—Review—

Immune Checkpoint Inhibitors and Associated Pituitary Dysfunctions: A Mini-Review

Izumi Fukuda

Department of Endocrinology, Metabolism and Nephrology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

Immune checkpoint inhibitors (ICIs) are widely used for various types of advanced cancers. Currently, three types of ICIs are clinically available, a monoclonal antibody targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and antibodies targeting the programmed cell death protein-1 (PD-1) and its ligand, programmed cell death ligand 1 (PD-L1). Although ICIs have improved the survival rates of several types of cancers, they induce immune-related adverse events (irAE) by their enhancement of immune responses. The pituitary gland is one of the common targets of irAE. In general, different clinical presentations of autoimmune pituitary dysfunctions are observed between anti-CTLA-4 and anti-PD-1/anti-PD-L1 antibodies, with anti-CTLA-4 inducing hypophysitis with multiple pituitary hormone deficiencies and targeting the PD-1/PD-L1 axis inducing isolated adrenocorticotropic hormone deficiency.

This review describes the current understanding of the pathophysiology, clinical manifestation, and management of hypophysitis caused by ICIs. (J Nippon Med Sch 2023; 90: 149–156)

Key words: hypophysis, isolated ACTH deficiency, immune checkpoint inhibitors

Introduction

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block T cell inactivation. ICIs induce markedly improved survival rates in several types of advanced cancers. Currently, three types of ICIs are clinically available, monoclonal antibodies targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), the programmed cell death protein-1 (PD-1), or its ligand, PD-L 1. To promote tumor proliferation, cancer cells dominate immune checkpoint systems resulting in immune evasion. ICIs can block this immune tolerance situation induced by cancer cells. For this reason, when ICIs remove the inactivation signal to T cells, the immune response is enhanced, resulting in anti-tumor effects and also inducing immune-related adverse events (irAE). Numerous organs are possible targets of ICI-induced irAE, including several endocrine organs, such as the pituitary gland, thyroid gland, and islet cells of the pancreas.

This review describes the current understanding of the pathophysiology, clinical manifestation, and management of hypophysitis caused by ICIs.

Mechanism of Actions of Immune Checkpoint Inhibitors

In lymph nodes, the first activation signal is initiated when the T cell receptor (TCR) of naïve T cells binds to a specific antigen (non-self) presented by the major histocompatibility complex (MHC) on the surface of antigen-presenting cells. However, this first signal is insufficient to activate the T cell response. CD28 is a T cell costimulatory receptor expressed on the surface of T cells. As a second signal, CD28 binds to its ligand B7, which is mainly expressed on antigen-presenting cells. This process activates T cells to attack cells expressing antigens it recognizes, such as cancer cells. CTLA-4, an inhibitory molecule expressed on T cells, is a member of the immunoglobulin superfamily and a negative regulator of T cell activation. CTLA-4 is located intracellularly in resting T cells, but when T cells are activated, CTLA-4 is translocated from the lysosome to the surface of T cells. As

Correspondence to Izumi Fukuda, MD, PhD, Department of Endocrinology, Metabolism and Nephrology, Graduate School of Medicine, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: i-fukuda@nms.ac.jp
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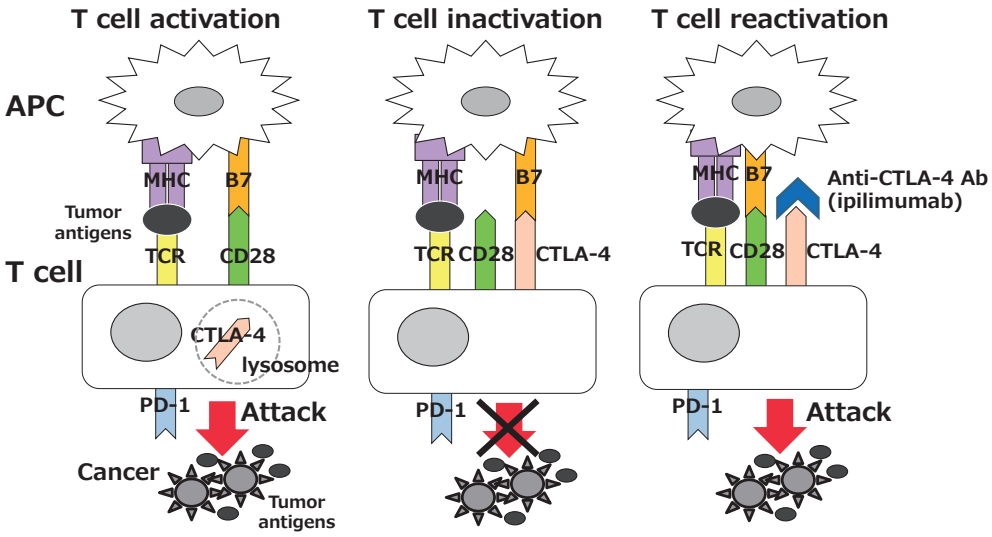

