Clinical Characteristics, Management, and Potential Biomarkers of Endocrine Dysfunction Induced by Immune Checkpoint Inhibitors

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Immune-related adverse events (irAEs) affecting the endocrine glands are among the most frequent irAEs induced by immune checkpoint inhibitors (ICIs) and include hypopituitarism, primary adrenal insufficiency, thyrotoxicosis, hypothyroidism, hypoparathyroidism, and type 1 diabetes mellitus. Since the incidence and clinical features of endocrine irAEs vary according to the ICI used, it is important to understand the characteristics of these irAEs and to manage each one appropriately. Since some endocrine irAEs, including adrenal crisis and diabetic ketoacidosis, are potentially life-threatening, predicting the risk of endocrine irAEs before their onset is critical. Several autoantibodies have been detected in patients who develop endocrine irAEs, among which anti-thyroid antibodies may be predictive biomarkers of thyroid dysfunction. In this review, we describe the clinical features of each endocrine irAE induced by ICIs and discuss their potential biomarkers, including autoantibodies.

Keywords: Hypopituitarism; Hypophysitis; Adrenal insufficiency; Thyrotoxicosis; Hypothyroidism; Hypoparathyroidism; Diabetes mellitus, type 1; Immune checkpoint inhibitors; Autoantibodies

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are widely used to treat several types of advanced malignancies, including malignant melanoma and non-small cell lung carcinoma. However, ICIs can cause characteristic adverse events, termed immune-related adverse events (irAEs), in a variety of organs including the lung, skin, liver, colon, and endocrine glands [1,2]. Endocrine irAEs include dysfunction of the pituitary, adrenal gland, thyroid, parathyroid, and pancreatic β cells [3-6] and can cause life-threatening consequences, such as adrenal crisis and diabetic ketoacidosis. On the other hand, it has been reported that the development of pituitary [7,8] or thyroid [8-10] dysfunction is associated with better outcomes after ICI treatment. Therefore,
endocrine irAEs should be diagnosed promptly and managed appropriately. Establishing biomarkers is also important for identifying patients at risk of developing endocrine irAEs before initiating ICI treatment.

**PITUITARY DYSFUNCTION**

**Epidemiology**

Pituitary dysfunction is induced by all ICI types, including anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), anti-programmed cell death-1 (PD-1), and anti-programmed cell death-1 ligand 1 (PD-L1) antibodies. A systematic review reported that the incidences of pituitary dysfunction induced by anti-CTLA-4, anti-PD-1, combination anti-CTLA-4/anti-PD-1, and anti-PD-L1 antibodies were 3.2%, 0.4%, 6.4%, and <0.1%, respectively [11]. In contrast, our prospective study indicated much higher incidences of pituitary dysfunction induced by anti-CTLA-4 (24%; 6/25 patients) and anti-PD-1 (6%; 10/167 patients) antibodies [8], suggesting that pituitary dysfunction may be overlooked by attending physicians due to non-specific symptoms such as general fatigue and appetite loss.

**Clinical types**

Pituitary dysfunction induced by ICIs can be classified into two clinical types: isolated adrenocorticotropic hormone (ACTH) deficiency (IAD), which is not associated with pituitary enlargement, and hypophysitis, which is associated with deficiencies in multiple anterior pituitary hormones accompanied by pituitary enlargement [8]. Both types of pituitary dysfunction are always accompanied by ACTH deficiency [8,12]. Treatment with an anti-CTLA-4 antibody causes both IAD and hypophysitis, whereas treatment with an anti-PD-1 or PD-L1 antibody causes only IAD [8]. ICI treatment rarely causes central diabetes insipidus due to impaired hypothalmo-neurohypophysial function [12], although a few cases of central diabetes insipidus have been reported [13,14]. Most patients treated with an anti-CTLA-4 antibody (ipilimumab) developed pituitary dysfunction within several months (median 10 weeks) after treatment initiation [12]. In contrast, there appears to be no period of greater susceptibility to developing pituitary dysfunction induced by anti-PD-1 or anti-PD-L1 antibodies; pituitary dysfunction can develop several months to over a year after treatment initiation [15-17]. In general, the duration from the initial treatment administration to the onset of pituitary dysfunction is longer with anti-PD-1 than anti-CTLA-4 treatment [8].

