 60% males) who had received at least one infusion of pembrolizumab, 13 (14%) showed abnormal thyroid function test results following initiation of pembrolizumab with a median follow-up of 8 months (range: 3-41). Twelve of these 13 patients had metastatic malignant melanoma and one non-small cell lung carcinoma. Thyroiditis (defined by the presence of a suppressed TSH level [< 0.3 mIU/L] but normal or elevated FT4 or T3 that spontaneously resolved or progressed to overt hypothyroidism) occurred in seven of the thirteen patients (54%). New onset of hypothyroidism (overt or subclinical, defined by an elevated TSH > 10 mIU/L with or without low FT4 and an elevated TSH (between 4.2 and 10 mIU/L) with normal serum FT4, respectively) was observed in three patients. Anti-thyroid peroxidase autoantibodies were positive only in a minority of the patients (4/13 [31%]). The 18-fludeoxyglucose PET/CT scan performed at some point during oncologic surveillance showed a diffuse increase of thyroid gland uptake in the majority (7/11 [64%]) of patients. Further investigation into the mechanism underlying thyroiditis development showed that there were more circulating CD56+CD16+ natural killer cells and elevated HLA-DR surface expression in the inflammatory intermediate CD14+CD16+ monocytes in anti-PD-1-treated patients; these pathways indicate a destructive process occurring in the thyroid gland, independent of thyroid auto-antibodies[72].

Both anti-PD-1/PD-L1 have gained increasing interest with respect to the diagnosis, prognosis, and management of autoimmune thyroid disease and cancer[73]. In a study that screened the frequency of PD-L1 expression using a rabbit monoclonal anti-

body (clone SP142) in a large cohort of 407 patients with primary thyroid cancer, the authors found that tumoral PD-L1 was expressed in 6.1% of papillary thyroid carcinomas, 7.6% of follicular thyroid carcinomas, and 22.2% of anaplastic thyroid carcinomas, with the distribution of PD-L1 positivity differing with the histological type of the cancer ($p < 0.001$). The authors concluded that with the findings of high PD-L1 expression in a subset of patients with advanced thyroid cancer (e.g., follicular and anaplastic thyroid carcinoma), identification of PD-L1 expression may have direct therapeutic relevance for patients with thyroid cancer refractory to other conventional therapeutics[74].

Although the clinical features of thyrotoxicosis usually precede the development of secondary hypothyroidism as the presentation of biphasic thyroiditis induced by ICI therapy, Graves' disease (GD) caused by ICIs due to the stimulating activity of TSH-receptor autoantibodies (TRAb) has been rarely reported[75]. Initial presentations of clinical features and thyroid hormone profiles may not be easily discernible between thyroiditis and GD, but can be differentiated using further tests for thyrotropin receptor antibody or thyroid-stimulating immunoglobulins, both of which are mostly positive in GD[76,77]. Scintigraphy of the thyroid gland uptake ratio can also be applied because a higher uptake than normal would be found in GD. Differential diagnosis is important for determining the treatment modality, as thyrotoxicosis from thyroiditis is mostly a transient presentation and no anti-thyroid medication is required; instead, thyroxine replacement may be required in the follow-up period when hypothyroidism develops and diagnosis is confirmed. During or after the use of ICIs, hypothyroidism may develop as a primary form or may be preceded by transient hyperthyroidism.

For the treatment of thyroid dysfunction induced by ICIs, clinical guidelines recommend glucocorticoid therapy for patients with grade 3 to 4 toxicity, and when severe symptoms or concern for thyroid storm are present (prednisone 1-2 mg/kg/day or equivalent, tapered over 1 to 2 weeks), with the aim of minimizing the inflammatory reactions of the endocrine organ and preserving its normal function after the episode[78]. Given that the clinical course of ICI-induced thyroid disorder mostly follows that characterized by thyroiditis[79] and that HDG treatment has been found to be effective in early clinical remission and shows a protective effect against permanent hypothyroidism in subacute thyroiditis[80], it would be rational to administer HDG in ICI-induced thyroid disorders to reduce its high risk of progressing to permanent hypothyroidism. The clinical course and outcomes of thyroid function in 53 patients who were treated with various ICIs (anti-PD-1 and anti-CTLA-4, alone or in combination) were retrospectively examined and compared between those who had received HDG therapy (n = 15) or not (n = 38). HDG was administered in different modalities pertaining to daily doses/treatment and tapering duration as follows: prednisone (30-260 mg/2-46 weeks), dexamethasone (2-36 mg/9 days-55 weeks), methylprednisolone (40-260 mg/1 day-8 days), or hydrocortisone (50-150 mg/1 day-2 weeks), alone or in various combinations or sequences of administration. The results showed no significant differences between the HDG and non-HDG groups in terms of the median duration of thyrotoxicosis: 28 (range, 7-85) *vs.* 42 (range, 14-273) days, the median time to conversion from thyrotoxicosis to hypothyroidism: 39 days (range, 14-169) *vs.* 42 days (range, 14-315) days, and the median time to onset of hypothyroidism: 63 (range, 21-190) *vs.* 63 (range, 14-489) days. Consistent with previous work, most ICI-related thyroid disorders followed the typical time course of thyroiditis in this study, and 96% of the patients developed hypothyroidism. In patients who needed levothyroxine supplementation, the median maintenance dose did not differ regardless of HDG treatment (1.5 [range, 0.4-

