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 adrenocorticotrophic 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.
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, 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 was discharged with symptomatic improvement, and she is being followed to the posterior lobe. The patient was discharged with nutritional status and dehydration 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 mAbs (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,
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.

<table>
<thead>
<tr>
<th>rapid ACTH</th>
<th>min</th>
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<th>60</th>
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<tbody>
<tr>
<td>ACTH (pg/mL)</td>
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<td>15.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F (µg/dL)</td>
<td></td>
<td>4.81</td>
<td>13.0</td>
<td>14.7</td>
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<table>
<thead>
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<th>30</th>
<th>60</th>
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<td>ACTH (pg/mL)</td>
<td></td>
<td>9.3</td>
<td>19.7</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td>F (µg/dL)</td>
<td></td>
<td>7.13</td>
<td>10.4</td>
<td>10.1</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
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<th>min</th>
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<tbody>
<tr>
<td>TSH (µIU/mL)</td>
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<td>6.520</td>
<td>11.020</td>
<td>10.700</td>
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<tr>
<td>PRL (ng/mL)</td>
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<td>23.3</td>
<td>101.3</td>
<td>88.1</td>
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<table>
<thead>
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<th>30</th>
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<tbody>
<tr>
<td>LH (mIU/mL)</td>
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<td>53.3</td>
<td>89.8</td>
<td>113.2</td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
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<td>123.0</td>
<td>135.1</td>
<td>143.5</td>
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<table>
<thead>
<tr>
<th>GHRP-2</th>
<th>min</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
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</thead>
<tbody>
<tr>
<td>GH (ng/mL)</td>
<td></td>
<td>2.40</td>
<td>84.2</td>
<td>99.0</td>
<td>81.2</td>
<td>64.4</td>
</tr>
</tbody>
</table>

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).
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

| 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 [580–480×10⁴/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.
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.

ACKNOWLEDGMENTS

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REFERENCES