**Symptoms**

Most symptoms seen in patients with pituitary dysfunction induced by ICIs are caused by secondary adrenal insufficiency. Such symptoms include tiredness, weakness, anorexia, weight loss, digestive symptoms, decreased blood pressure, psychiatric disturbance, fever, hypoglycemic symptoms, joint pain, headache, and visual field disturbance [3].

**Endocrinological assessments**

Endocrinological tests show decreased levels of hormones secreted from the anterior pituitary and in the targeted organs [3]. For example, patients with ACTH deficiency show low levels of plasma ACTH and serum cortisol.

**Imaging**

Magnetic resonance imaging reveals pituitary enlargement in patients who develop hypophysitis induced by anti-CTLA-4 antibodies, while the enlargement usually improves in a few months [8,18]. Patients who develop IAD show no abnormalities in the pituitary gland.

**Diagnosis**

Hypopituitarism induced by ICIs is diagnosed when the levels of hormones secreted from the anterior pituitary and in the targeted organs at baseline, or the responses of pituitary hormones in loading tests, are decreased [3].

**Treatments and outcomes**

ACTH deficiency should be managed by replacement therapy with physiological doses of hydrocortisone (10 to 20 mg/day) [3]. There is no evidence suggesting any effect of high glucocorticoid doses on treatment outcomes or recovered pituitary dysfunction and enlargement [7,18]. Thyroid-stimulating hormone (TSH) deficiency can be managed by replacement therapy with levothyroxine. The dose of levothyroxine should be adjusted according to the serum level of free thyroxine (FT4). When patients simultaneously develop ACTH and TSH deficiencies, hydrocortisone must be administered first, followed by levothyroxine replacement at a low dose (12.5 to 25 μg/day) 5 to 7 days later. Once the general conditions stabilize after appropriate treatments, the use of ICIs can be considered for patients with pituitary dysfunction. Some studies have shown an association between the development of pituitary dysfunction and ICI treatment outcomes [7,8].
Pathology and mechanisms
An autopsy case report described the pathological features of the pituitary gland in a patient who developed hypophysitis induced by tremelimumab (anti-CTLA-4 antibody) [12]. That study demonstrated T and B cell infiltration in the anterior pituitary gland, which contained necrotic lesions, and positivity for a complement component of C4d in some anterior pituitary cells [12]. In a mouse model of hypophysitis induced by repeated injections of an anti-CTLA-4 antibody, C4d expression was detected in anterior pituitary cells secreting TSH and prolactin, suggesting that injected anti-CTLA-4 (immunoglobulin G1 subclass) can bind to CTLA-4, which was shown to be non-canonically expressed in TSH- and prolactin-secreting cells [19]. Although these data suggest that complement activation may contribute to the development of pituitary inflammation following administration of an anti-CTLA-4 antibody [20], further studies are needed to clarify the mechanism of how pituitary inflammation induced by this ICI leads to autoimmunity against pituitary glands. In addition, the mechanism of IAD induced by ICIs is unknown, since there are no histopathological reports of patients who developed IAD after ICI treatment and no animal models of pituitary dysfunction induced by anti-PD-1 or anti-PD-L1 antibodies.

Biomarkers
One study using serological analysis of recombinant cDNA expression reported that the titers of anti-guanine nucleotide-binding protein G(o1f) subunit alpha and anti-integral membrane protein 2B antibodies were increased after the development of pituitary dysfunction [21]. In addition, the titer of the anti-guanine nucleotide-binding protein G(o1f) subunit alpha antibody at baseline was higher in patients with pituitary dysfunction than in those without it [21]. Although these autoantibodies may be a potential biomarker predicting a risk of pituitary dysfunction, the results were validated in only five patients with pituitary dysfunction, including IAD and hypophysitis [21].

Anti-pituitary antibodies (APAs) measured by indirect immunofluorescence in human pituitary sections as a substrate can predict the presence of autoimmunity in pituitary glands [22] and are present in several pituitary diseases [22-25]. APA positivity was observed after the development of hypophysitis induced by ipilimumab in all seven patients evaluated in that study (Table 1) [19]. APAs were also positive at the onset of pituitary dysfunction in two patients treated with atezolizumab (an anti-PD-L1 antibody) and combination therapy of ipilimumab and nivolumab, respectively (Table 1) [26,27]. It is unknown whether APAs are positive at baseline or become positive before the onset of pituitary dysfunction; thus, further studies are needed to clarify the utility of APAs as a biomarker of pituitary irAEs.