Fig. 1 Roles of CTLA-4 in the anti-tumor immune response

Left (T cell activation)

1. In lymph nodes, the first activation signal is initiated when the T cell receptor (TCR) of naïve T cells binds to tumor antigens (TAs) presented by the major histocompatibility complex (MHC) on the surface of antigen-presenting cells (APC).
2. This first signal is not enough to activate the T cell response. As a second signal, the costimulatory binding of CD28 to B7 is crucial.

Middle (T cell inactivation)

3. CTLA-4 is upregulated on the surface of T cells shortly after T cell activation.
4. CTLA-4, acting as an immune checkpoint, inhibits the second signal by binding to B7 at a higher affinity than CD28, limiting excessive activation of the T cell.

Right (T cell reactivation by anti-CTLA-4 antibody)

5. Blocking CTLA-4 pharmacologically removes the "brakes on T cell activation" and allows the reactivation of the second signal.
6. Activated T cells migrate to the periphery, where they encounter TAs at the tumor site and induce anti-tumor responses.

CTLA-4: cytotoxic T lymphocyte-associated protein 4

CTLA-4 has a higher affinity for B7, it competes with CD 28 for blocking T cell activity. This system of modulating the immune response is indispensable for maintaining self-tolerance. Anti-CTLA-4 antibodies prevent CTLA-4-B 7 binding and augment CD28-B7 binding, resulting in persistent T cell reactivation for attacking cancer cells[1,2] (**Fig. 1**).

In humans, CTLA-4 is expressed in lymphoid tissues and several organs, such as the lungs or urinary bladder[3]. In addition, expression of CTLA-4 was also confirmed in anterior pituitary endocrine cells and pituitary neuroendocrine tumors[4,5].

PD-1 is a receptor expressed on the surface of activated T cells to attenuate their function. PD-L1 is a ligand of PD-1 and is expressed on the surface of antigen-presenting cells[1]. When PD-1 binds to PD-L1, it limits the T cell response to prevent autoimmune reactions. In certain cancer cells, upregulation of PD-L1 expression is observed. This phenomenon is thought to allow cancers to escape destruction by the immune system. Currently, agents targeting PD-1 (nivolumab, pembrolizumab, and cemiplimab) and its ligand, PD-L1 (atezolizumab, avelumab, and durvalumab), are available for prolonging the activation of T cells directed against cancers (**Fig. 2**).

The pituitary gland is one of the common targets of ICI-induced irAE, but clinical manifestation and incidence of pituitary disorders differ by the types of ICI administered. Namely, the anti-CTLA-4 antibody ipilimumab may induce hypophysitis with multiple pituitary hormone deficiencies, while anti-PD-1 or anti-PD-L1 antibodies may induce isolated adrenocorticotropic hormone (ACTH) deficiency.

