Management of immune-related adverse events in endocrine organs induced by immune checkpoint inhibitors: clinical guidelines of the Japan Endocrine Society

Hiroshi Arima¹, Shintaro Iwama², Hidefumi Inaba³, Hiroyuki Ariyasu³, Noriko Makita⁴, Michio Otsuki⁵, Kazunori Kageyama⁶, Akihisa Imagawa⁷ and Takashi Akamizu³

¹Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan
²Department of Endocrinology and Diabetes, Nagoya University Hospital, Nagoya 466-8560, Japan
³The First Department of Medicine, Wakayama Medical University, Wakayama 641-8509, Japan
⁴Division of Nephrology and Endocrinology, University of Tokyo Graduate School of Medicine, Tokyo 113-8655, Japan
⁵Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Suita 565-0871, Japan
⁶Department of Endocrinology and Metabolism, Hirosaki University Graduate School of Medicine, Hirosaki 036-8562, Japan
⁷Department of Internal Medicine (I), Osaka Medical College, Takatsuki 569-8686, Japan

Abstract. Immune checkpoint inhibitors (ICIs) have become a promising treatment for advanced malignancies. However, these drugs can induce immune-related adverse events (irAEs) in several organs, including skin, gastrointestinal tract, liver, muscle, nerve, and endocrine organs. Endocrine irAEs comprise hypopituitarism, primary adrenal insufficiency, thyroid dysfunction, hypoparathyroidism, and type 1 diabetes mellitus. These conditions have the potential to lead to life-threatening consequences, such as adrenal crisis, thyroid storm, severe hypocalcemia, and diabetic ketoacidosis. It is therefore important that both endocrinologists and oncologists understand the clinical features of each endocrine irAE to manage them appropriately. This opinion paper provides the guidelines of the Japan Endocrine Society and in part the Japan Diabetes Society for the management of endocrine irAEs induced by ICIs.

Key words: Hypopituitarism, Adrenal insufficiency, Thyroid dysfunction, Hypoparathyroidism, Diabetes

Introduction

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies against cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death (PD)-1, and its ligand (PD-L1) that have been approved as anti-cancer drugs and are used widely as promising treatment for several advanced malignancies (Table 1). The ICIs have prominent anti-tumor effects which are considered to be mediated via activation of immune systems. However, ICIs may also cause immune-related adverse events (irAEs) in several tissues such as skin, gastrointestinal tract, liver, lung, muscle, nerve and endocrine organs [1]. The endocrine irAEs include hypopituitarism, primary adrenal insufficiency, thyroid dysfunction, hypoparathyroidism, and type 1 diabetes mellitus [2]. Symptoms caused by endocrine irAEs such as fatigue, appetite loss, and weight loss are frequently observed in patients with malignancies, and attending physicians may therefore overlook endocrine irAEs in clinical practice if they are not aware of them. In order to avoid serious outcomes it is therefore important that endocrinologists and oncologists understand possible endocrine irAEs induced by ICIs.

In 2018, the American Society of Clinical Oncology [3] and the Society for Endocrinology in the UK [4] both published guidelines for the management of endocrine irAEs induced by ICIs. The Japan Endocrine Society also published the Japanese version of the guidelines in the same year [5]. This opinion paper reports the updated English version of these guidelines.
Summary of Recommendations

Hypopituitarism

Overview

The incidence of hypopituitarism associated with anti-CTLA-4 or anti-PD-1 antibody treatment is reported to be around 10% or <1%, respectively [6-11]. For anti-CTLA-4 antibodies, hypopituitarism develops in most cases approximately 10 weeks after the start of treatment [6]. In contrast, the duration from initiation of treatment with anti-PD-1 or anti-PD-L1 antibodies to the onset of hypopituitarism can be longer, up to several months or even a year [12-14]. Hypopituitarism induced by ICls can develop even after the withdrawal of the drugs. Given the functional mechanisms of these drugs and the fact that the clinical features such as the enlargement of the pituitary gland and/or a stalk are similar to those seen in patients with autoimmune hypophysitis, it is possible that hypopituitarism induced by ICIs results from inflammation of the pituitary glands. Deficiency of adrenocorticotropic hormone (ACTH) secretion is observed in almost all patients who develop hypopituitarism induced by ICIs [6]. While TSH and/or gonadotropin deficiency is often accompanied by ACTH deficiency in patients treated with anti-CTLA-4 antibodies, almost all patients who develop pituitary dysfunction with anti-PD-1 or anti-PD-L1 antibodies show isolated ACTH deficiency [15]. Central diabetes insipidus is rarely induced by ICIs [6].

