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【 CASE REPORT 】

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

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Introduction

Immune checkpoint inhibitors (ICIs), including the anti-programmed death receptor 1 (PD-1), anti-PD-1 ligand (PD-L1), and anti-cytotoxic T lymphocyte-associated antigen 4 antibodies, have already been approved for treating melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma, bladder cancer, squamous cell carcinoma of the head and neck, and microsatellite instability high cancer. PD-1 is an inhibitory receptor expressed on the surface of activated T cells (1) that binds to PD-L1 and PD-L2, which are associated proteins expressed on antigen-presenting cells, nonimmune tissues, and tumor cells (2). On binding to a ligand, PD-1 blunts T-cell receptor signaling and downregulates T-cell activation and the T-cell-mediated antitumor immune response (3, 4).

Immune-related adverse events (irAEs) associated with ICIs have been reported in clinical trials. In organ-specific irAEs, the most common endocrine adverse event associated with PD-1 antibody is hypothyroidism (5); PD-1 antibody-induced hypophysitis is extremely rare (<1%) (6). However, it is essential to assess the presence and extent of these endocrine disorders because both severe hypothyroidism and adrenal insufficiency are fatal if not adequately treated.

In the present case, pembrolizumab was used to treat relapsed adrenal metastatic NSCLC. Pembrolizumab caused severe primary hypothyroidism with subsequent isolated adrenocorticotropic hormone (ACTH) deficiency even though pembrolizumab had been discontinued for four months. Repeated corticotropin-releasing hormone (CRH) and rapid ACTH tests revealed the gradual deterioration of the pituitary and adrenal function. It would therefore be extremely beneficial to monitor pituitary and adrenal function in such patients via repeated CRH and rapid ACTH tests.

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).

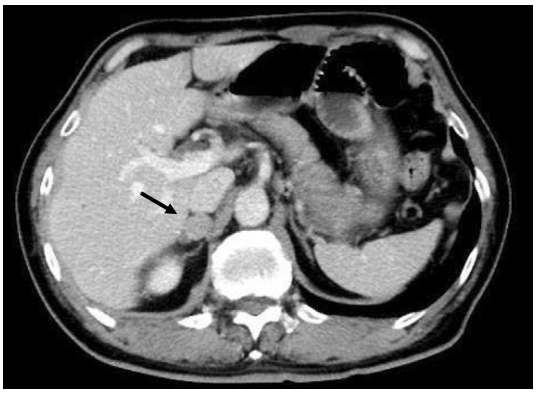

Figure 1. Abdominal computed tomography (CT). One year after chemotherapy, CT shows a right adrenal gland tumor (19 mm; arrow).