Hypophysis Caused by Anti-CTLA-4 Antibody Treatment

The first case of hypophysitis caused by ICIs was re-

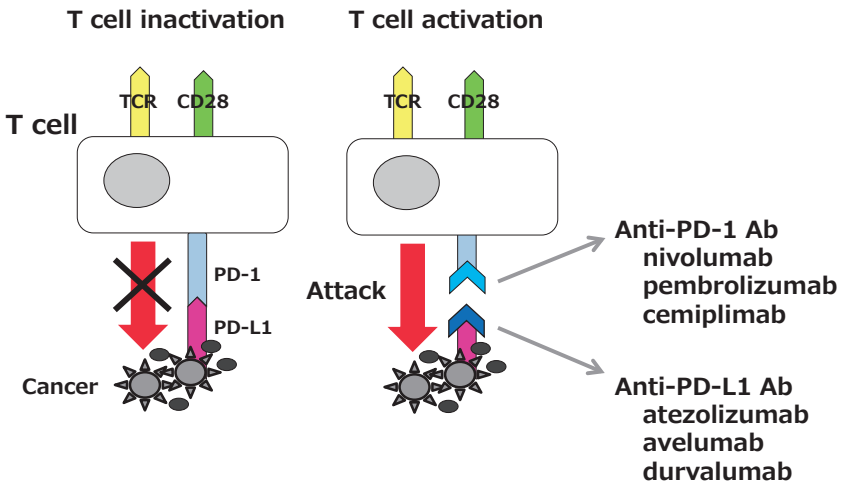

Fig. 2 Roles of PD-1 and PD-L1 in the anti-tumor immune response
Left
PD-1, a receptor on T cells, is upregulated and binds to one of its ligands (PD-L1), expressed on various cells, including cancer cells, to limit an ongoing immune response.
Right
By blocking either PD-1 or PD-L1, anti-PD-1/anti-PD-L1 antibodies enable T cells to have continuous anti-tumor activity.
Ab: antibody, PD-1: programmed cell death protein 1, PD-L1: programmed cell death ligand 1

ported in 2003 in a patient with melanoma treated with the anti-CTLA-4 antibody ipilimumab[6]. The prevalence of hypophysitis in patients who received ipilimumab is up to 10%[4]. The median time to occurrence of hypophysitis is between 9 to 12 weeks after the first administration of ipilimumab, although the timing of onset is difficult to predict. The onset of hypophysitis has been reported as late as 19 months after initiating ipilimumab[7]. There is a relationship between the dose of ipilimumab and the prevalence of hypophysitis, though there have been conflicting findings regarding this point[2]. Hypophysitis was observed in 13% of patients with melanoma treated with 5 mg/kg ipilimumab, whereas it occurred in 21% of patients treated with 9 mg/kg ipilimumab in the study reported by Marker *et al*.[8,9].

Clinical symptoms of hypophysitis caused by ICIs are unspecific and may include general fatigue, loss of libido, and appetite loss, which are mainly caused by adrenal insufficiency due to ACTH deficiency. Those symptoms often overlap with those of cancer-related complications. In some cases, headaches and visual field defects are observed due to pituitary gland swelling.

Hyponatremia, which reflects adrenal insufficiency, is often observed in initial laboratory work.

If hypophysitis is suspected, first simultaneous measurements of basal levels of all pituitary hormones (growth hormone (GH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), ACTH, and prolactin (PRL)) and their target organ hormones (insulin-like growth factor (IGF)-I, free triiodothyronine (fT3), free thyroxine (fT4), cortisol, and testosterone for men and estradiol for women) are required.

At diagnosis, not only ACTH but also TSH and gonadotropin deficiency are frequently observed. In ipilimumab-induced hypophysitis, the incidences of pituitary hormone deficiency are reported to be TSH (93%), gonadotropin (86%), or ACTH deficiencies (75%)[10].

Low morning cortisol levels (less than 5 μg/dL at 8 A.M.) without elevated ACTH levels suggest secondary adrenal insufficiency (ACTH deficiency). A previous or current history of taking oral or topical steroids should be confirmed as these alter the endogenous cortisol secretion status. For further evaluation of the pituitary-adrenal axis, a corticotropin-releasing hormone (CRH) test (administration of 100 μg CRH) or insulin tolerance test (ITT) is performed. ITT and CRH tests stimulate the CRH (hypothalamus)-ACTH (pituitary)-cortisol axis at the hypothalamus and pituitary levels, respectively. If the detected peak cortisol level is below 18 μg/dL for these stimulation tests, adrenal insufficiency should be considered. Although ITT is the gold standard test for diagnos-

ing adrenal insufficiency, hypoglycemia induced by ITT is a risk for aging patients with malignant disease. Moreover, it is contraindicated for patients with convulsions.

The rapid ACTH test (administration of 0.25 mg tetracosactide) stimulates adrenal glands directly. Adrenal insufficiency should be considered if the peak cortisol response is low (< 18 μg/dL). In cases of secondary adrenal insufficiency, the cortisol response to ACTH administration might be normal when an ACTH test is performed shortly after the onset of the ACTH deficiency, as it takes about six weeks after the loss of ACTH for the adrenal function to deteriorate.

