Secondary Adrenal Insufficiency Following Nivolumab Therapy in a Patient with Metastatic Renal Cell Carcinoma

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Currently, nivolumab (an anti-programmed cell death-1 receptor monoclonal antibody) is available for many types of advanced cancers in Japan. However, there have been few detailed case reports about endocrine-related adverse events of this therapy. Here, we report a patient with metastatic renal cell carcinoma who presented with secondary adrenal insufficiency following nivolumab therapy. Endocrinological assessment by rapid adrenocorticotropic hormone (ACTH) and corticotropin-releasing hormone (CRH) tests revealed that the patient's disorder was a secondary adrenal insufficiency due to pituitary dysfunction. Moreover, the results of the thyrotropin-releasing hormone (TRH), luteinizing hormone-releasing hormone (LH-RH) and growth hormone-releasing peptide-2 (GHRP-2) tests showed that only the ACTH function was destroyed (isolated ACTH deficiency). The magnetic resonance imaging (MRI) findings of hypophysitis, which is the major cause of isolated ACTH deficiency, usually demonstrate enlargement of the pituitary gland. However, the MRI findings of our case showed no abnormalities of the pituitary gland and stalk. Therefore, not only oncologists, but also other specialists, including doctors in emergency units, should have knowledge of this specific feature. Our clinical observation could be useful to avoid a delay in diagnosis and to treat life-threatening adverse effects of nivolumab therapy, such as secondary adrenal insufficiency.

Key words: adrenal insufficiency, pituitary dysfunction, nivolumab, programmed cell death-1, renal cell carcinoma

INTRODUCTION

Recent strategies of anticancer immunotherapy have begun to take off the brake, such as tumor-induced immune tolerance [1, 2]. Among these strategies, immune checkpoint inhibitors, such as human monoclonal antibodies (mAb) against the cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death-1 (PD-1) receptors, have demonstrated improvements in overall survival for a number of advanced malignancies [3–5]. However, these blockades can also block immune self-tolerance and result in the induction of immune-related adverse events (IRAEs), including those in the gastro-intestinal tract, liver, skin, and endocrine system [6, 7].

In 2011, the United States Food and Drug Administration (FDA) approved ipilimumab, an anti-CTLA-4 receptor mAb for the treatment of advanced malignant melanoma. Since then, IRAEs of anti-CTLA-4 receptor mAb therapy have been described in depth [6–8]. In regard to endocrine IRAEs, Corsello *et al.* demonstrated that the spectrum of endocrine disease most commonly includes hypophysitis, more rarely includes thyroid disease or abnormalities in thyroid function tests, and occasionally includes primary adrenal insufficiency [9]. Hypophysitis has been emphasized because this condition can lead to life-threatening adverse effect as a result of secondary adrenal insufficiency [9]. By contrast, nivolumab, an anti-PD-1 receptor mAb was approved in 2014 for the treatment of patients with advanced malignant melanoma in the United States and Japan. Compared with ipilimumab, there have been few published investigations of endocrine IRAEs [9–11]. Eigentler *et al.* reported that the thyroid gland was most affected and that hypophysitis, hypopituitarism, and type 1 diabetes mellitus were uncommon in patients taking anti-PD-1 receptor mAb therapy [11].

Currently, nivolumab is available for an increasing number of advanced cancers in Japan. It is expected that not only oncologists, but also other specialists, including doctors in emergency units, will see patients experiencing IRAEs caused by anti-PD-1 receptor mAb therapy and will be required to respond immediately to diagnose and treat these adverse events. However, few detailed case reports of life-threatening adverse effects of nivolumab therapy, such as adrenal insufficiency, have been published [12–16]. Therefore, here we describe a patient with metastatic renal cell carcinoma (RCC) who presented with secondary adrenal insufficiency following nivolumab therapy, and discuss both the detailed endocrinological assessment and the management of this adverse event.