Symptoms

The symptoms of hypopituitarism induced by ICIs include tiredness, weakness, anorexia, weight loss, digestive symptoms (nausea, vomiting, and diarrhea), decreased blood pressure, psychiatric disturbance (apathy, anxiety, and depression), fever, hypoglycemic symptoms, joint pain, headache, or visual field disturbance.

Testing

Laboratory data show decreased levels of hormones secreted by the pituitary and the targeted organs.

Additional findings

MRI of the pituitary shows enlargement of the pituitary gland and/or a stalk with gadolinium-enhancement in some patients.

Diagnosis

Hypopituitarism induced by ICls is diagnosed based on findings of decreased basal levels of hormones secreted by the pituitary and targeted organs, or decreased responses of pituitary hormones in loading tests.

Treatment

Hydrocortisone (10–20 mg/day) should be administered for ACTH deficiency. High doses of glucocorticoids are not recommended because there is no evidence that the use could improve the pituitary function or the survival outcomes [16, 17]. However, glucocorticoids can be administered to patients with marked enlargement of the pituitary gland accompanied by headaches and disturbances of vision or the visual field. In such cases, reference doses of glucocorticoids are those used for patients with autoimmune hypophysitis (e.g. 0.5–1.0 mg/kg/day of prednisolone).

In cases of adrenal crisis, the treatment should be referred to the guideline [18].

If patients have both ACTH and TSH deficiency, hydrocortisone must be administered before starting thyroid hormone replacement. It is recommended to start administration of levothyroxine at low doses (12.5–25 μg/day) 5–7 days after the administration of hydrocortisone, with the dose adjusted according to the serum level of FT4.

The use of ICls in patients with hypopituitarism should be withheld until the general conditions are stabilized by treatment.

Primary adrenal insufficiency

Overview

While primary adrenal insufficiency induced by ICls may result from inflammation in the adrenal glands, the number of cases reported to date is small and there is no histological evidence showing the presence of inflammation in the adrenal glands. Case reports showed that primary adrenal insufficiency developed 10 weeks after initiation of anti-PD-1 antibody treatment [19] and 16 weeks after initiation of anti-CTLA-4 antibody treatment [20]. A systematic review has reported that the incidence was 0.7% (43 of 5,871) [9], although this may be an underestimate due to the use of glucocorticoids as cancer therapy or concomitant secondary adrenal insufficiency.

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Table 1  Immune checkpoint inhibitors approved in Japan

<table>
<thead>
<tr>
<th>Class</th>
<th>Anti-CTLA-4 antibody</th>
<th>Anti-PD-1 antibody</th>
<th>Anti-PD-L1 antibody</th>
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<tr>
<td>Ipilimumab</td>
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CTLA-4, cytotoxic T lymphocyte antigen-4; PD-1, programmed cell death-1; PD-L1, a ligand of PD-1
caused by hypopituitarism.

Symptoms

The symptoms of primary adrenal insufficiency induced by ICIs include general fatigue, tiredness, weakness, loss of muscle strength, weight loss, anorexia, digestive symptoms (nausea, vomiting, and diarrhea), psychiatric symptoms (apathy, anxiety, and depression), impaired consciousness, or decreased blood pressure.

Testing

Laboratory data shows decreased levels of serum cortisol with normal or increased levels of plasma ACTH, increased levels of plasma renin activity (or renin concentration), hyponatremia, hyperkalemia, or hypoglycemia.

Additional findings

It has been reported that PET scans showed bilateral increased uptake of FDG in adrenal glands [19], while abdominal CT showed bilateral enlargement of the adrenal glands [20]. However, it should be noted that these findings can also be observed in primary or metastatic cancer of adrenal glands.

Diagnosis

Primary adrenal insufficiency induced by ICIs is diagnosed based on data of decreased levels of serum cortisol with normal or increased levels of plasma ACTH, a decreased response of cortisol secretion in the ACTH stimulation test, and the presence of ACTH secretion in response to corticotropin-releasing hormone.

Treatment

Hydrocortisone (10–20 mg/day) should be administered for cortisol deficiency without delay [18]. High doses of glucocorticoids are not recommended because there is no evidence to support their use for primary adrenal insufficiency. In cases of adrenal crisis, treatment should be in accordance with the guidelines for adrenal crisis. Fludrocortisone (0.05–0.2 mg/day) can be administered in combination with hydrocortisone if patients show hyponatremia, hypotension, or salt-wasting symptoms.