Low fT4 levels with inappropriately low or normal TSH levels indicate central hypothyroidism (TSH deficiency). Low sex hormone levels (testosterone for men and estradiol for premenopausal women) without significantly elevated LH and FSH levels indicate hypogonadotropic hypogonadism (gonadotropin deficiency). For postmenopausal women, "low or normal" basal FSH and LH levels suggest gonadotropin deficiency, as FSH and LH levels are typically physiologically elevated in the postmenopausal period. To evaluate the GH secretory status, a GH stimulating test (such as GH-releasing peptide-2; GHRP-2 or ITT) is required. Serum IGF-I levels are often normal (or low), even in patients with severe GH deficiency. Therefore, GH deficiency cannot be ruled out, even if IGF-I levels appear normal.

A pituitary magnetic resonance imaging (MRI) analysis is important to rule out sellar metastasis. A pituitary MRI reveals diffuse and symmetrical enlargement of the pituitary gland in patients with hypophysitis. The findings using contrast enhancement may be homogeneous or heterogeneous[7]. However, enlargement is sometimes mild and subtle in hypophysitis caused by ICIs and is recognized only when compared with previous imaging[3]. Therefore, normal pituitary findings do not rule out hypophysitis induced by ICIs.

Several mechanisms behind the development of ipilimumab-induced-hypophysitis have been suggested. Pituitary endocrine cells express CTLA-4, but the clinical significance of pituitary CTLA-4 has not been fully elucidated[4]. The levels of CTLA-4 expression on the pituitary gland vary among individuals, and this variability might influence the susceptibility to develop hypophysitis caused by anti-CTLA-4 antibody treatment. Circulating anti-pituitary antibodies, which were absent prior to ipilimumab administration, can be detected in patients with hypophysitis caused by anti-CTLA-4 treatment[5]. The antibodies specifically recognize thyrotrophic, gonadotrophic (FSH-producing cells), and corticotrophic cells[5,11].

Compared with primary lymphocytic hypophysitis, which is typically observed in women during pregnancy or the postpartum period, ACTH, TSH, and gonadotropin deficiencies are significantly more common in ICI-induced hypophysitis. On the contrary, GH deficiency, prolactin abnormalities (hyperprolactinemia or PRL deficiency), and central diabetes insipidus are less common in ICI-induced hypophysitis[3]. Regarding MRI findings, compared with primary hypophysitis, compression of the optic chasm or swelling of the pituitary stalk is rarely observed[3]. ICI-induced hypophysitis is more common in men over the age of 60 years, although this finding may reflect the higher incidence of underlying cancers in this group of patients[3].

A pituitary biopsy is usually not conducted for ICI-induced hypophysitis in clinical practice. A published report showed that an autopsy of the pituitary gland in a patient with pleural mesothelioma associated with anti-CTLA-4 antibody-induced hypophysitis showed complete destruction of the anterior pituitary gland due to necrosis and fibrosis[4]. Moreover, gonadotrophic and thyrotrophic cells had disappeared. The histopathologic analysis suggested that treatment with anti-CTLA-4 antibody might cause hypophysitis, especially in patients whose pituitary gland expresses high levels of CTLA-4 antigen. This effect might be caused by type II (IgG-dependent) immune mechanisms, which induce classical complement activation and type IV (T cell-dependent) immune mechanisms that induce diffuse infiltration of autoreactive T cells (**Fig. 3**).

Management of Hypophysis Caused by Anti-CTLA-4 Antibody Treatment

Glucocorticoid replacement therapy is required for ACTH deficiency. In most patients, 15 (-20) mg of oral hydrocortisone (splitting the dose between 10 mg in the morning and 5 mg in the evening to imitate the circadian rhythm) results in physiologic replacement doses for secondary adrenal insufficiency. In acute illness, a stress dose of steroids (up to 300 mg/24 hr) should be administered. In general, lifelong glucocorticoid replacement will be necessary. On the contrary, TSH and gonadotropin deficiencies are often transient and reversible in this pathology. Recoveries of TSH and gonadotropin deficiencies range between 6-64% and 12-57%, respectively[12]. In a case of persistent central hypothyroidism (low free thyroxine levels without corresponding elevated TSH), levothyrox-