Susceptibility alleles of human leucocyte antigen (HLA) have been reported in patients with pituitary dysfunction induced by ICIs. One study that analyzed 11 cases of pituitary dysfunction (both hypophysitis and IAD) induced by ICIs reported that the frequencies of HLA-DR15, -B52, and -Cw12 were higher in patients with pituitary dysfunction induced by ICIs than in healthy individuals from Japan [28]. Another study reported that the frequencies of HLA-DQB1*06:01, DPB1*09:01, and -DRB5*01:02 were higher in patients with IAD induced by an anti-PD-1 antibody.

| Type of endocrine irAE | Clinical type                | At baseline | At onset |
|-----------------------|-----------------------------|-------------|----------|
| Pituitary dysfunction | Hypophysitis                 | Unknown     | APA      |
|                       | IAD                          | Unknown     | APA      |
| Primary adrenal insufficiency | Destructive thyroiditis | Unknown     | 21-Hydroxylase Ab |
| Thyroid dysfunction   | Hypothyroidism               | TgAb, TPOAb | TgAb, TPOAb |
|                       | Hyperthyroidism              | TgAb, TPOAb | TgAb, TPOAb |
|                       |                               | Unknown     | TRAb     |
| Hypoparathyroidism    | Unknown                      | Anti-CaSR Ab|          |
| Type 1 diabetes mellitus | GADA, IA-2Ab, ZnT8Ab | GADA, IA-2Ab, ZnT8Ab, IAA, ICA |

irAE, immune-related adverse event; APA, anti-pituitary antibody; IAD, isolated adrenocorticotropic hormone (ACTH) deficiency; 21-hydroxylase Ab, autoantibody against 21-hydroxylase; TgAb, anti-thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TRAb, anti-TSH receptor antibody; Anti-CaSR Ab, anti-calcium-sensing receptor antibody; GADA, anti-glutamic acid decarboxylase antibody; IA-2Ab, anti-islet antigen 2 antibody; ZnT8Ab, anti-zinc transporter 8 antibody; IAA, insulin autoantibody; ICA, islet cell antibody.

*Autoantibodies detected before the initiation of immune checkpoint inhibitors; *Autoantibodies detected at the onset of endocrine irAEs.
These candidate HLA susceptibility alleles need to be validated in a larger number of cases and in both clinical types of pituitary dysfunction (hypophysitis and IAD).

### PRIMARY ADRENAL INSUFFICIENCY

#### Epidemiology
Primary adrenal insufficiency induced by ICIs is a rare adverse event, with an incidence of only 0.7% (43/5,831 patients), according to a systematic review of 62 study cohorts [11]. That review also reported that the incidence of primary adrenal insufficiency is higher after combination therapy with anti-CTLA-4 and anti-PD-1 antibodies (4.2%; 11/262). Primary adrenal insufficiency has been reported after treatment with anti-CTLA-4 [30], anti-PD-1 [31], and anti-PD-L1 [11] antibodies. The period of greatest susceptibility to developing primary adrenal insufficiency remains unknown.

#### Symptoms
The following symptoms are observed in patients who develop primary adrenal insufficiency induced by ICIs: general fatigue, tiredness, weakness, weight loss, anorexia, digestive symptoms, loss of muscle strength, impaired consciousness, psychiatric symptoms, and decreased blood pressure [3].

#### Endocrinological assessments
Endocrinological tests show decreased levels of serum cortisol, increased levels of plasma ACTH, and increased levels of plasma renin activity (or renin concentration), resulting in the development of hyponatremia, hyperkalemia, or hypoglycemia [3].

#### Imaging
In case reports, abdominal computed tomography (CT) showed bilateral enlargement of the adrenal glands [6,30], while positron emission tomography revealed increased uptake of $^{18}$F-fluorodeoxyglucose in the adrenal glands [31]. However, primary adrenal insufficiency should be carefully diagnosed because the above radiological findings are also observed in patients with primary or metastatic cancer in the adrenal glands.