The use of ICIs in patients with primary adrenal insufficiency should be withheld until the general conditions are stabilized by treatment.

Thyroid dysfunction

Overview

The incidence of thyroid dysfunction following treatment with anti-PD-1 antibodies is reported to be 5–10%, which is higher than that observed with anti-CTLA-4 antibodies (0–5%) [8-10]. Treatment with anti-PD-L1 antibodies also leads to thyroid dysfunction (0–5%) [8-10]. Low T3 syndrome, often seen in patients with advanced malignancies, should be differentiated. Thyroid dysfunction induced by ICIs is classified into thyrotoxicosis and hypothyroidism. Thyrotoxicosis develops 2–6 weeks after the administration of ICIs in most cases, and is often followed by the development of hypothyroidism [21]. It is possible that activation of pre-existing autoimmunity against thyroid glands is involved in the pathogenesis of thyroid dysfunction induced by ICIs. For example, the incidence of thyroid dysfunction is reportedly higher in patients who have anti-thyroglobulin antibodies (TgAb) and/or anti-thyroid peroxidase antibodies (TPOAb) prior to the initiation of the treatment with nivolumab than in patients without these antibodies [22, 23].

Symptoms

1) The symptoms of thyrotoxicosis induced by ICIs include palpitations, sweating, fever, diarrhea, tremor, weight loss, or general fatigue.
2) The symptoms of hypothyroidism induced by ICIs include general fatigue, anorexia, constipation, bradycardia, or weight gain.

Testing and diagnosis

1) Thyrotoxicosis induced by ICIs is diagnosed based on suppressed levels of serum TSH and elevated levels of serum FT4 and/or FT3. Anti-TSH receptor antibodies are rarely positive.
2) Hypothyroidism induced by ICIs is diagnosed based on increased levels of serum TSH and low levels of serum FT4 and/or FT3.

In most cases of thyroid dysfunction induced by ICIs, thyroid ultrasonography shows diffuse enlargement of the thyroid gland accompanied by decreased internal blood flow and low internal echogenicity, while thyroid scintigraphy shows decreased uptake of isotope, suggestive of destructive thyroiditis.

Treatments

1) Thyrotoxicosis

β blockers (e.g. propranolol 30 mg/day) is effective for relieving symptoms. In cases of Graves’ disease treatment with anti-thyroid drugs should be considered.

2) Hypothyroidism

Administration of levothyroxine is started at 25–50 μg/day (12.5 μg/day in elderly or patients with cardiac diseases), with the dose adjusted according to serum TSH levels. It is unclear whether thyroid function may recover or not. Effectivity of high doses of glucocorticoids for thyroid dysfunction is also unclear.

The use of ICIs in patients with thyroid dysfunction should be withheld until the general conditions are stabilized by treatment.

Hypoparathyroidism

Overview

While it is possible that hypoparathyroidism induced by ICIs results from inflammation in the parathyroid
glands, the number of cases reported to date is small and there is no histological evidence showing the presence of such inflammation. There is evidence that patients treated with an anti-PD-1 antibody alone or in combination with anti-CTLA-4 antibodies developed hypoparathyroidism 1–4 months after the initiation of the drugs [24-27]. Because serum calcium levels can be affected by advanced malignancies per se or by treatment, evaluation of serum calcium levels, intact PTH, 25-OH vitamin D, phosphorus, and magnesium, as well as urinary excretion of calcium and magnesium should be performed for differential diagnosis.

**Symptoms**

The symptoms of acute hypocalcemia due to hypoparathyroidism induced by ICIs are neuromuscular symptoms (numbness in the limbs or tetany) or convulsions.

**Testing and diagnosis**

Hypoparathyroidism induced by ICIs is diagnosed based on decreased levels of serum intact PTH, hypocalcemia, and hyperphosphatemia.

**Additional findings**

Hypocalcemia associated with hypomagnesemia should be diagnosed differentially. It is possible that increased bone absorption due to thyrotoxicosis induced by ICIs may mask hypocalcemia due to hypoparathyroidism.