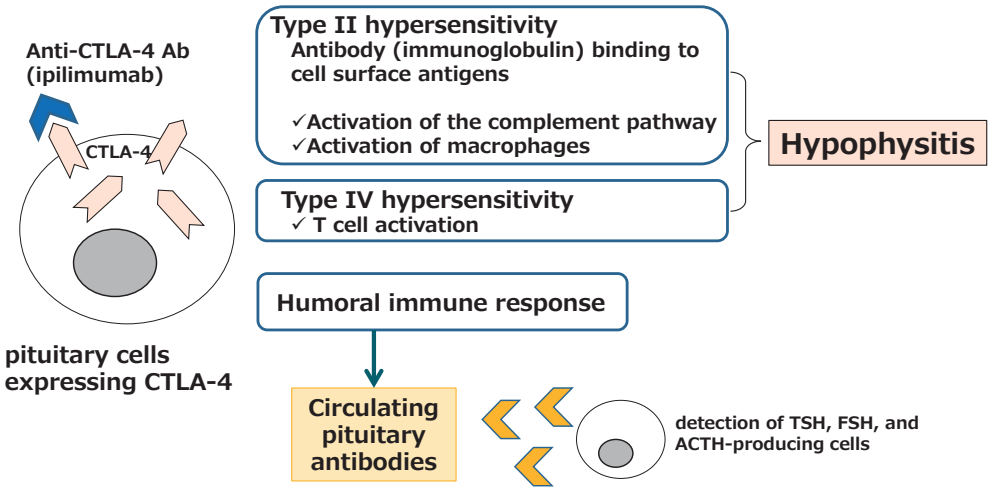

Fig. 3 The mechanisms of hypophysitis induced by anti-CTLA-4 antibody therapy
The anti-CTLA-4 antibody binds to CTLA-4 expressed on anterior pituitary cells, inducing inflammation by type II and IV hypersensitivity reactions.
Moreover, circulating antibodies that recognize TSH-, FSH-, and ACTH-producing cells are detected in patients with anti-CTLA-4 antibody-induced hypophysitis.
Ab: antibody, ACTH: adrenocorticotropic hormone, CTLA-4: cytotoxic T lymphocyte-associated protein 4, FSH: follicle-stimulating hormone, TSH: thyroid-stimulating hormone

ine is started after glucocorticoid replacement is stabilized, to avoid an adrenal crisis. Levothyroxine should be adjusted until serum-free thyroxine levels increase to values within the normal range (usually, a levothyroxine dose of up to about 1.1 μg/kg is needed)[7]. GH replacement therapy is contraindicated in patients with active malignancy.

A pharmacological dose of steroid therapy is usually not recommended for ICI-induced hypophysitis. Le Min et al. compared the improvement of ipilimumab-related hypophysitis between those with and without systemic high-dose corticosteroids treatment[13]. There were no significant differences in outcomes between two groups, including resolution of pituitary enlargement and endocrinopathies. They concluded as systemic high-dose corticosteroids therapy in patients with ipilimumab-related hypophysitis might not be indicated. Furthermore, patients who were administered high-dose steroids had worse survival rate outcomes compared with patients treated with a physiological replacement dose of steroids[14].

Adverse events of ICIs are classified into five grades as follows; Grade 1: mild, Grade 2: moderate, Grade 3: severe, defined as requiring hospitalization, Grade 4: life-threatening, and Grade 5: death. In most cases (Grade 1-2), discontinuation of ICIs is unnecessary once the general condition is stabilized for patients with hypophysitis, as it is well controlled by appropriate hormone replacement. Moreover, several studies reported that the development of hypophysitis as irAE is associated with a better clinical response to ICIs and survival rates[15–17].

ACTH Deficiency Caused by Anti-PD-1 Antibody/ Anti-PD-L1 Antibody Treatment

In contrast to anti-CTLA-4 antibody-induced hypophysitis that involves multiple pituitary hormone deficiencies, anti-PD-1/anti-PD-L1 antibodies selectively affect corticotropic cells. Isolated ACTH deficiency occurs in about 0.5 to 1% of patients who receive anti-PD-1 /anti-PD-L1 antibody treatment[18]. ACTH deficiency develops on average at 27 weeks after the initiation of anti-PD-1 antibody therapy and 27.8 weeks after the initiation of anti-PD-L1 antibody therapy[3]. Isolated ACTH deficiency is mostly characterized by a lack of imaging abnormality on the pituitary MRI, and patients do not have symptoms caused by mass effects[3,19].