#### Diagnosis
Primary adrenal insufficiency induced by ICIs is defined as a decreased level of serum cortisol, increased level of plasma ACTH, decreased response of cortisol secretion in the ACTH stimulation test, and a normal ACTH response to corticotropin-releasing hormone [3].

### THYROID DYSFUNCTION

#### Epidemiology
Thyroid dysfunction can be caused by all ICI types, including anti-CTLA-4, anti-PD-1, and PD-L1 antibodies. A systematic review reported that the incidences of hypothyroidism and thyrotoxicosis were 3.8% and 1.7% after treatment with an anti-CTLA-4 antibody, 7.0% and 3.2% after treatment with an anti-PD-1 antibody, 3.9% and 0.6% after treatment with an anti-PD-L1 antibody, and 13.2% and 8.0% after combination therapy with anti-CTLA-4 and anti-PD-1 antibodies, respectively [11]. The incidence of thyroid dysfunction was significantly higher after treatment with anti-PD-1 antibodies or anti-CTLA-4/anti-PD-1 combination therapy compared with anti-CTLA-4 antibodies [11].
Clinical types
Thyroid dysfunction induced by ICIs can be classified into thyrotoxicosis and hypothyroidism [3]. The main cause of thyrotoxicosis is destructive thyroiditis, which consists of transient thyrotoxicosis followed by hypothyroidism [33,34]. In contrast, the development of hyperthyroidism (Graves’ disease) after ICI treatment is quite rare [35,36]. Thyroid dysfunction is usually observed 2 to 6 weeks after ICI administration [3]. In our prospective study evaluating the effect of anti-PD-1 antibodies on the development of endocrine irAEs in 209 patients, 12 (57.4%), seven (33.5%), and one (0.5%) patient developed destructive thyroiditis, hypothyroidism without a prior thyrotoxicosis phase, and hyperthyroidism, respectively [35]. Although the severity of thyroid dysfunction, according to the CTCAE 5.0 criteria, is usually low, there was one case of thyroid storm induced by ipilimumab plus nivolumab combination therapy [37].

Symptoms
The following symptoms are observed in patients with thyrotoxicosis: general fatigue, palpitations, sweating, weight loss, fever, diarrhea, and tremor [3]. In contrast, the symptoms of hypothyroidism include general fatigue, weight gain, constipation, anorexia, and bradycardia [3].

Endocrinological assessments
Patients who develop destructive thyroiditis induced by ICIs show suppressed levels of serum TSH, elevated levels of serum FT4 and/or free triiodothyronine, and negativity for anti-TSH receptor antibodies [3]. Patients are clinically diagnosed with hyperthyroidism if they show thyrotoxicosis with positivity for anti-TSH receptor antibodies [36] and are definitively diagnosed if they show increased uptake of radionuclides, including 99mTc pertechnetate, in the thyroid [35]. Patients with hypothyroidism induced by ICIs show increased serum TSH and decreased serum FT4 levels [3].

Imaging
Thyroid ultrasonography shows hypoecchogenicity and/or an irregular echo pattern in patients with destructive thyroiditis and hypothyroidism induced by ICIs. Thyroid scintigraphy shows decreased uptake of radionuclides in destructive thyroiditis and hypothyroidism but increased uptake in hyperthyroidism.

Diagnosis
Thyrotoxicosis induced by ICIs is defined as a suppressed serum TSH level and elevated serum FT4 and/or free triiodothyronine levels. Hypothyroidism induced by ICIs is defined as increased serum TSH and decreased serum FT4 levels.

Treatments and outcomes
Symptoms caused by thyrotoxicosis are relieved by β blockers. Anti-thyroid drugs can be considered in patients who develop hyperthyroidism [3]. Hypothyroidism is treated with levothyroxine, starting at 25 to 50 μg/day (12.5 μg/day in the elderly or patients with cardiac diseases). The levothyroxine dose should be adjusted according to the serum TSH level [3]. A retrospective study showed no positive effect of high glucocorticoid doses on thyroid dysfunction [38]. Once the general conditions have stabilized after appropriate treatment, the use of ICIs can be considered for patients with thyroid dysfunction. Some studies have shown an association between thyroid dysfunction development and ICI treatment outcomes [8-10,39].