2.3] mg/kg/day *vs.* 1.3 [range, 0.3-2.5]). From this study, the authors concluded that HDG treatment did not alter the course of revolution or improve the outcome of ICI-induced thyroid disorders, and indicated that routine use of HDG in patients with ICI-induced thyroid disorders is not recommended[81].

Supplementation of levothyroxine for hypothyroidism depends on the degree of TSH elevation and severity of symptoms. When the serum TSH level is < 10 mIU/L and the patient is asymptomatic, ICIs can be continued with close follow-up monitoring of TSH and FT4 levels at 4-6-week intervals. In patients who are symptomatic with any degree of TSH elevation, or in asymptomatic patients with TSH levels that are persistently > 10 mIU/L, thyroid hormone supplementation should be started at a dose of approximately 1.6 μg/kg body weight/day in patients without underlying cardiovascular disease. For patients who are elderly or fragile, or with multiple comorbidities, the dose should start low at 25-50 μg/day with gradual titration according to the hormonal profile monitored every 4-6 weeks apart. Notably, adrenal dysfunction, when present, should always be replaced before thyroid hormone therapy is initiated to avoid adrenal crisis[82]. Thionamides as anti-thyroid drugs should be reserved until the diagnosis of GD is firmly established because of a higher rate of clinical features of thyrotoxicosis and a thyroid hormonal profile of transient thyroiditis that may mimic those in Graves' hyperthyroidism[78].

2.4 Insulin-dependent diabetes mellitus

Among the irAEs associated with ICIs, new-onset diabetes (NOD) has gained increasing attention as an emerging side effect as the use of ICIs has increased. New onset of IDDM is estimated to occur in 0.2-1.0% of patients treated with ICIs[68,83,84]. In a study that reviewed the electronic health records of patients treated with ICIs over the same 6-year period (2012-2018) at two academic institutions (Yale New Haven Hospital, and University of California, San Francisco Medical Center), 27 cases of IDDM were identified in a total of 2,960 patients who had received ICI therapy, with a prevalence of approximately 0.9% (27/2,960). Fifty-nine percent of these patients (16/27) presented with DKA, an average glucose level of 653 mg/dL (range: 240-1,765) and an average HbA1c of 7.95% (range: 6.0-10.5%) at diagnosis, suggesting that some degree of hyperglycemia had been present prior to the acute presentation of hyperglycemia or DKA. In 85% (23/27) of the subjects, there was significant loss of β-cell function evidenced by the acute progression from normoglycemia to hyperglycemia in the presence of low (1.1 ng/mL; reference range: 1.1-4.4 ng/mL) or undetectable levels of random C-peptide levels at diagnosis. Other biochemical tests showed elevated levels of lipase and/or amylase (2- to >10-fold above the upper limit of normal) in 32% of the patients on the day of diagnosis. An immunological study found that in 25 patients tested, at least one autoantibody was positive in 40% (10/25), and two or more autoantibodies were positive in 21% (5/24) of the cases. Patients with any positive autoantibody characteristic of type 1 DM (T1DM) (autoantibodies to glutamate decarboxylase, islet antigen-2, insulin, or zinc transporter-8) developed ICI-induced diabetes after fewer cycles than those without autoantibodies. Surveys on other endocrine functions revealed that 44% (12/27) had endocrine irAEs prior to or concurrent with the development of diabetes. The majority (11/12) had primary thyroid dysfunction that presented as hypothyroidism or thyroiditis (thyrotoxicosis followed by hypothyroidism)[83].

