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Case report

A case of nivolumab-induced isolated adrenocorticotropic hormone (ACTH) deficiency

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ABSTRACT

One of the novel PD-1 antibodies/immune checkpoint inhibitors, nivolumab is reported to be associated with a wide range of immune-related adverse events (irAEs). We hereby report a case of isolated adrenocorticotropic hormone (ACTH) deficiency developing in a patient with squamous cell lung cancer (SCC) during nivolumab therapy.

Case: A 79-year-old man with SCC was started on nivolumab therapy as a fifth-line treatment after 4 lines of cytotoxic anticancer therapy. After 20 courses of nivolumab therapy, he had nausea, appetite loss, and difficulty walking. A close laboratory examination led to the diagnosis of isolated ACTH deficiency in this patient. Hydrocortisone replacement therapy led to amelioration of his symptoms and allowed him to continue with nivolumab therapy. The present case of isolated ACTH deficiency was characterized by a slowly progressive decline in the serum sodium level, which became manifest well before appearance of any clinical symptoms, suggesting that the serum sodium level may be used to predict progression to isolated ACTH deficiency.

Thus, not only serum sodium levels need to be monitored in patients suspected of having isolated ACTH deficiency, but ACTH and cortisol levels need to be monitored in those exhibiting a decline in serum sodium levels. Again, nivolumab-induced isolated ACTH deficiency needs to be appropriately diagnosed and treated to ensure that patients continue with, and maximize survival benefit from, nivolumab therapy.

1. Introduction

Immune checkpoint inhibitors (ICIs) represent a novel class of anticancer agent that has become a mainstay of treatment for a wide variety of malignancies with their excellent efficacy profile based on a unique immunological mechanism of action [1]. Of these, nivolumab, a fully humanized IgG4 antibody and a representative ICI, is shown to bind to programmed cell death-1 (PD-1) receptor expressed on the surface of active T cells thereby blocking the binding of the PD-1 receptor to programmed cell death ligand-1 (PD-L1) or PD-L2 expressed on the surface of cancer cells [2].

Unlike conventional cytotoxic anticancer agents, ICIs, including nivolumab, are shown to be associated with a range of immune-related adverse events (irAEs), of which endocrinopathy is of particular note as wide-ranging, and include hypophysitis, thyroid disorders, hyperglycemia and adrenal failure [1,3].

Of these, isolated adrenocorticotropic hormone (ACTH) deficiency is a rare disease characterized by secondary adrenal failure, normal secretion of pituitary hormones other than ACTH, and structural pituitary deficits [4]. Among anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and PD-1 antibodies, both of which are known to be associated with hypopituitarism, compared to the *anti*-CTLA-4 antibody ipilimumab, which is shown to be associated with hypopituitarism in about 10–15% of patients receiving the drug [5], the PD-1 antibody nivolumab is shown to be rarely associated with hypopituitarism in patients receiving the drug (0.5–0.9%) [6]. It is also reported that patients with ICI-induced endocrinopathy are expected to benefit from ICI therapy through endocrine hormone replacement.

We hereby report a case of nivolumab-induced isolated ACTH deficiency developing in a patient with squamous cell lung cancer (SCC) who was able to continue with ICI therapy through steroid hormone replacement.

Abbreviations: PD-1, Programmed death 1; CTLA-4, Cytotoxic T-lymphocyte-associated antigen 4; irAEs, Immune-related adverse events; ICIs, Immune checkpoint inhibitors; PD-L1, Programmed cell death ligand-1; PD-L2, Programmed cell death ligand-2