Pathology and mechanisms
One report showed, as a histopathological feature, infiltration of cytotoxic T cells (CD8+) in the thyroid gland of a patient who developed thyroid dysfunction induced by the anti-PD-1 antibody nivolumab [40]. Given that the incidence of thyroid dysfunction is higher in patients with anti-thyroid antibody positivity, compared with negativity, at baseline [33,35,41], pre-existing autoimmunity in the thyroid may be involved in the pathogenesis of thyroid dysfunction induced by ICIs. However, the contribution of cellular and/or humoral immunity remains unknown.

Biomarkers
Anti-thyroid antibodies, including anti-thyroglobulin antibodies and anti-thyroid peroxidase antibodies, are positive in some patients who develop thyroid dysfunction not only at the onset of thyroid dysfunction but also at baseline (before the initiation of ICIs) (Table 1) [9,33-35,41,42]. Our prospective study revealed that the incidence of thyroid dysfunction induced by anti-PD-1 antibodies was higher in patients with anti-thyroid antibody positivity (34.1%; 15/44) compared with negativity (2.4%; 4/165) [35]. Furthermore, among the patients with positive anti-thyroid antibodies, a much higher incidence of thyroid dysfunction was observed in those with an irregular versus regular echo pattern in the thyroid glands (56.5% [13/23] vs. 5.3% [1/19]) [35], suggesting that the risk of thyroid dysfunction can be predicted by evaluating anti-thyroid antibodies followed by thyroid ultrasonography. In a retrospective study, multivariate logistic regression analysis showed that anti-thyroglobulin antibody
positivity at baseline and an elevated TSH level (>5 μIU/mL) were independent risk factors for thyroid dysfunction induced by nivolumab [41]. Another retrospective study reported that increased uptake of 18F-fluorodeoxyglucose in the thyroid glands on positron emission tomography was associated with a higher incidence of thyroid dysfunction induced by nivolumab [10].

HYPOPARATHYROIDISM

Epidemiology
Hypoparathyroidism has been reported in patients treated with an anti-PD-1 antibody [43-45] or combination therapy with anti-CTLA-4 and anti-PD-1 antibodies [46-48]. However, the number of case reports is limited and the incidence of hypoparathyroidism unknown.

Symptoms
Hypocalcemia is associated with neuromuscular symptoms (numbness in the limbs or tetany) and convulsions [3].

Endocrinological assessments
Endocrinological tests show decreased levels of serum intact parathyroid hormone (PTH), hypocalcemia, and hyperphosphatemia.

Imaging
There are no reports showing imaging data from patients who developed hypoparathyroidism induced by ICIs.

Diagnosis
Hypoparathyroidism induced by ICIs is defined as a decreased serum intact PTH level, hypocalcemia, and hyperphosphatemia [3].

Treatments and outcomes
In patients who require emergency medical care, hypocalcemia should be treated by intravenous administration of calcium gluconate [3]. In patients who do not require emergency medical care, hypocalcemia can be treated by oral administration of active vitamin D [3]. There is no reported evidence for an effect of high-dose glucocorticoids on the recovery of parathyroid function. Once the general conditions are stabilized after appropriate treatments, the use of ICIs can be considered for patients with hypoparathyroidism. There are no studies showing the association of the development of hypoparathyroidism with outcomes of ICI treatment.

Pathology and mechanisms
The pathological characteristics of the parathyroid glands in patients with ICI-induced hypoparathyroidism have not been reported. Although it is possible that hypoparathyroidism induced by ICIs results from inflammation in the parathyroid glands, several case reports have demonstrated the presence of anti-calcium-sensing receptor antibodies, suggesting the involvement of humoral immunity in the pathogenesis of ICI-induced hypoparathyroidism [43,45,47].

Biomarkers
Although several case reports detected functional autoantibodies against calcium-sensing receptor (Table 1) [43,45,47], it remains unknown if these antibodies can serve as biomarkers of hypoparathyroidism induced by ICIs.