Cho *et al*. reported that among clinical findings that would indicate adrenal insufficiency due to ACTH deficiency, such as general fatigue, hypotension, hypoglycemia, and hyponatremia, hyponatremia was the most powerful predictor of the development of ACTH deficiency associated with nivolumab therapy. In their study, hyponatremia had already been observed at the last administration of nivolumab prior to the overt ACTH deficiency[20].

Recently, we analyzed differences in clinical character-

istics and HLA (human leukocyte antigen) frequencies between ICI-induced and idiopathic-isolated ACTH deficiency[21]. Age at diagnosis (71 vs. 57 years) and body mass index (20.9 vs. 17.9 kg/m^2) were higher, while the rate of weight loss was lower in patients with ICI-induced ACTH deficiency compared with idiopathic ACTH deficiency. Those findings were probably caused by the fact that the patients in the ICI-induced ACTH deficiency group had attended a hospital more frequently and were diagnosed with adrenal insufficiency earlier than the idiopathic ACTH deficiency group. Blood analysis showed no differences between the ICI-induced ACTH deficiency and idiopathic ACTH deficiency groups in the frequency of hyponatremia, hypoglycemia, or eosinophilia. There were no specific HLAs related to ICI-induced ACTH deficiency, whereas several HLAs in strong linkage disequilibrium were associated with idiopathic ACTH deficiency.

Different from CTLA-4, PD-1 expression on human pituitary cells has not been investigated[22], and the pathogenesis of isolated ACTH deficiency induced by anti-PD-1 or anti-PD-L1 remains unclear[15]. In 2021, Kanie *et al*. reported that among 20 patients with ACTH deficiency treated with PD-1/PD-L1 inhibitors with or without anti-CTLA-4 antibodies, two patients had detectable anti-corticotropin antibodies in the circulation[23]. The circulating antibodies recognized proopiomelanocortin (POMC; a precursor of ACTH). The types of tumors in those two patients were malignant melanoma and renal cell carcinoma, and both tumors exhibited ectopic ACTH expression. From these findings, the researchers hypothesized that 10% of PD-1/PD-L1 inhibitor-related ACTH deficiency should be considered a paraneoplastic syndrome, and that ectopic expression of ACTH in tumors might induce anti-corticotropin antibodies that attack corticotropic cells of the pituitary gland, resulting in the occurrence of ACTH deficiency.

For isolated ACTH deficiency, glucocorticoid replacement therapy is necessary. In general, lifelong hormone replacement is required.

Case Presentation of Anti-PD-1-Induced Isolated ACTH Deficiency

Here, a typical clinical course of a patient with anti-PD-1 antibody-induced isolated ACTH deficiency is presented.

A 70-year-old man was treated with pembrolizumab (anti-PD-1 antibody) for recurrent lung squamous cell carcinoma. After the second cycle, he had transient thyrotoxicosis followed by hypothyroidism. He was diagnosed with destructive thyroiditis. His thyroid function did not recover. At this point (after the second cycle), plasma ACTH was 54.6 pg/mL and cortisol levels were 10.6 μg/dL. Replacement therapy with L-thyroxine was started for persistent hypothyroidism, after which pembrolizumab was continued. One month later, he had appetite loss and general fatigue, and his cortisol and ACTH levels suddenly decreased to 0.2 μg/dL and <1.5 pg/mL, respectively. Replacement of hydrocortisone was added to his treatment regimen, and he was admitted to the hospital for further evaluation of pituitary functions. MRI of the sellar region showed no remarkable findings and no evidence of metastasis (**Fig. 4**). Based on the basal levels of pituitary and peripheral hormones, and provocative tests using 100 μg of CRH, thyroid-releasing hormone (TRH: 500 μg), luteinizing hormone-releasing hormone (LHRH: 100 μg), and growth hormone-releasing peptide-2 (GHRP-2: 100 μg), he was diagnosed with isolated ACTH deficiency caused by pembrolizumab (**Table 1**). His symptoms disappeared with hydrocortisone and L-thyroxine replacement therapy.