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2. Case presentation

An abnormal chest x-ray finding in a 79-year-old man during a health checkup program in X-6 led him to consult a nearby physician. Suspected of having lung cancer, the patient presented to our department on October 28, X-6. He was confirmed to have a history of pulmonary tuberculosis, disc herniation, and chronic obstructive pulmonary disease (COPD) but no particular family history. He reported having smoked 20 cigarettes a day between the ages of 20 and 72 years and having had 1 cup of distilled spirits a day. A bronchoscopic examination performed on November 2 led to the diagnosis of EGFR mutation-negative SCC cT2aN0M1b stage IV (M1, bone metastasis) in this patient. Thus, he underwent 4 courses of first-line chemotherapy with CBDCA and S-1 from January 17, X-5 onwards, followed by an additional course of treatment with S-1, after which he was diagnosed with progressive disease (PD) with enlargement of the primary lesion. All bone metastases were shown to have disappeared on PET, which led to the patient being down-staged as cT2N0M0 stage IIA. Preferring not to be operated on for his cancer, the patient chose to undergo radical radiotherapy with 50-Gy (five fractions at 10-Gy) between January 22 and February 4, X-4 but was diagnosed with PD on CT in September the same year with enlargement of the primary lesion. Subsequently, he underwent 5 courses of chemotherapy with docetaxel from October 1 onwards, 4 courses of chemotherapy with carboplatin plus paclitaxel from February 18 onwards, and 19 courses of chemotherapy with gemcitabine from January 13, X-2 onwards. Finally, diagnosed with PD again, he was started on nivolumab as a fifth-line treatment from August 23, X-1 onwards, which elicited PR in this patient thus leading to the regimen being continued up to 20 courses (final administration, May 2, X). A blood sample was drawn from him on May 9, X, which revealed his serum sodium level to be 134 mmol/L. The patient began to complain of nausea, appetite loss, and difficulty walking from around May 13, X and further complained of worsening nausea on May 15, X and was symptomatically treated with drip infusions and oral agents. However, he had persistent nausea, difficulty eating, and abdominal bloating until he was found to have difficulty walking, dyspnea, and oliguria on May 18 and was immediately admitted on the same day.

At admission, he had clear consciousness with clear breath sounds (body temperature, 34.9 °C; blood pressure, 114/58 mmHg; pulse rate, 83/minute; breathing rate, 20 times/minute; and SpO_2 at room temperature, 98%), with no signs of jaundice or anemia in bulbar conjunctiva, cardiac murmur, or abdominal bloating or tenderness, and with no neurological findings suggestive of paralysis.

Hematological findings at admission are summarized in Table 1. Chest roentgenogram findings at admission (Fig. 1a) included a tumor mass shadow in the upper lung field, left costophrenic (CP) angle blunting, and a central venous access port device planted in the left subclavian vein. Plain chest-abdominal CT findings (Fig. 1b) included a 50-mm tumor mass shadow in the left superior lobe, left pleural effusion, and absence of gut distention or niveau formation.

After admission, the patient was being observed while being treated with drip infusions, with no clues available as to the cause of nausea and appetite loss in this patient. However, on the third day of admission, he was found to have a decline in blood pressure, when adrenal failure was suspected and hydrocortisone was administered at a daily dose of 500 mg, which led to an increase in blood pressure as well as improvements in activities of daily living (ADL) and appetite in this patient. On the fifth day of admission, ACTH and cortisone levels were confirmed to have decreased based on a blood sample drawn before hydrocortisone administration, which led to the diagnosis of adrenal failure in this patient. With attention given to monitoring his symptoms and serum sodium levels, hydrocortisone was gradually down-titrated to be maintained at 15 mg/day. Subsequently, an array of endocrinological investigations were conducted to identify the organ responsible for adrenal failure as well as to assess hormone secretory status in this patient (Table 2). The insulin hypoglycemia test, GH-releasing peptide 2 (GHRP-2) test, and corticotrophin-releasing hormone (CRH) test elicited a poor ACTH/cortisol response, while the thyrotropin-releasing hormone (TRH) test and luteinizing hormone-releasing hormone (LHRH) test elicited an intact TRH/LHRH response, in this patient, which led to the diagnosis of isolated ACTH deficiency, with the pituitary determined as the responsible organ. Again, based on the pituitary MRI (Fig. 2) finding suggestive of no pituitary enlargement and the fact that this ACTH deficiency developed during nivolumab therapy, the condition was finally diagnosed as nivolumab-induced isolated ACTH deficiency.

Table 1
Hematological findings at admission.