The trends in reporting NOD associated with ICIs were analyzed in a study using a database obtained from VigiBase, the World Health Organization's database of individual case safety reports[85]. In total of 283 cases of NOD between 2014 and April 2018 were identified following treatment with ICIs. The authors found that there was a marked increase in the reporting of ICI-related NOD over this period,

with over 50% of cases reported in 2017. The onset of DM ranged from 5 to 790 days after the first dose of ICI (median, 116 days; interquartile range: 58-207.5, n = 91). Over half of the patients (50.2%) presented with DKA at the time of NOD diagnosis. Most cases occurred in individuals treated with anti-PD-1 monotherapy (52.7% nivolumab, 23.3% pembrolizumab), whereas only a small fraction was observed in patients treated with anti-PD-L1 monotherapy (1.4% each for atezolizumab and durvalumab). Seventeen percent of NOD cases were treated with dual therapy, with either anti-PD-1 or anti-PD-L1 plus anti-CTLA4 (ipilimumab)[86]. The increasing trend could be attributable to the increased use of anti-PD-1 and anti-PD-L1 therapies across cancers or to the differences in patient populations recruited between clinical trials and those treated in clinical practice[84].

To understand the timing and factors associated with anti-PD-1/anti-PD-L1-induced T1DM, a systematic review and meta-analysis was conducted by searching the MEDLINE, EMBASE, SCOPUS, and Cochrane databases (August 2000-2018) for studies with any design including ICIs. A total of 71 cases (F/M = 45/55%) were retrieved and reviewed out of 56 publications, after the cases of pre-existing DM diagnosis were excluded. The mean ± SD age at diabetes presentation was 61.7 ± 12.2 years. Melanoma (53.5%) was the most frequent cancer, followed by lung cancer (26.8%). The most frequently used ICIs were PD-1 inhibitors (nivolumab and pembrolizumab) in 90% of the cases, whereas the remaining 10% included PD-L1 inhibitors (atezolizumab, avelumab, or durvalumab). The median time to diabetes onset was 49 (range: 5-448) days, and 71% of the patients developed new-onset T1DM within 3 months after the first exposure to anti-PD-1/PD-L1 treatment. None of the cases were associated with the use of ipilimumab (a CTLA-4 inhibitor) as a single agent. DKA was initially presented in 76% of the cases. The mean ± SD HbA1c concentration was 7.84 ± 1.0% at presentation. In the 55 cases in which C-peptide was measured, the levels either undetectable or inappropriately low for the ambient blood glucose concentrations observed. All patients required continuous exogenous insulin therapy throughout the course of follow-up, and none could be weaned from therapy. Half of the cases had autoantibodies associated with T1DM at onset, with anti-GAD being the most frequent. Patients with antibodies showed a more rapid onset (55 *vs.* 117 days [95% CI, 33.25-76.75 vs 78.03-155.51]; $p = 0.005$) and a higher incidence of DKA (30/35 [86%] *vs.* 18/30 [60%]; $p = 0.02$) than that in subjects without antibodies. It is unclear from this analysis whether these antibodies could have preceded the start of ICI therapy or only developed after exposure to ICIs, even though pre-existing antibodies such as anti-GAD (an IgG isotype involved in memory immune responses) before anti-PD-1 treatment have been reported to contribute to the abrupt onset of DKA in another study[84,87].

In a more recently published study that examined the electronic medical records in a single tertiary medical center spanning the years 2013-2018, 5 (0.38%) patients were identified as having T1DM out of the 1,327 patients who had received anti-PD1 or anti-CTLA-4 therapy. Four of these five patients were newly diagnosed with diabetes, whereas the fifth patient had a former diagnosis of type 2 DM but was later diagnosed with immunotherapy-induced T1DM after testing positive for autoantibodies against both GAD and islet antigen. All patients with diabetes were treated with anti-PD-1 therapy (nivolumab or pembrolizumab). Four patients presented with DKA and a high HbA1c level of 9.1% at the time of diagnosis. Although C-peptide levels were not assessed at disease onset or during progression, patients presented typical clinical features of DKA with polyuria, polydipsia, abdominal pain, nausea, and emesis, as well as laboratory profiles supporting the diagnosis of DKA. The time from the

first cycle of immunotherapy to subsequent DKA occurrence varied from 20 to 972 days. Two patients who tested positive for GAD antibodies presented with DKA at 20 and 106 days, respectively, from the first anti-PD-1 administration, whereas the other two who were autoantibody negative developed DKA more than a year later. The presence of GAD autoantibodies could lead to an earlier onset of diabetes. Additional endocrinopathies diagnosed along with T1DM included AI in one patient and hypothyroidism in another[88].