Pituitary irAE and Combination Regimens of ICIs

Recently, combination regimens of anti-CTLA-4 and anti-PD-1/anti-PD-L1 antibodies have been more often used because of their potential synergistic effects. However, combination therapy has a higher risk of hypophysitis than monotherapy. A meta-analysis among 6,472 patients revealed that 85 patients experienced hypophysitis caused by ICIs[24]. Compared with patients who received ipilimumab or anti-PD-1 antibody, those who received combination therapy were at significantly higher risk of developing hypophysitis (Odds Ratio, 2.2; 95% confidence interval, 1.39-3.60; p=0.001)[7,24]. The incidence of hypophysitis induced by combination therapy was 8.5-9.0%[25]. The median time to occurrence of hypophysitis is also earlier in combination therapy than in monotherapy, at an average of 30 days[15].

Conclusions

In conclusion, the pituitary gland is one of the common targets of irAE caused by ICIs. ICI-induced hypophysitis may bring a worse quality of life to patients with advanced cancer. Early diagnosis of hypophysitis and initiation of appropriate hormone replacement is essential. Close collaboration between oncologists and endocrinologists is indispensable.

Conflict of Interest: None declared.

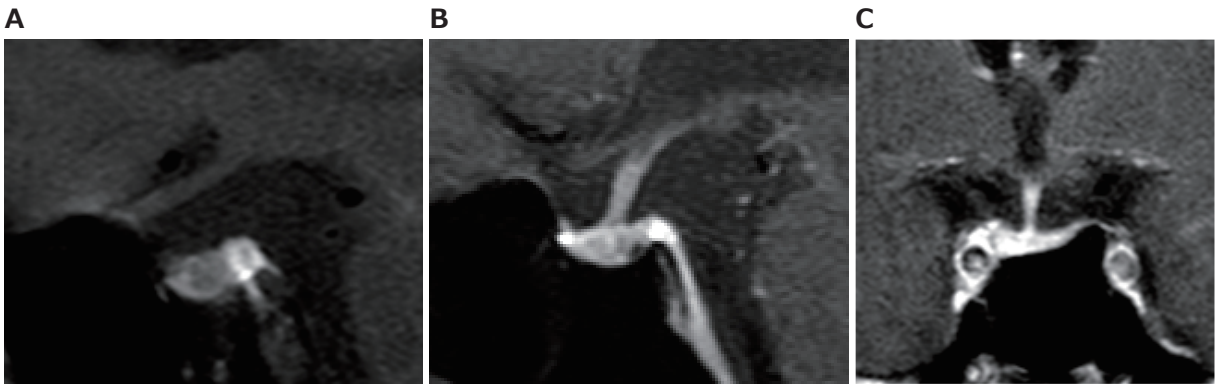

Fig. 4 Pituitary MRI

A: T1-weighted plain MRI (sagittal section), B: T1-weighted gadolinium-enhanced MRI (sagittal section), C: T1-weighted gadolinium-enhanced MRI (coronal section).

All are unremarkable findings.

MRI: magnetic resonance imaging

Table 1 Endocrinological data

GH	0.24 ng/mL	ACTH	<1.5 pg/mL
IGF-I	110 ng/mL (63-206)	Cortisol	0.2 μg/dL
PRL	7.4 ng/mL	DHEA-S	259 ng/mL (24-2,440)
TSH	2.37 μIU/mL	LH	3.7 mIU/mL
fT3	3.46 pg/mL	FSH	4.9 mIU/mL
fT4	0.90 ng/dL	Testosterone	4.96 ng/mL

CRH test

(min)	0	30	60	90	120
ACTH (pg/mL)	<1.5	<1.5	<1.5	<1.5	<1.5
Cortisol (μg/dL)	0.2	0.2	0.3	0.3	0.3

Rapid ACTH test

(min)	0	30	60	90	120
Cortisol (μg/dL)	0.5	5.0	6.7	7.4	7.4

Parentheses indicate reference values. The results of LHRH, TRH, and GHRP-2 tests were normal (data not shown). Adrenal insufficiency should be considered if the peak cortisol response is less than 18 μg/dL for rapid ACTH test.

ACTH: adrenocorticotropic hormone, CRH: corticotropin-releasing hormone, DHEA-S: Dehydroepiandrosterone sulfate, FSH: follicle-stimulating hormone, fT3: free triiodothyronine, fT4: free thyroxine, GH: growth hormone, GHRP: growth hormone releasing peptide, IGF: insulin-like growth factor, LH: luteinizing hormone, LHRH: luteinizing hormone-releasing hormone, PRL: prolactin, TRH: thyrotropin-releasing hormone, TSH: thyroid-stimulating hormone

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