Cell blood count	
WBC (μL)	4000
Neutrophil (%)	49.5
Lymphocyte (%)	30.2
Eosinophil (%)	4
RBC (μL)	382×10^4
Hemoglobin (g/dL)	13.2
Platelet (μL)	14.9×10^4
Blood chemistry	
Total protein (g/dL)	5.8
Albumin (g/dL)	3.1
AST (IU/L)	41
ALT (IU/L)	15
LDH (IU/L)	178
CK (IU/L)	129
BUN (mg/dL)	19.1
Creatinine (mg/dL)	1.23
UA (mg/dL)	8.9
Na (mEq/L)	129
K (mEq/L)	4
Cl (mEq/L)	92
Ca (mg/dL)	10.1
Casual blood glucose (mg/dL)	55
C-reactive protein (mg/dL)	5.42
Endocrinology	
TSH (μIU/mL)	1.58
FT3 (pg/mL)	1.85
FT4 (ng/dL)	0.96
Free testosterone (pg/mL)	< 3.5
ACTH (pg/mL)	< 1.0
Cortisol (μg/dL)	0.2
PRL (ng/mL)	30.8
LH (mIU/mL)	10.2
FSH (mIU/mL)	14.5
GH (ng/mL)	0.53
IGF-1 (ng/mL)	69
Anti-pituitary cell antibody	Negative

Abbreviations: ACTH, adrenocorticotropic hormone; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CK, creatinine kinase; FSH, follicle stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; GH, growth hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; PRL, prolactin; RBC, red blood cell; TSH, thyroid stimulating hormone; UA, uric acid; WBC, white blood cell.

Hydrocortisone administration led to an improvement in PS and the patient was discharged on the 22nd day of admission. Subsequently, the patient was restarted on nivolumab therapy from September, X, and is currently receiving the 44th course of nivolumab therapy, which continued to elicit PR from the patient, with no evidence of recurrent adrenal failure.

3. Discussion

Recent reports demonstrate that up to about 10%–15% of patients receiving the *anti*-CTLA-4 antibody ipilimumab are associated with pituitary disorders, with the median time to onset of these disorders being 9 weeks (range, 5–36 weeks) [5], while the PD-1 antibodies nivolumab and pembrolizumab are shown to be associated with pituitary disorders in 0.5–0.9% of patients receiving these agents [6].

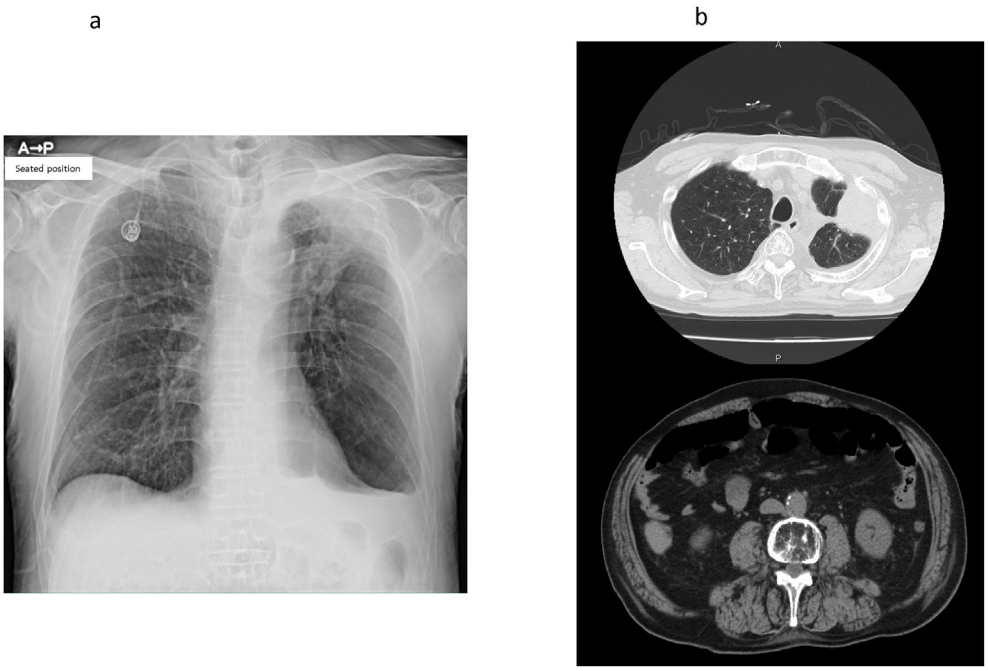

Fig. 1. a. Chest roentgenogram. X-ray findings at admission included a tumor mass shadow in the upper lung field, left costophrenic (CP) angle blunting, and a central venous access port device planted in the left subclavian vein. b. Plain chest-abdominal computed tomography (CT). CT findings included a 50-mm tumor mass shadow in the left superior lobe, left pleural effusion, and absence of gut distention or niveau formation.