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CASE REPORT

A 74-year-old woman was referred to our hospital for evaluation of a left pulmonary hilar tumor. She did not smoke or drink alcohol. There was no known family history of endocrine disease or malignant tumors. The patient had a history of left lobe thyroidectomy for thyroid cancer 20 years prior as well as a left nephrectomy for RCC 18 years prior. Her other medical history included hypertension and dyslipidemia, and she was taking amlodipine at 2.5 mg, azilsartan at 40 mg, atorvastatin at 5 mg and levothyroxine at 100 μg. A computed tomography scan revealed a well-circumscribed tumor that was 28 mm in diameter in the left hilar area, and no lesions were observed in other areas, such as the liver and bone (data not shown). At our hospital, a left pulmonary tumor biopsy was performed by a posterolateral thoracotomy, and the diagnosis of the patient was pulmonary metastasis of RCC based on the pathological results. Radical resection was judged to be difficult due to the area of tumor; therefore, chemotherapy with axitinib and everolimus was initially administered to the patient. However, both drugs had to be discontinued due to the appearance of drug-induced renal dysfunction. Thus, she began to receive intravenous administration of nivolumab (3 mg/kg) once every 2 weeks as a substitute treatment. The patient developed general fatigue, appetite loss, nausea and mild hyponatremia following the fifth administration and, after the sixth administration, she was admitted as an emergency case due to worsening symptoms and progressive hyponatremia.

Upon physical examination at admission, she presented with low-grade fever (37.4 ˚C); her pulse was 111 beats/min, her blood pressure was 108/79 mmHg, and her respiratory rate was 20 breaths/min. Her blood pressure was lower than usual, although she was unable to take antihypertensive drugs due to vomiting. The patient's visual field and acuity were normal, and there was no peripheral edema, or dry skin. Routine laboratory examinations revealed an increase in eosinophils (7.2 %) as well as anemia (RBC; 324×10^4/μL, Hb; 9.3 g/dL and Ht; 29.4 %) and hyponatremia (126 mEq/L). Her serum creatinine (2.31 mg/dL) was elevated, but her renal dysfunction was unchanged from the usual level. Urine protein had been observed from before, and urine ketone bodies were found due to poor feeding. A decrease in the levels of TP (6.0 g/dL), Alb (2.9 g/dL) and plasma osmolality (257 mOsm/kg) and an increase in the level of CRP (1.56 mg/dL) indicated malnutrition, dehydration and chronic inflammation. Liver function (AST; 17 IU/L, ALT; 6 IU/L and γ-GTP; 8 IU/L), glucose (75 mg/dL) and HbA1c (5.3 %) were normal. As shown in Table 1-1, despite the patient's low cortisol (F) level, adrenocorticotropic hormone (ACTH) was not elevated. Her free triiodothyronine (FT3) level was low and prolactin (PRL) level was high, and the cause was presumed to be the influence of malnutrition and administration of domperidone for the treatment of nausea, respectively. Other hormones were normal for a postmenopausal woman. Given that the possibility of primary or secondary adrenal insufficiency was considered as a result of the aforementioned results, a rapid ACTH test and a corticotropin-releasing hormone (CRH) test were performed (Table 2-1). The results of the rapid ACTH test showed a low cortisol response, and the CRH test showed a low ACTH response. Additionally, a thyrotropin-releasing hormone (TRH) test, a luteinizing hormone-releasing hormone (LH-RH) test and a growth hormone-releasing peptide-2 (GHRP-2) test were performed for evaluation of other pituitary functions (Table 2-2). Oral drugs, such as levothyroxine, were discontinued due to vomiting, and loading tests were performed. The secretion of thyroid-stimulating hormone (TSH), PRL, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and growth hormone (GH) showed a normal response for a postmenopausal woman. Next, we performed unenhanced pituitary magnetic resonance imaging (MRI) because of renal dysfunction. MRI showed no abnormalities of the pituitary gland and stalk (Figure). Additionally, a normal hyperintense signal in the posterior pituitary lobe was confirmed. We then performed examinations related to systemic and autoimmune diseases (Table 1-2), and no abnormality was observed, except for inflammatory disease. Based on these investigations, we diagnosed the patient's disorder as a secondary adrenal insufficiency due to pituitary dysfunction.

