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Letter to the Editor

# Hyponatremia can be a powerful predictor of the development of isolated ACTH deficiency associated with nivolumab treatment

*Dear Editor,*

The report of nivolumab-induced hypophysitis by Okano *et al*. was of great interest to us [1]. We have experienced four cases of isolated ACTH deficiency after nivolumab administration, suggesting that decreased sodium (Na) concentrations during nivolumab therapy may predict the acute development of isolated ACTH deficiency.

The underlying diseases in these four patients were malignant melanoma (case 1) [2] or non-small cell lung carcinoma (cases 2–4) >stage 4 (Table 1). Nivolumab (2 mg/kg, every 3 weeks) was effective for treating the cancer in three patients (cases 1–3), while case 4 was considered to have progressive disease and the treatment was discontinued after the 6th administration. All patients experienced fatigue, appetite loss, nausea, and body pain from the 6th to 10th nivolumab administrations. All four patients had low blood pressure and hyponatremia with markedly low ACTH and cortisol levels on admission. Neither ACTH nor cortisol responded to CRH stimulation tests, and the cortisol reaction to the conventional-dose short ACTH stimulation test (250 μg) was lower than normal. Cortisol was secreted following prolonged-stimulation tests in cases 1 and 2 (not determined in cases 3 and 4). The secretion of other pituitary hormones was normal. Magnetic resonance imaging showed no abnormalities. Based on these findings, the patients were diagnosed with isolated ACTH deficiency induced by nivolumab treatment. Their symptoms resolved and general conditions improved promptly after initiation of hydrocortisone (15–20 mg/day). There was no appearance of polyuria after hydrocortisone replacement.

Symptoms such as fatigue developed within 6 days after the last nivolumab treatment, and hydrocortisone was initiated from 7–14 days after treatment in three of the four patients. None of the apparent clinical symptoms that would indicate adrenal insufficiency had been observed at the last administration of nivolumab. However, we noted hyponatremia (serum Na levels <135 mEq/L) in two patients (cases 1 and 2) [3] in the absence of such symptoms. In addition, serum Na levels in three patients (cases 1–3) were clearly reduced by the time of the last administration. Hyponatremia could thus be the first manifestation indicating ACTH deficiency in patients treated with nivolumab, followed by other symptoms or physical findings. A previous report by Asano *et al*. showed that hyponatremia was frequently detected in elderly patients with hypopituitarism, most of whom had ACTH deficiency, and the mechanism of hyponatremia in these patients may have involved augmented release of arginine vasopressin due to impaired pituitary–adrenal axis function [4]. A similar mechanism may have been responsible for the nivolumab-induced hyponatremia in ACTH deficiency in the patients (54–76 years old) in our study.

Adrenocortical failure caused by isolated ACTH deficiency may be life-threatening, especially in frail patients with cancer. Our cases highlight the importance of comparing serum Na levels before and during treatment, and measuring ACTH and cortisol levels in patients with hyponatremia during nivolumab treatment.

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**Table 1** Clinical features and treatment in four cancer patients who developed nivolumab-associated isolated ACTH deficiency

| Case | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Age (y.o.) | 76 | 54 | 64 | 57 |
| Sex | Female | Male | Male | Male |
| Disease | Malignant melanoma | Poorly differentiated lung carcinoma | Lung adenocarcinoma | Large cell lung carcinoma |
| Nivolumab administration (times) | 9 | 8 | 7 | 6 |
| Symptoms | Fatigue<br>Appetite loss | Fatigue<br>Nausea | Fatigue<br>Appetite loss | Appetite loss<br>Nausea<br>Body pain |
| Period from last administration to (days) | | | | |
| Onset of symptoms | 4 | 4 | 6 | 26 |
| Hydrocortisone initiation | 7 | 8 | 14 | 40 |
| On admission | | | | |
| ACTH (pg/mL) | 6.7 | 7.0 | < 2.0 | 2.9 |
| Cortisol (μg/dL) | < 1.0 | < 1.0 | < 1.0 | < 1.0 |
| Effect on hydrocortisone | Effective | Effective | Effective | Effective |
| Symptoms | | | | |
| 3 weeks before from last administration | (–) | (–) | (–) | (–) |
| Last administration | (–) | (–) | (–) | (–) |
| On admission | (+) | (+) | (+) | (+) |
| Blood pressure (mmHg) | | | | |
| 3 weeks before from last administration | 122/55 | 133/84 | 135/72 | 108/64 |
| Last administration | 122/67 | 143/89 | 130/82 | 103/73 |
| On admission | 102/63 | 117/79 | 142/90 | 92/57 |
| Plasma glucose (mg/dL) | | | | |
| 3 weeks before from last administration | 129 | 95 | 96 | 96 |
| Last administration | 104 | 99 | 85 | 151 |
| On admission | 83 | 85 | 72 | 81 |
| Serum sodium (mEq/L) | | | | |
| 3 weeks before from last administration | 141 | 143 | 141 | 138 |
| Last administration | 131 * | 134 * | 137 | 137 |
| On admission | 123 * | 130 * | 127 * | 137 |

y.o., years old; (–), no symptoms; (+), symptoms present. * Hyponatremia (serum Na levels <135 mEq/L).

## References


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