Table 2
Endocrinological investigations.

Insulin hypoglycemia test	0 min	30 min	45 min	60 min	90 min
Blood glucose (mg/dL)	83	34	40	68	137
ACTH (pg/mL)	< 1.0	< 1.0	< 1.0	< 1.0	< 1.0
Cortisol (μg/dL)	1.1	1.1	1.5	1.4	1.2
GH (ng/mL)	2.76	2.35	4.83	4.75	4.43
GHRP-2 test	**0 min**	**15 min**	**30 min**	**45 min**	**60 min**
GH (ng/mL)	1.35	69.3	45.41	29.77	18.46
ACTH (pg/mL)	< 1.0	< 1.0	< 1.0	< 1.0	< 1.0
Cortisol (μg/dL)	2.4	2.4	1.6	1.5	1.3
CRH test	**0 min**	**30 min**	**60 min**	**90 min**	**120 min**
ACTH (pg/mL)	< 1.0	< 1.0	< 1.0	< 1.0	< 1.0
Cortisol (μg/dL)	1.8	1.3	1	1.2	0.9
TRH test	**0 min**	**15 min**	**30 min**	**60 min**	
PRL (ng/mL)	10.3	85.4	95.2	56.5	
TSH (μU/ml)	3.12	12.98	20.91	18.24	
LHRH test	**0 min**	**30 min**	**60 min**	**90 min**	**120 min**
LH (mlU/mL)	5.7	24.7	32.7	31.9	27.7
FSH (mlU/mL)	14.3	19.6	22.2	24.1	24.9

Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotrophin-releasing hormone; FSH, follicle stimulating hormone; GH, growth hormone; GHRP-2, GH-releasing peptide 2; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; PRL, prolactin; TRH, thyrotropin-releasing hormone; TSH, thyroid stimulating hormone.

Again, *anti*-CTLA-4 antibodies are shown to be associated with findings of pituitary and pituitary stalk enlargement on pituitary MRI [7,8], while pituitary disorders associated with nivolumab are shown to present with normal MRI findings [10]. Furthermore, while pituitary disorders associated with PD-1 antibodies are assumed to differ in their mechanisms of onset from those associated with *anti*-CTLA-4 antibodies based on their frequency and MRI findings, their mechanisms remain largely unclear.

This was a case of isolated ACTH deficiency in a patient with SCC who developed nausea, appetite loss, and difficulty walking after 20 courses of nivolumab therapy and was diagnosed as isolated ACTH deficiency after a close laboratory examination and in whom hydrocortisone replacement therapy led to amelioration of these symptoms and allowed him to continue to benefit from nivolumab therapy.

Isolated ACTH deficiency is known to be associated with nonspecific symptoms, such as asthenia, appetite loss, weight loss, hypoglycemia, and hyponatremia, thus making it less readily amenable to differential diagnosis [1,4].

The symptoms observed at admission (i.e., nausea, appetite loss and difficulty walking) were nonspecific and may be accounted for by various factors and may also have been linked one with another. However, not only no abnormal changes had been noted in vital signs at admission (i.e., no signs of jaundice or anemia in bulbar conjunctiva, cardiac murmur, or abdominal bloating or tenderness, and with no neurological findings suggestive of paralysis) but no abnormal hematological or imaging findings had been noted in this patient, other than hypoglycemia, which was later thought to be associated with ACTH deficiency. Again, while this study involved no in-depth investigations (e.g., fecal occult blood testing, gastroendoscopy or colonoscopy), despite drip infusion therapy which also aimed at glycemic correction, a decline in blood pressure was noted in the patient, for which, given that no new findings were available to suggest its cause, a definitive diagnosis of ACTH deficiency was made based on endocrine/cortisol test results (which was later confirmed upon normalization of blood pressure with hydrocortisone replacement therapy alone).