TYPE 1 DIABETES MELLITUS

Epidemiology
Type 1 diabetes mellitus (T1DM) is a rare, yet potentially life-threatening, endocrine irAE. According to a systematic review, the incidence of T1DM development after ICI treatment is 0.2% [11]. Although most reported cases of T1DM are associated with anti-PD-1 or anti-PD-L1 antibody treatment [49,50], there is a report of T1DM developing after anti-CTLA-4 antibody (ipilimumab) monotherapy [51].

Clinical types
ICI treatment can cause acute-onset as well as fulminant T1DM [49]. Fulminant T1DM is a subtype of T1DM first reported in Japan and is characterized by diabetic ketoacidosis and rapid destruction of pancreatic β cells [52]. In a case series involving 22 Japanese patients who developed T1DM induced by ICIs, 50% of the patients fulfilled the criteria of fulminant T1DM [49]. The median duration from the initiation of ICI treatment to the development of T1DM is 5 to 6 months, but the range is 1 week to over 1 year [49,50].

Symptoms
The symptoms of hyperglycemia include thirst, polydipsia, and polyuria. In addition, ketosis or ketoacidosis causes general fatigue and impaired consciousness or coma [3].

Endocrinological assessments
Glucose levels are increased in the blood and urine. The hemoglobin A1c level is also elevated, but the increase may be rela-
Histopathological analysis of this patient showed infiltration of CD3+ T cells not only around the pancreatic islets but also throughout the pancreas. Among the T cell populations in the pancreas, the number of CD8+ T cells was dominant over that of CD4+ T cells [55]. These findings suggest the involvement of cytotoxic T cells in the development of ICI-induced T1DM.

**Biomarkers**

In a case series analyzing autoantibodies associated with T1DM in 27 patients who developed ICI-induced T1DM (Caucasians, n=24; non-Hispanics, n=1; Asians, n=1; non-Hispanic and other races, n=1), the prevalences of anti-glutamic acid decarboxylase (GAD), anti-islet antigen 2 (IA2), anti-zinc transporter 8, and islet cell antibodies were 36% (9/25 patients), 21% (5/24), 10% (2/20), and 11% (2/19), respectively (Table 1) [50]. In contrast, a study of Japanese patients who developed T1DM induced by ICIs reported that only one of 20 (5%) patients was positive for anti-GAD antibodies [49], suggesting that the prevalence of autoantibodies associated with T1DM varies among races. Interestingly, positivity for anti-GAD, anti-IA2, and anti-zinc transporter 8 antibodies before the initiation of ICI treatment was reported in a patient with ICI-induced T1DM (Table 1) [50], suggesting that these autoantibodies at baseline may be a biomarker of T1DM development in a subset of patients. In addition, a case series reported that the prevalence of HLA-DR4 was higher in patients with ICI-induced T1DM (76%, 16/21) than in U.S. Caucasians (17.3%) [50]. Although HLA susceptibility alleles may be useful biomarkers, further studies involving more cases are needed to clarify this.

**CONCLUSIONS**

Endocrine irAEs are one of the most frequent adverse events induced by ICIs. Since most symptoms are not specific, oncologists must understand the clinical characteristics of each endocrine irAE to manage it appropriately. The development of endocrine irAEs may result in life-threatening consequences, including adrenal crisis and diabetic ketoacidosis, but it is sometimes associated with better ICI treatment outcomes, especially in patients with pituitary or thyroid dysfunction. Therefore, management of endocrine irAEs contributes not only to treatment of endocrine dysfunction but also to better ICI treatment outcomes. Identification of specific biomarkers of individual endocrine irAEs will improve the outcomes of cancer immunotherapy using ICIs.
CONFLICTS OF INTEREST

Shintaro Iwama is a consultant/advisory board member on endocrinological adverse events for Ono Pharmaceutical Company, Bristol–Myers Squibb, and Chugai Pharmaceutical Co. Ltd., and received personal fees from Ono Pharmaceutical Company, Bristol–Myers Squibb, Chugai Pharmaceutical Co., Ltd., and MSD K.K outside of this study. Hiroshi Arima received grants from Ono Pharmaceutical Company, MSD K.K., and Chugai Pharmaceutical Co. Ltd., as well as personal fees from Ono Pharmaceutical Company, Bristol–Myers Squibb, and MSD K.K outside of this study.

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