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

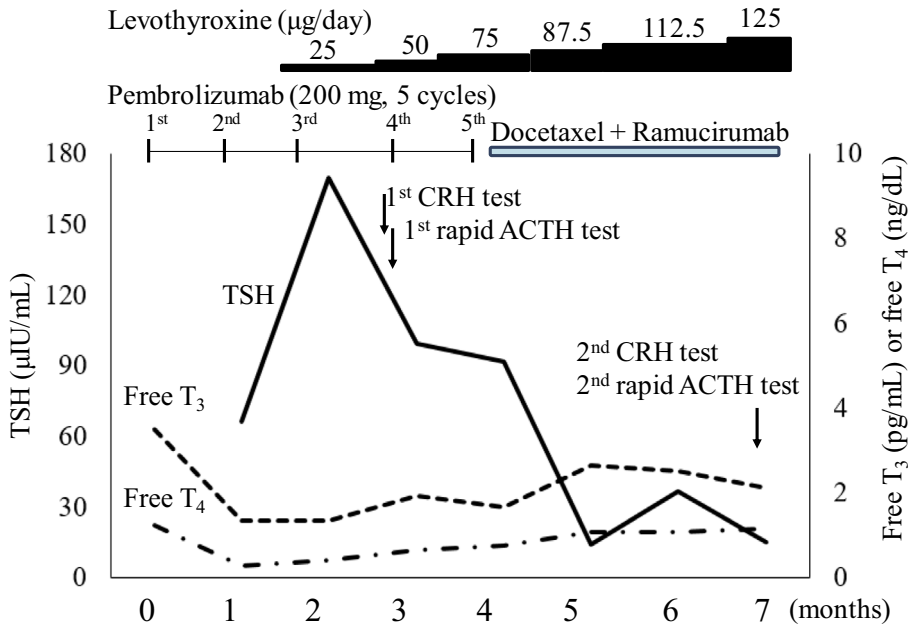

Figure 2. Changes in thyroid hormone levels during the clinical course. Levothyroxine sodium supplementation was started three weeks after the second administration of pembrolizumab. TSH: thyrotropin-stimulating hormone, ACTH: adrenocorticotropic hormone, CRH: corticotropin-releasing hormone

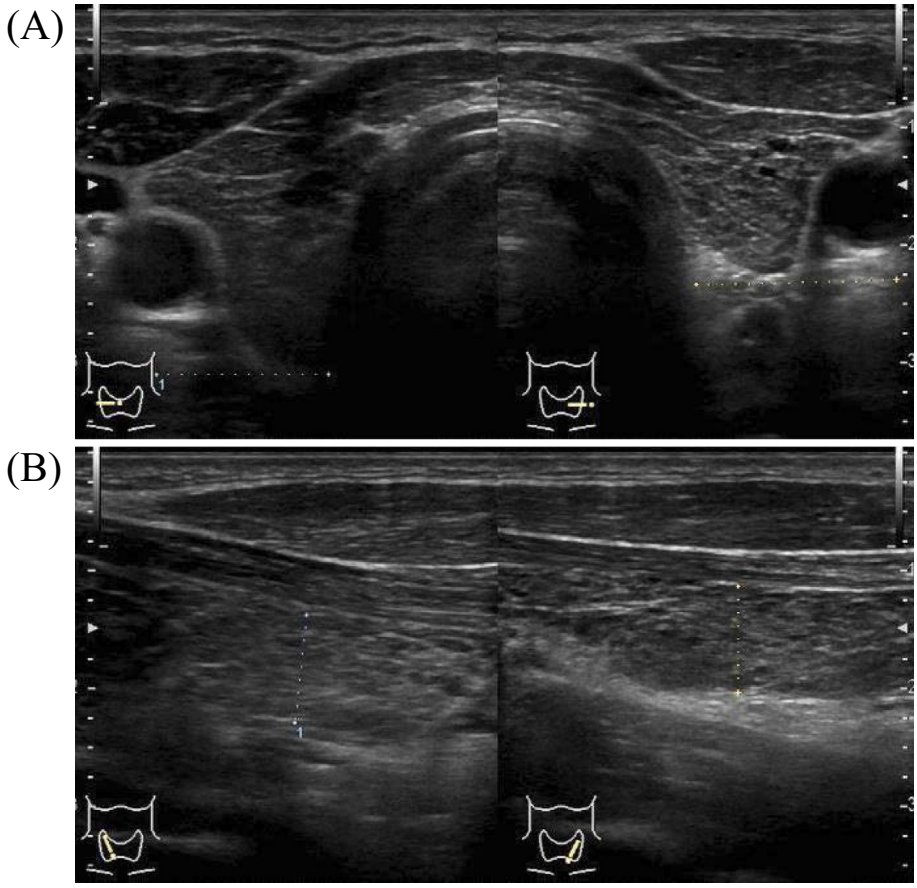

Figure 3. **Thyroid ultrasonography (USG). USG shows heterogeneous echotexture mixed with diffuse hypoechoic areas in the thyroid gland.**