Consistently with the recent urgent warning that patients with nivolumab-induced isolated ACTH deficiency may likely present with hyponatremia before any of the clinical symptoms associated with the condition [10], having developed isolated ACTH deficiency while on nivolumab, the patient with SCC being reported here was shown to be associated with a slowly progressive decline in serum sodium level as assessed based on blood samples well before any associated clinical symptom became manifest, suggesting that monitoring serum sodium levels may lead to isolated ACTH deficiency being suspected in patients with any such nonspecific symptoms while on nivolumab therapy.

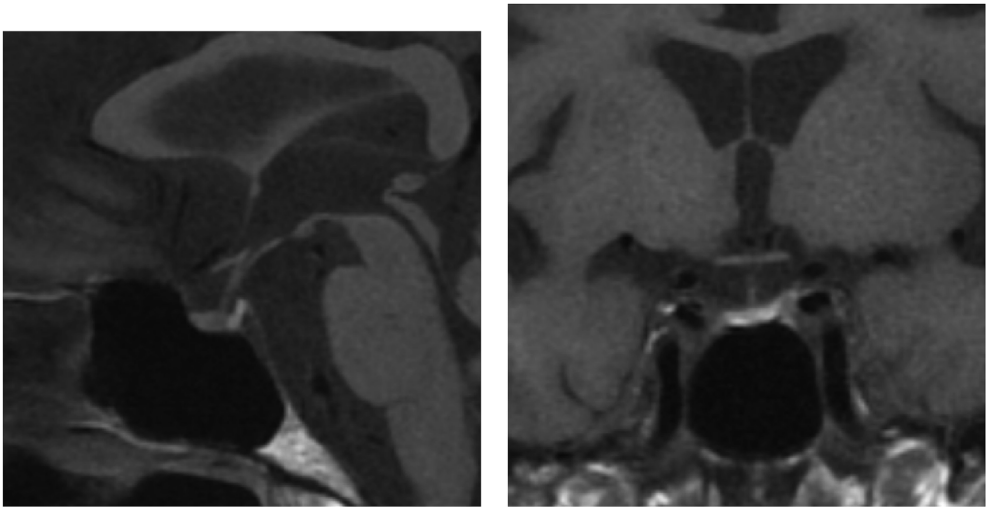

Fig. 2. Pituitary MRI. MRI findings revealed no pituitary enlargement.

Furthermore, hydrocortisone replacement therapy led to symptomatic improvements in this patient with established nivolumab-induced isolated ACTH deficiency and allowed him to continue to benefit from nivolumab therapy. Given that patients who develop irAEs while on ICI therapy are reported to fare better than those who do not [9], it appears critically important to ensure that irAEs are appropriately controlled, and ICI-based cancer therapy is continued as long as possible to maximize its benefit.

While the patient's serum sodium level had been shown to be in the normal range between 138 and 140 mEq/L under usual circumstances, his sodium level began to be decreased at 134 mEq/L 9 days before admission. Given that all reported cases are shown to occur 3–9 months after initiation of nivolumab [11–16] in the literature, this does not represent a typical case of ACTH deficiency due to nivolumab. Again, while causes of ACTH deficiency include trauma, irradiation to brain tumors, and autoimmune disease following lymphocytic hypophysitis, the patient had no history of trauma or brain tumor including brain metastasis or symptoms suggestive of lymphocytic hypophysitis or showed no evidence of pituitary enlargement on pituitary MRI while on treatment with the immune checkpoint inhibitor, and was diagnosed with ACTH deficiency due to nivolumab despite the time to its onset following initiation of the drug being longer than that reported in the literature.

We hereby reported a case of nivolumab-induced isolated ACTH deficiency, which appears to provide the following lessons: nonspecific symptoms, such as nausea and appetite loss, in patients on nivolumab therapy may be best managed with isolated ACTH deficiency in mind. Again, the serum sodium level, which is reported to be useful in predicting progression to isolated ACTH deficiency [8], was shown to be useful in our case as well. Thus, not only serum sodium levels need to be monitored in patients suspected of having isolated ACTH deficiency, but also ACTH and cortisol levels need to be immediately monitored in those demonstrating a decline in their serum sodium levels. Furthermore, nivolumab-induced isolated ACTH deficiency needs to be appropriately diagnosed and treated to ensure that patients continue with, and maximize survival benefit from, nivolumab therapy.

Disclosure statements

No conflict of interest has been declared by the authors. Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.rmcr.2019.01.021.

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