We immediately started steroid replacement treatment for adrenal insufficiency. The patient was administered 10 mg of oral hydrocortisone twice daily, and the symptoms of general fatigue, appetite loss and nausea disappeared promptly. The level of eosinophils as well as her hyponatremia also normalized after 1 week of administration. Nutritional status and dehydration were improved and reduction of inflammatory response was also observed (Table 3). The patient's blood pressure returned to its usual level, and we resumed antihypertensive drugs. Additionally, thirst, polydipsia and polyuria due to masked diabetes insipidus did not appear after hydrocortisone treatment, and pituitary dysfunction was considered to not extend to the posterior lobe. The patient was discharged with symptomatic improvement, and she is being followed by the division of Nephrology, Endocrinology and Metabolism.

DISCUSSION

Endocrine IRAEs caused by anti-CTLA-4 receptor mAb (ipilimumab) therapy have been described in detail [6–9] because the FDA approved ipilimumab for the treatment of advanced malignant melanoma in 2011. By contrast, anti-PD-1 receptor mAb (nivolumab) therapy was approved in 2014 for the treatment of patients with advanced malignant melanoma in the United States and Japan. Compared with ipilimumab, there have been few published investigations of endocrine IRAEs [9–11]. With regard to the endocrine toxicities related to primary or secondary adrenal insufficiency, these reports demonstrated that ipilimumab most commonly included hypophysitis and occasionally included primary adrenal insufficiency. However, these reports, including clinical trials or post-marketing surveillance revealed that hypophysitis, hypopituitarism, and primary adrenal insufficiency were uncommon in nivolumab therapy, although there was no detailed endocrinological assessment [9–11, 17]. In our case,

Table 1-1 Endocrine examination on admission.

Endocrine examination			
neurohypophysis		PRL	226.3 ng/mL [< 30]
ADH	1.5 pg/mL [≦ 3.6]	GH	2.58 ng/mL [0.28–1.64]
adenohypophysis		IGF-I	61 ng/mL [53–165]
ACTH	14.4 pg/mL [7.2–63.3]	FSH	51.1 mIU/mL [≦ 157.8]
F	2.34 μg/dL [4.0–18.3]	LH	102.1 mIU/mL [5.7–64.3]
TSH	1.150 μIU/mL [0.27–4.20]	E2	< 25 pg/mL [≦ 77]
FT3	1.94 pg/mL [2.30–4.00]	Prog	0.1 ng/mL [< 0.67]
FT4	1.12 ng/dL [1.00–1.80]		

Abbreviations: ADH, antidiuretic hormone; ACTH, adrenocorticotrophic hormone; F, cortisol; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; PRL, prolactin; GH, growth hormone; IGF-1, insulin-like growth factor-1; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; Prog, progesterone; [ ], reference range.

Table 1-2 Laboratory data related to the immune system.

sIL-2R	830 U/mL [145–519]	TPOAb	11 IU/mL [< 16]
$1.25(OH)_2D_3$	40 pg/mL [20–60]	TgAb	11 IU/mL [< 28]
ACE	23.8 IU/L [7–25]	TRAb	4.0 % [< 15]
MPO-ANCA	< 1.0 U/mL [< 3.5]	anti-GAD Ab	< 5.0 U/mL [< 5.0]
PR3-ANCA	< 1.0 U/mL [< 3.5]	IgG	962 mg/dL [870–1700]
ANA	negative	IgG4	40.0 mg/dL [4.5–117]
C3c	74.8 mg/dL [85–160]	APA	negative
C4	20.1 mg/dL [15–40]		