2.5 Other rare endocrinopathies

Rare cases have been reported for primary AI[53], ACTH-dependent Cushing's syndrome[89], and hypoparathyroidism[90], during or after the use of ICIs in various malignancies. Clinical features as well as laboratory chemistry are required for timely diagnosis and treatment.

3. Conclusion

With the breakthrough success of immune checkpoint inhibitors applied to the treatment of various malignancies in the past decade, a new spectrum of side effects brought about by these novel anti-cancer agents due to immune function alterations has emerged and termed as immune-related adverse events. These multi-faceted side effects include endocrine organs such as the pituitary gland, thyroid gland, and endocrine pancreas. Hypophysitis may cause central adrenal insufficiency and central hypothyroidism; further, thyroiditis may cause hypothyroidism in the long run in most affected subjects. Among subjects with evidence of autoimmune injury to the pancreatic β-cells, half may develop insulin-dependent diabetes mellitus.

In patients treated with monotherapy, the incidence of hypophysitis is higher with anti-CTLA-4 therapy, whereas thyroid dysfunction occurs more frequently in patients receiving anti-PD-1 agents. Combination therapy results in significantly higher adverse events than those with monotherapy alone.

The clinical features of adrenal insufficiency may be vague and non-specific, but high clinical vigilance is needed along with the applied laboratory tests for a proper diagnosis. When confirmed, adrenal insufficiency must be promptly treated with glucocorticoid therapy to regain the general well-being of patients. When hypothyroidism is present (central or primary), thyroid hormone supplementation must be preceded by glucocorticoid therapy to avoid adrenal crisis. Insulin-dependent diabetes mellitus may present abruptly as severe hyperglycemia or DKA. Most of the patients have been found to have low C-peptide levels, and insulin therapy needs to be introduced immediately, and needs to be continued for long-term glycemic control.

As the indications for ICIs expand, irAE events are expected to increase. Clinicians in multiple subspecialties encompassing oncology, endocrinology, and emergency medicine should thus be vigilant regarding these ICI-induced endocrinopathies for providing timely diagnosis and treatment.

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免疫檢查點抑制劑引起之內分泌功能異常-簡短文獻回顧

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摘　要

在癌症治療的藥物發展史中，免疫檢查點抑制劑的發明堪稱具突破性的里程碑，自第一個該類藥物在2011年被核准上市以來，其臨床應用為癌症病患帶來新的希望，也為兩位發明者帶來諾貝爾生醫獎的殊榮。然而，也因該類藥物作用於免疫系統之調節機制，在消滅癌細胞的同時，亦導致了自體免疫機制的抑制作用無法運作，因而導致數種內分泌器官功能異常之產生。最常發生的內分泌腺病症為腦下垂體炎。發炎反應可進一步造成中樞性腎上腺機能不全，此現象是極為嚴重的副作用，需要即刻給予糖皮質激素藥物的治療，以避免腎上腺危象的產生。藥物直接引起的甲狀腺發炎反應，因為甲狀腺細胞受到破壞及甲狀腺激素的大量釋放，在臨床上初期的表現大部分為類似亞急性甲狀腺炎的亢進症狀，隨後則轉變為甲狀腺低能症，需要甲狀腺素製劑的補充治療。當胰臟 β 細胞受到免疫發炎影響時，可急速並大量受到破壞，導致胰島素分泌不足，血糖急速升高，甚至酮酸血症的發生，臨床表徵及實驗室數據皆指向胰島素依賴型糖尿病的診斷，一半以上的患者血液中可檢驗出抗胰島細胞的自體抗體，尤以anti-GAD65為最常見；糖尿病一旦發生，絕大多數患者需要長期以胰島素療法控制血糖。隨著免疫檢查點抑制劑在癌症病患日漸廣泛的使用，內分泌功能異常之疾病亦隨之增加，臨床醫師應保持高度之臨床敏銳度，適時做出診斷與治療。