Progression of Hypopituitarism and Hypothyroidism after Treatment with Pembrolizumab in a Patient with Adrenal Metastasis from Non-small-cell Lung Cancer

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Abstract:
Pembrolizumab, or anti-programmed death receptor 1 antibody, is an immune checkpoint inhibitor that can cause immune-related adverse events. We herein report for the first time the progression of hypopituitarism and hypothyroidism after treatment with pembrolizumab in a patient with adrenal metastasis of non-small-cell lung cancer. Severe primary hypothyroidism occurred three weeks after the first administration of pembrolizumab. Four months after the discontinuation of pembrolizumab, isolated adrenocorticotropic hormone (ACTH) deficiency was noted. Corticotropin-releasing hormone and rapid ACTH tests performed repeatedly showed that the patient’s pituitary and adrenal function had been gradually deteriorating. It is important to diagnose adrenal insufficiency without delay in order to prevent adrenal crisis.

Key words: immune-related adverse events, pembrolizumab, hypopituitarism, hypothyroidism

Case Report

A 59-year-old man was referred to our department for the treatment of hypothyroidism. Two years earlier, he had been diagnosed with NSCLC, and the inferior lobe of the right lung had been removed. The PD-L1 expression was detected

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in NSCLC tissue. The cancer was considered to be T2bN2M0 or stage IIIA (TNM staging), and the patient was treated with cisplatin (CDDP) plus vinorelbine (VNR) as adjuvant chemotherapy for four cycles. However, 1 month after chemotherapy, a right adrenal gland tumor (18 mm) was detected on computed tomography (CT). Enhanced CT suggested adrenal metastasis of lung cancer, so four courses of carboplatin (CBDCA) plus pemetrexed (PEM) chemotherapy were used as a first-line treatment for advanced NSCLC. Although the right metastatic adrenal tumor shrank following treatment, it grew again to 19 mm by 1 year after treatment (Fig. 1).

Because of re-enlargement of the adrenal tumor, pembrolizumab monotherapy (200 mg/course, every 3 weeks) was adopted to treat this PD-L1-positive NSCLC. Before the treatment, the plasma ACTH and cortisol levels at 9:30 am were 24 pg/mL and 6.8 μg/dL, respectively. On the day before treatment, the plasma ACTH and cortisol levels at 9:00 am were 42 pg/mL and 6.8 μg/dL, respectively. Although anti-thyroid peroxidase antibody (TPO Ab; 579 U/mL [reference range: <15]) and anti-thyroglobulin antibody (Tg Ab; 274 IU/mL [reference range: <27]) were both positive, his thyroid function was normal before the start of pembrolizumab. Three weeks after the second administration of pembrolizumab, primary hypothyroidism was detected along with an elevated thyrotropin-stimulating hormone level (66.4 μIU/mL [reference range: 0.5-5]). The free triiodothyronine (FT3, 1.35 pg/mL) and free thyroxine (FT4, 0.29 ng/dL) levels were both low (reference ranges: 2.3-4.0 pg/mL and 0.9-1.7 ng/dL, respectively). We therefore started levothyroxine sodium (25 μg/day) supplementation (Fig. 2).

Thyroid ultrasonography showed heterogeneous echotexture mixed with diffuse hypoechoic areas (Fig. 3). One month after levothyroxine supplementation, both the TPO Ab (>600 U/mL) and Tg Ab (425 IU/mL) levels were increased. Three months after the first administration of pembrolizumab (third administration: total dose of 600 mg), the plasma ACTH and cortisol levels at 9:30 am had decreased to 16.4 pg/mL and 4.1 μg/dL, respectively. A spot test for the urinary free cortisol level showed a low value (18.5 μg/g creatinine). The CRH stimulation test indicated low levels of basal plasma ACTH and cortisol levels (9.7 pg/mL and 6.3 μg/dL, respectively, at 9:30 am) and a blunting of the responsiveness of cortisol (14.3 μg/dL) despite a normal responsiveness of ACTH (Fig. 4). In contrast, the rapid ACTH test (250 μg Synacthen) revealed a peak cortisol level of

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**Figure 1.** Abdominal computed tomography (CT). One year after chemotherapy, CT shows a right adrenal gland tumor (19 mm; arrow).