Abbreviations: sIL-2R, soluble interleukin-2 receptor; $1.25(OH)_2D_3$, 1.25-dihydroxyvitamin D_3; ACE, angiotensin-converting enzyme; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3-ANCA; ANA, anti-nuclear antibody; C3c/4, complement 3c/4; TPOAb, anti-thyroid peroxidase antibody; TgAb, anti-thyroglobulin antibody; TRAb, anti-thyroid-stimulating hormone receptor antibody; GAD Ab, glutamic acid decarboxylase antibody; APA, anti-pituitary antibody; [ ], reference range.

endocrinological assessment by rapid ACTH and CRH tests revealed that the patient's disorder was a secondary adrenal insufficiency due to pituitary dysfunction. Moreover, the results of the TRH, LH-RH and GHRP-2 tests showed that only the ACTH function was destroyed (isolated ACTH deficiency).

It is well known that hypophysitis causes isolated ACTH deficiency by an autoimmune-related mechanism [18]. In addition to the abovementioned endocrinological results, the MRI findings of hypophysitis usually demonstrate enlargement of the pituitary gland [19]. Many reports of hypophysitis caused by ipilimumab therapy have described this typical MRI finding [6–9]. In cases of nivolumab therapy, Okano *et al.* recently reported typical MRI finding of hypophysitis [15]. However, another report recorded no signs of pituitary swelling [14]. We believe that nivolumab-induced hypophysitis might have different clinical characteristics from other forms of hypophysitis. Indeed, we could not confirm this hypothesis because there have been no reports of the pathogenesis of nivolumab-induced hypophysitis. Thus, although our case as well as recent reports [12, 13] did not present the aforementioned MRI findings, we could not rule out the possibility of hypophysitis as a cause of isolated ACTH deficiency. Currently, nivolumab is available for many types of advanced cancers in Japan. Therefore, not only oncologists, but also other specialists, including doctors in emergency units, should have knowledge of this specific feature. Our clinical observation could be useful to avoid a delay in diagnosis and to treat life-threatening adverse effects of nivolumab therapy, such as secondary adrenal insufficiency.

An important question remaining is why MRI revealed no enlargement of the pituitary gland in recent reports, including our case. This problem could be resolved by the pathogenesis of hypophysitis induced by immune checkpoint inhibitors. Addressing this issue, Iwama *et al.* established a model of secondary hypophysitis by repeated injection of a CTLA-4-blocking Ab into mice and showed that the mice developed lymphocytic infiltration of the pituitary gland and circulating pituitary Abs [20]. The authors hypothesized that the injected CTLA-4 Ab could cause pituitary toxicity if bound to CTLA-4 antigens expressed ectopically on pituitary endocrine cells [20]. In addition, Caturegli *et al.* performed an autopsy analysis of the pituitary glands of patients with cancer treated with CTLA-4 blockade, and found that CTLA-4 antigen was expressed by pituitary endocrine cells in all patients but at different levels [21]. This study suggested that administration of CTLA-4-blocking Abs to patients who express high levels of CTLA-4 antigen in the pituitary could cause an aggressive form of hypophysitis through type IV and

Table 2-1 Results of rapid ACTH and CRH tests.

rapid ACTH				
min	0	30	60	
ACTH (pg/mL)	15.0			
F (μg/dL)	4.81	13.0	14.7	
CRH				
min	0	30	60	90
ACTH (pg/mL)	9.3	19.7	15.8	
F (μg/dL)	7.13		10.4	10.1

Abbreviations: ACTH, adrenocorticotropic hormone; F, cortisol; CRH, corticotropin-releasing hormone.

Table 2-2 Results of TRH, LH-RH and GHRP-2 test.

TRH					
min	0	30	60		
TSH (μIU/mL)	6.520	11.020	10.700		
PRL (ng/mL)	23.3	101.3	88.1		
LH-RH					
min	0	30	60	90	
LH (mIU/mL)	53.3	89.8	113.2		
FSH (mIU/mL)	123.0		135.1	143.5	
GHRP-2					
min	0	15	30	45	60
GH (ng/mL)	2.40	84.2	99.0	81.2	64.4

Abbreviations: TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; PRL, prolactin; LH-RH, luteinizing hormone-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GHRP, growth hormone-releasing peptide; GH, growth hormone.