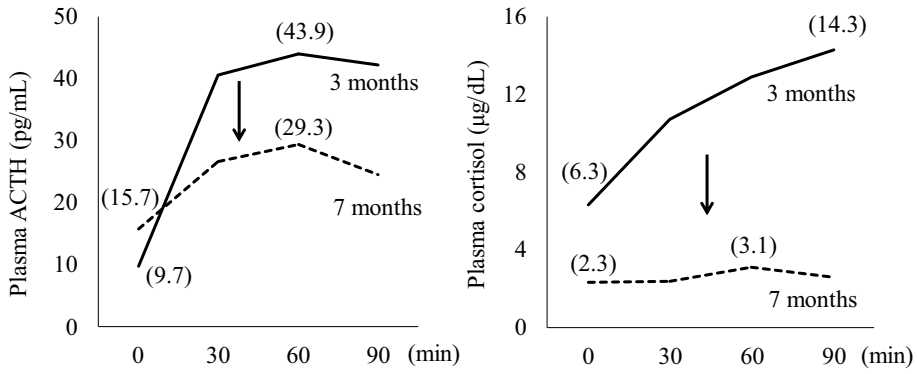

Figure 4. **Corticotropin-releasing hormone test. Solid and dotted lines indicate tests at three and seven months, respectively, after the first administration of pembrolizumab. Each basal and peak hormonal level is shown in parentheses.**

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: 31-313)]. Hypophysitis was suspected, and the CRH test was performed again during hospitalization. In the CRH stimulation test, the peak plasma

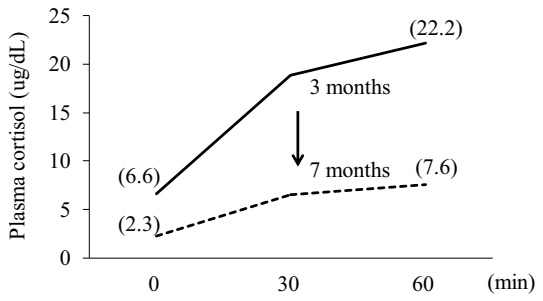

Figure 5. **Rapid adrenocorticotropic hormone (ACTH) test. Solid and dotted lines indicate tests at three and seven months, respectively, after the first administration of pembrolizumab. Each basal and peak hormonal level is shown in parentheses.**

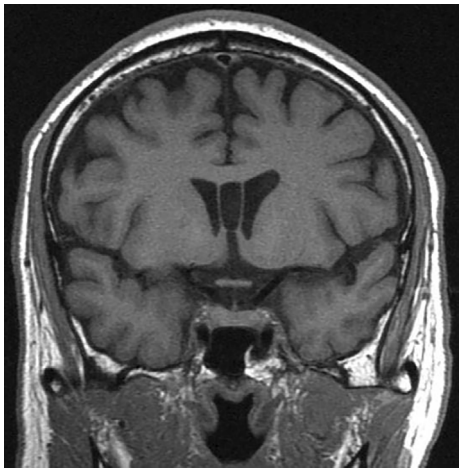

Figure 6. **Coronal T1-weighted magnetic resonance imaging (MRI) of the pituitary gland. MRI shows no enlargement of the pituitary gland or thickening of the pituitary stalk.**

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-hour urinary free cortisol level was below measurement sensitivity (reference range: 11-80 μg/day), whereas 24-hour 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)], testosterone [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 be-

low 500 nmol/L (18 μg/dL) are indicative (19). The ITT is considered the gold standard for the evaluation of secondary adrenal insufficiency (20), 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 (21-23). 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 progress 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 asymptomatically; 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).