**Figure 2.** Changes in thyroid hormone levels during the clinical course. Levothyroxine sodium supplementation was started three weeks after the second administration of pembrolizumab. TSH: thyrotropin-stimulating hormone, ACTH: adrenocorticotropic hormone, CRH: corticotropin-releasing hormone.
22.2 μg/dL, suggesting that the patient’s adrenocortical function had been maintained (Fig. 5). There was no eosinophilia, hypoglycemia, or hyponatremia.

After the fifth administration of pembrolizumab (total dose of 1,000 mg), respiratory physicians at our hospital opted to discontinue it because the right adrenal metastatic lesion had enlarged. Subsequently, combination therapy of docetaxel plus ramucirumab, an anti-vascular endothelial growth factor receptor 2 (VEGFR2) antibody, was started. At this point, the plasma ACTH and cortisol levels at 9:00 am were 34 pg/mL and 7.9 μg/dL, respectively.

Four months after the discontinuation of pembrolizumab, the patient developed anorexia, fatigue, and a slight fever with mild hyponatremia (137 mmol/L). The plasma ACTH and cortisol levels at 10:00 am were 17.3 pg/mL and 0.89 μg/dL, respectively. Furthermore, his dehydroepiandrosterone-sulfate (DHEA-S) level was low (17 μg/dL [reference range: 31-131]). Hypophysitis was suspected, and the CRH test was performed again during hospitalization. In the CRH stimulation test, the peak plasma
ACTH and cortisol levels decreased to 29.3 pg/mL and 3.1 μg/dL, respectively (Fig. 4). The rapid ACTH test also indicated the existence of adrenal insufficiency because the peak cortisol level was decreased (7.6 μg/dL) (Fig. 5). The plasma aldosterone concentration and renin activity were 5.6 ng/dL and 0.3 ng/mL/h, respectively. The rapid ACTH test revealed a peak plasma aldosterone level of 16.2 ng/dL. The 24-h urinary free cortisol level was below measurement sensitivity (reference range: 11-80 μg/day), whereas 24-h urinary aldosterone was 8.2-9.4 μg/day (reference range: 0-10).

Gadolinium-enhanced magnetic resonance imaging (MRI) showed no enlargement of the pituitary gland or thickening of the pituitary stalk (Fig. 6). An insulin tolerance test (ITT) revealed that the basal plasma ACTH and cortisol levels were 17.2 pg/mL and 1.7 μg/dL, respectively, and the peak ACTH and cortisol levels were 25.5 pg/mL and 3.2 μg/dL, respectively, which was consistent with secondary adrenal insufficiency. There were no abnormalities in other pituitary or related hormone levels: luteinizing hormone (7.5 mIU/mL [reference range: 2.2-8.4]), follicle-stimulating hormone (33.2 mIU/mL [reference range: 1.8-12]), growth hormone (0.52 ng/mL [reference range: 0-2.47]), insulin-like growth factor-1 (99 ng/mL [reference range: 80-233]), prolactin (14.8 ng/mL [reference range: 4.3-13.7]), testoterone (504 ng/dL [reference range: 131-871]). Therefore, the patient was diagnosed with isolated ACTH deficiency and now requires replacement treatment of 15 mg/day of hydrocortisone and 125 μg/day of levothyroxine sodium.

**Discussion**

Pembrolizumab is a human IgG4 monoclonal antibody and ICI. Thyroid dysfunction is one of the most common irAEs, occurring in 6.9%-21% of patients with NSCLC (5, 7). Anti-thyroid antibodies are found in 80% of patients who have pembrolizumab-induced hypothyroidism, while they are positive in only 8% of non-hypothyroid patients (7). Therefore, the presence of thyroid antibodies may help identify patients at risk of pembrolizumab-induced thyroid dysfunction (8). In our case, both anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies were positive before treatment with pembrolizumab.