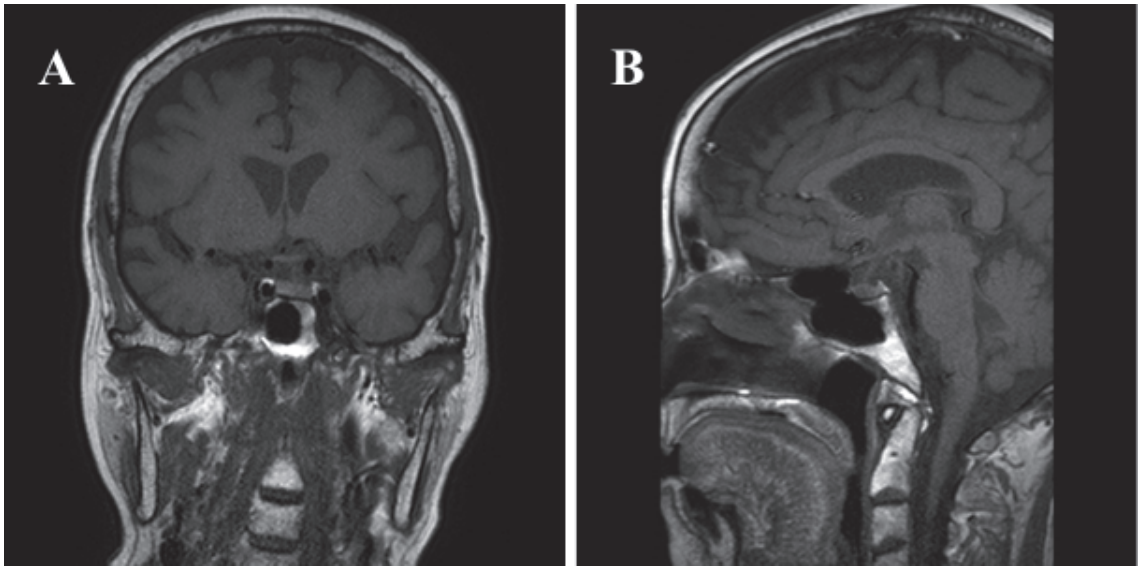

Figure Magnetic resonance imaging (MRI) findings on admission. The MRI showed no abnormal findings of the pituitary gland (A: unenhanced coronal T1-weighted image, B: unenhanced sagittal T1-weighted image).

Table 3 Routine laboratory examinations before and after hydrocortisone treatment.

	Before treatment	After treatment
Urinalysis		
protein	(1+)	(1+)
occult blood	(-)	(-)
glucose	(-)	(-)
ketone body	(2+)	(-)
osmolality [50–1300 mOsm/kg]	174	150
Hematological examination		
WBC [4000–8000/μL]	3800	4500
Neu [40–70 %]	45.6	55.1
Lym [20–40 %]	38.7	35.1
Eo [1–4 %]	7.2	2.9
RBC [380–480×104/μL]	324	286
Hb [11.5–15.5 g/dL]	9.3	8.6
Ht [34.0–42.0 %]	29.4	28.5
Plts [14.0–40.0×104/μL]	27.4	15.4
Blood chemistry		
CRP [< 0.3 mg/dL]	1.56	< 0.09
TP [6.5–8.0 g/dL]	6.0	6.8
Alb [3.9–4.8 g/dL]	2.9	3.8
Na [136–145 mEq/L]	126	145
K [3.5–4.8 mEq/L]	4.3	4.6
Cl [98–108 mEq/L]	94	109
BUN [8–20 mg/dL]	16	30
Cr [0.5–0.8 mg/dL]	2.31	2.28
UA [3.0–6.0 mg/dL]	6.2	6.7
plasma osmolality [275–290 mOsm/kg]	257	309