**Treatment**

Calcium gluconate should be administered intravenously to urgently treat patients with symptoms associated with hypocalcemia [e.g. intravenous injection of 8.5% calcium gluconate (10–20 mL) for 10–20 min, followed by injection at the rate of 2–4 mL/hr]. In patients who do not require emergency medical care, administration of active vitamin D is started (e.g. 1–3 μg/day of alfalcacidol). In chronic phase, to prevent urinary stones and kidney dysfunction the dose of active vitamin D should be adjusted so that serum calcium levels are kept in the range of 7.5–8.5 mg/dL and urine calcium/creatinine ratio <0.3. In most cases, supplementation with calcium is not necessary.

The use of ICIs in patients with hypoparathyroidism should be withheld until the general conditions are stabilized by treatment.

**Type 1 diabetes mellitus [28]**

**Overview**

Although the incidence of type 1 diabetes mellitus induced by ICIs is <1%, it has been reported that treatment with anti-PD-1 antibodies is more likely to induce type 1 diabetes mellitus than treatment with anti-CTLA-4 antibodies [29]. The reported duration from initiation of anti-PD-1 antibody treatment to the onset of type 1 diabetes mellitus ranges from 13 to 504 days [29].

As impaired beta cell function is generally irreversible, and inappropriate management can directly affect prognosis, it is important to start insulin therapy as soon as possible after the early diagnosis of type 1 diabetes mellitus.

**Symptoms**

The symptoms of type 1 diabetes mellitus induced by ICIs are thirst, polydipsia and polyuria due to hyperglycemia, general fatigue, and impaired consciousness or coma due to ketosis or ketoacidosis.

**Testing and diagnosis**

Laboratory data show increased levels of glucose in the blood and urine. Although blood glucose levels may increase to around 1,000 mg/dL, they may be lower in some cases (e.g. 200–300 mg/dL). The levels of ketone bodies are increased in blood and urine, indicating ketosis or ketoacidosis. Hemoglobin A1c (HbA1c) levels are also elevated, although the increase may be relatively small compared to the raised levels of plasma glucose. C peptide levels gradually decrease in serum and urine. Anti-GAD antibodies are generally negative.

**Treatment**

Insulin therapy must be started for type 1 diabetes mellitus induced by ICIs. In cases of ketosis or ketoacidosis, intravenous administration of insulin and saline is required. After ketosis or ketoacidosis has improved, intensive insulin therapy (subcutaneous injections) is recommended to control glucose levels. Subcutaneous insulin injections instead of intravenous injections can be started at the beginning if patients do not develop ketosis and the increases in blood glucose are small.

It is important to diagnose type 1 diabetes mellitus before hyperglycemia is accompanied by ketoacidosis. Therefore, blood glucose levels must be measured at each visit after treatment with ICIs is started. Attending physicians (oncologists) should check the glucose levels on the visit day and consult diabetologists or endocrinologists as soon as possible if blood glucose levels are increased (fasting blood glucose ≥126 mg/dL, casual blood glucose ≥200 mg/dL). Patients treated with ICIs should be informed of the possibility that they may develop type 1 diabetes mellitus following treatment with ICIs. It is also important for patients to be aware of the symptoms of hyperglycemia (thirst, polydipsia, and polyuria), so that they can immediately contact attending physicians as soon as these symptoms develop.

Glucocorticoids are not recommended for the treatment of type 1 diabetes mellitus because there is no evidence to support their use and blood glucose levels would be increased by glucocorticoids. If patients require a high dose of glucocorticoids for treatment of other adverse effects, blood glucose levels should be monitored carefully.
The use of ICIs in patients with type 1 diabetes mellitus should be withheld until the general conditions are stabilized by treatment.

**Comments**

Endocrine irAEs can lead to life-threatening consequences such as an adrenal crisis, thyroid storm, severe hypocalcemia, and diabetic ketoacidosis. Therefore, endocrinologists and oncologists should understand the clinical features of endocrine irAEs induced by ICIs.

Because endocrine dysfunction in irAEs is irreversible in most cases [8], therapy for each endocrine irAE must be continued. There is no evidence to support the use of high doses of glucocorticoids for endocrine irAEs, although severe irAEs in other than endocrine organs are often treated with high doses of these agents.

In clinical practice, it would be beneficial to identify, in advance, which patients are at greatest risk of developing an endocrine irAE induced by an ICI. It has been reported that the presence of TgAb and/or TPOAb in serum may be potential biomarkers of thyroid dysfunction induced by the anti-PD-1 antibody [22, 23]. On the other hand, there are no reports to date that have shown predictive biomarkers for endocrine irAEs other than thyroid dysfunction.

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**Author Contributions**

All authors discussed these guidelines. S.I. and H.A. wrote the manuscript. All authors assisted with revision of the manuscript.

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