In the present case, hypopituitarism was considered to have been induced by pembrolizumab, an anti-PD-1 antibody. There were no signs of pituitary metastasis of NSCLC, a pituitary tumor, sarcoidosis, or malignant lymphoma. Anti-CTLA-4 antibody can cause autoimmune hypophysitis in up to 10% of patients (9). However, anti-PD-1 antibody-induced hypophysitis is extremely rare (<1%) (10, 11). Nonspecific symptoms, such as headache, fatigue, and appetite loss, are also common in ICI-induced hypophysitis. MRI findings for hypophysitis usually show symmetrical enlargement of the pituitary gland or homogeneous enhancement (12, 13). However, some cases of nivolumab-induced hypophysitis have shown no abnormalities in the pituitary gland (14, 15). Lymphocytic hypophysitis can accompany other endocrine diseases, including chronic thyroiditis, Addison’s disease, type 1 diabetes mellitus, and Graves’ disease (13), but the relationship between these autoimmune diseases and PD-1 antibody-induced hypophysitis has not been clarified.

Ectopic CTLA-4 expression has been detected in the human pituitary gland in anti-CTLA-4 antibody-induced hypophysitis. Anti-CTLA-4 antibodies activate the classical complement pathway, suggesting that anti-CTLA-4 induces hypophysitis (16). However, the pathogenic mechanisms of pembrolizumab-induced hypophysitis have not been elucidated. Mei et al. reported that some cases of pituitary adenoma overexpress PD-1/PD-L1 (17). However, the expression of PD-1/PD-L1 in the pituitary gland in cases of hypophysitis has not been clarified. In addition, PD-1 antibodies are less effective than CTLA-4 antibodies for antibody-dependent cell-mediated cytotoxicity. These findings may suggest why PD-1 antibody therapy induces fewer cases of hypopituitarism than anti-CTLA-4 antibody therapy (11, 18).

The rapid ACTH test is recommended as a tool for the diagnosis of adrenal insufficiency, and peak cortisol levels below 500 nmol/L (18 μg/dL) are indicative (22). The ITT is
considered the gold standard for the evaluation of secondary adrenal insufficiency (23), although it carries some risks, particularly for elderly patients. In contrast, the CRH test does not cause hypoglycemia, so it can be carried out repeatedly and safely even in elderly patients, except for those with pituitary macroadenoma. The CRH test selectively stimulates the secretion of ACTH from pituitary corticotroph cells; it is therefore helpful for detecting secondary adrenal insufficiency due to pituitary dysfunction (19-21). However, in patients with hypothalamic disorders, the results should be interpreted with caution due to an excessive ACTH response in such patients.

In the present case, the patient was diagnosed with isolated ACTH deficiency four months after pembrolizumab withdrawal. However, both the ACTH and cortisol levels had been dropping for three months after the start of pembrolizumab. In addition, the first CRH test revealed that the peak cortisol level had been low. Therefore, it is possible that the pituitary disorder had already existed three months after starting pembrolizumab and had continued to gradually deteriorate even after the discontinuation of pembrolizumab. The median time to the onset of pembrolizumab-related hypophysitis was reported to be 3.7 months (24). Otsubo et al. reported two cases of secondary adrenal insufficiency that occurred several months after nivolumab discontinuation (25). Recently, the first case of late-onset adrenal insufficiency that occurred 15 months after pembrolizumab discontinuation was reported, although the patient’s adrenal hormone levels before the diagnosis were not mentioned (26).

To our knowledge, we have presented the first report of a case in which the pituitary and adrenal function was monitored via repeated CRH and rapid ACTH tests after treatment with pembrolizumab. These tests captured the progression of pembrolizumab-induced hypopituitarism. The low level of DHEAS also suggested a lack of ACTH stimulation on adrenocortical cells. The recovery of the pituitary-thyroid axis has been reported in 37%-85% of cases in iRAEs, while dysfunction of the pituitary-adrenal axis is unlikely to recover in such cases (27). Therefore, most patients with adrenal insufficiency might need continuous replacement of hydrocortisone.

In conclusion, we herein report the progression of hypopituitarism and hypothyroidism after treatment with pembrolizumab in a patient with adrenal metastasis of NSCLC. Hypopituitarism induced by pembrolizumab can develop even after discontinuation of the agent. Repeated CRH and rapid ACTH tests enable monitoring of the pituitary and adrenal function. Adrenal insufficiency can progress asymptptomatically; therefore, in order to adequately identify adrenal insufficiency, it is essential to regularly monitor the levels of ACTH, cortisol, and electrolytes, as well as to evaluate the subjective symptoms.

The authors state that they have no Conflict of Interest (COI).

Disclosure
None of the authors have anything to disclose.

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