[ ], reference range.

type II immune mechanisms [21]. It seems that these reports do not differ greatly from the pathogenesis of previously described lymphocytic hypophysitis, which usually demonstrates enlargement of the pituitary gland [18, 19]. However, there have been no reports of the pathogenesis of nivolumab-induced hypophysitis. It is likely that some immune-related factors, including HLA types [22] as well as functional differences in the processes of T cell activation [23] play an important role in the different MRI findings between ipilimumab- and nivolumab-induced hypophysitis. However, further detailed investigations of nivolumab-induced hypophysitis are required to address this question.

Another problem with IRAEs in nivolumab therapy is how to treat the life-threatening adverse effects, such as adrenal insufficiency. The most important clinical point is whether high-dose glucocorticoids should be used. Some reports revealed that high-dose glucocorticoid treatment did not affect the anti-tumor efficacy of ipilimumab therapy [24]. However, Albarel *et al.* observed that high-dose glucocorticoids did not seem to change the natural history of ipilimumab-induced hypophysitis, especially concerning life-threatening corticotroph function: patients who had a corticotroph defect at diagnosis still had the defect at the end of the follow-up period, irrespective of the type of glucocorticoid treatment (high-dose or a physiological replacement dose) [25]. Moreover, the authors noted that another analysis recently found complications in five out of seven patients (four of whom needed to be hospitalized) after administration of high-dose corticosteroids for ipilimumab-induced hypophysitis, and partial or complete hypopituitarism remained in all patients [25, 26]. Based on these clinical reports of the treatment of ipilimumab-induced hypophysitis, we immediately started a physiological replacement dose of hydrocortisone after diagnosis of a secondary adrenal insufficiency due to pituitary dysfunction (isolated ACTH deficiency). We believe that a physiological replacement dose of hydrocortisone is recommended for our patient who did not present with serious pituitary enlargement-related symptoms, including significant hyponatremia, severe headaches, or visual-field disturbance. However, long-term follow-up of IRAEs in

nivolumab therapy is still required in order to determine the strict recommendations for the treatment of nivolumab-induced hypophysitis.

Another important clinical point is whether nivolumab can be continued under the appropriate replacement of corticosteroids. With regard to the treatment of ipilimumab-induced hypophysitis, Albarel *et al.* discussed that the benefits of ipilimumab, regarding survival in the context of a potentially fatal malignancy, greatly outweigh the risks of continuing therapy using an appropriate substitutive treatment [25]. Thus, such patients should not have ipilimumab treatment interrupted after adapted management of hypophysitis [25]. We also believe that nivolumab can be continued under the appropriate replacement of corticosteroids. Indeed, we are planning to resume nivolumab therapy. However, long-term follow-up of nivolumab-induced hypophysitis is still required in order to decide the strict recommendations for this clinical point.

In summary, we reported on a patient with metastatic RCC who presented with secondary adrenal insufficiency following nivolumab therapy. Based on the detailed endocrinological assessment, we diagnosed the patient's disorder as a secondary adrenal insufficiency due to pituitary dysfunction (isolated ACTH deficiency) and immediately started a physiological replacement dose of hydrocortisone according to the previous experience with ipilimumab-induced hypophysitis. We believe that isolated ACTH deficiency might be due to nivolumab-induced hypophysitis by a different mechanism than ipilimumab-induced hypophysitis. Currently, nivolumab is available in Japan for an increasing number of advanced cancers. It is expected that not only oncologists, but also other specialists, including doctors in emergency units, will see patients experiencing IRAEs caused by nivolumab therapy. Thus, detailed case reports of life-threatening adverse effects, such as adrenal insufficiency, resulting from nivolumab therapy are required. Our clinical observation could be useful to avoid a delay in the diagnosis and treatment of these adverse events.

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