References

1. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J **11**: 3887-3895, 1992.
2. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol **26**: 677-704, 2008.
3. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA **99**: 12293-12297, 2002.
4. McDermott DF, Atkins MB. PD-1 as a potential target in cancer therapy. Cancer Med **2**: 662-673, 2013.
5. Byun DJ, Wolchok JD, Rosenberg LM, Girotra M. Cancer immunotherapy-immune checkpoint blockade and associated endocrinopathies. Nat Rev Endocrinol **13**: 195-207, 2017.
6. Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ **360**: k793, 2018.
7. Osorio JC, Ni A, Chaft JE, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Ann Oncol **28**: 583-589, 2017.
8. Delivanis DA, Gustafson MP, Bornschlegl S, et al. Pembrolizumab-induced thyroiditis: comprehensive clinical review and insights into underlying involved mechanisms. J Clin Endocrinol Metab **102**: 2770-2780, 2017.
9. Bertrand A, Kostine M, Barnetche T, Truchetet ME, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. BMC Med **13**: 211, 2015.
10. Gangadhar TC, Salama AK. Clinical applications of PD-1-based therapy: a focus on pembrolizumab (MK-3475) in the management of melanoma and other tumor types. Onco Targets Ther **8**: 929-937, 2015.
11. Cukier P, Santini FC, Scaranti M, Hoff AO. Endocrine side effects of cancer immunotherapy. Endocr Relat Cancer **24**: T331-T347, 2017.
12. Mahzari M, Liu D, Arnaout A, Lochnan H. Immune checkpoint inhibitor therapy associated hypophysitis. Clin Med Insights Endocrinol Diabetes **8**: 21-28, 2015.
13. Bellastella G, Maiorino MI, Bizzarro A, et al. Revisitation of autoimmune hypophysitis: knowledge and uncertainties on pathophysiological and clinical aspects. Pituitary **19**: 625-642, 2016.
14. Ishikawa M, Oashi K. Case of hypophysitis caused by nivolumab. J Dermatol **44**: 109-110, 2016.
15. Okano Y, Satoh T, Horiguchi K, et al. Nivolumab-induced hypophysitis in a patient with advanced malignant melanoma. Endocr J **63**: 905-912, 2016.
16. Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med **6**: 230ra45, 2014.
17. Mei Y, Bi WL, Greenwald NF, et al. Increased expression of programmed death ligand 1 (PD-L1) in human pituitary tumors. Oncotarget **7**: 76565-76576, 2016.
18. Vidarsson G, Dekkers G, Rispens T. IgG subclasses and allotypes: from structure to effector functions. Front Immunol **5**: 520, 2014.
19. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab **101**: 364-389, 2016.
20. Fish HR, Chernow B, O'Brian JT. Endocrine and neurophysiologic responses of the pituitary to insulin-induced hypoglycemia: a review. Metabolism **35**: 763-780, 1986.
21. Sauter NP, Toni R, McLaughlin CD, Dyess EM, Kritzman J, Lechan RM. Isolated adrenocorticotropin deficiency associated

with an autoantibody to a corticotroph antigen that is not adrenocorticotropin or other proopiomelanocortin-derived peptides. J Clin Endocrinol Metab **70**: 1391-1397, 1990.

22. Schmidt IL, Lahner H, Mann K, Petersenn S. Diagnosis of adrenal insufficiency: evaluation of the corticotropin-releasing hormone test and Basal serum cortisol in comparison to the insulin tolerance test in patients with hypothalamic-pituitary-adrenal disease. J Clin Endocrinol Metab **88**: 4193-4198, 2003.

23. Maghnie M, Uga E, Temporini F, et al. Evaluation of adrenal function in patients with growth hormone deficiency and hypothalamic-pituitary disorders: comparison between insulin-induced hypoglycemia, low-dose ACTH, standard ACTH and CRH stimulation tests. Eur J Endocrinol **152**: 735-741, 2005.

24. Merck & Co., Inc., Whitehouse Station (NJ). KEYTRUDA (Pembrolizumab) Prescribing Information [Internet]. [cited 2017 Dec 1]; Available from: http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

25. Otsubo K, Nakatomi K, Furukawa R, et al. Two cases of late onset secondary adrenal insufficiency after discontinuation of nivolumab. Ann Oncol **28**: 3106-3107, 2017.

26. Boudjemaa A, Rousseau BG, Monnet I. Late-onset adrenal insufficiency more than 1 year after stopping pembrolizumab. J Thorac Oncol **13**: e39-e40, 2018.

27. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev **44**: 51-60, 2016.