

Refractory hypotension due to Nivolumab-induced adrenal insufficiency

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ABSTRACT

Nivolumab, a new immune checkpoint inhibitor that has been found to improve outcomes for patients with some advanced cancers, is being increasingly used. Immune checkpoint inhibitors can cause immune-related adverse events, including dermatitis, enterocolitis, hepatitis and hypophysitis, but adrenal insufficiency rarely occurs. We present a case of Nivolumab-induced adrenal insufficiency in a man who complained of refractory hypotension. A 52-year-old man with non-small cell lung cancer visited our emergency department complaining of fatigue and diarrhea. He had received Nivolumab every 2 weeks as third-line therapy for a total of 10 times. On arrival, his vital signs revealed shock: blood pressure, 68/48 mmHg; heart rate, 141 beats per minutes. Laboratory examination showed severe hemoconcentration with a hemoglobin level of 19.9 g/dL, normal electrolyte levels and hyperglycemia. We started intravenous infusion of 4.5 L of extracellular fluid, but his vital signs remained unstable. After admission, endocrine examination revealed abnormally low values of serum cortisol (4.86 µg/dL) and ACTH (<1.0 pg/mL), which had been normal at 2 months before admission (21.14 µg/dL and 20.1 pg/mL, respectively). We therefore made a diagnosis of adrenal insufficiency induced by Nivolumab and administered 100 mg hydrocortisone succinate sodium intravenously. He recovered soon after hydrocortisone replacement therapy. Nivolumab is a new immune checkpoint inhibitor and general physicians are not familiar with it. However, adverse events caused by Nivolumab, especially adrenal insufficiency, can lead to serious adverse outcomes if overlooked. We should recognize Nivolumab-induced adrenal insufficiency and administer a glucocorticoid immediately in cancer patients treated with immune checkpoint inhibitors.

Keywords: adrenal insufficiency, hypotension, immune checkpoint inhibitor

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INTRODUCTION

Recently, there has been an increasing number of patients with advanced cancer who receive therapy with immune checkpoint inhibitors such as antibodies directed against programmed cell death 1 (Nivolumab, Pembrolizumab) or cytotoxic T-lymphocyte antigen-4 (Ipilimumab), which

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have been shown to improve outcomes for patients with advanced melanoma, renal cell cancer and non-small cell lung cancer.¹⁻²⁾ Immune checkpoint inhibitors cause immune-related adverse events, affecting dermatological, gastrointestinal, hepatic endocrine and other systems, but adrenal insufficiency rarely occurs.³⁻⁴⁾ We present a case of Nivolumab-induced adrenal insufficiency in a man who complained of refractory hypotension.

CASE PRESENTATION

A 52-year-old man with non-small cell lung cancer visited our emergency department complaining of fatigue and diarrhea for 7 days. He had received Nivolumab at 3 mg/kg every 2 weeks as third-line therapy for a total of 10 times. On arrival, he looked pale and presented peripheral coldness, and his vital signs revealed shock: blood pressure (BP), 68/48 mmHg; heart rate (HR), 141 beats per minutes; and body temperature (BT) 36.8°C. Laboratory examination showed severe hemoconcentration with a hemoglobin level of 19.9 g/dL, normal electrolyte levels, and hyperglycemia (Table 1). Rapid ultrasound examination showed normal cardiac contraction and a collapsed inferior vena cava. We started intravenous infusion of 4.5 L of extracellular fluid, but his vital signs remained unstable: BP of 107/65 mmHg and HR of 130 beats per minutes. After admission, endocrine examination revealed that abnormally low values of serum cortisol (4.86 µg/dL) and ACTH (<1.0 pg/mL), which had been normal at 2 months before admission (21.14 µg/dL and 20.1 pg/mL, respectively). We therefore suspected adrenal insufficiency and administered 100 mg hydrocortisone succinate sodium intravenously. His vital signs became stable within 10 hours: BP, 149/85 mmHg; HR, 111 beats per minutes; BT, 36.7°C. Blood and stool cultures showed no evidence of sepsis or infectious colitis. Other pituitary hormone levels including prolactin, luteinizing hormone, follicle stimulating hormone and growth hormone were normal. With the results of endocrinal stimulation tests, we finally made a diagnosis of

Table 1 Patient's laboratory data at 2 months before admission and on admission

Laboratory Data	2 Months before Admission	On Admission
Hb (g/dL)	17.4	19.9
PLT (/µL)	280000	330000
WBC (/µL)	6200	18300
Sodium (mEq/L)	142.6	141.1
Potassium (mEq/L)	4.3	4.3
BUN (mg/dL)	8	16
Creatinine (mg/dL)	0.65	1.83
Glucose (mg/dL)	125	216
Cortisol (µg/dL)	21.14	4.86
ACTH (pg/mL)	20.1	<1.0
TSH (µU/mL)	1.31	1.05
Free T3 (pg/mL)	2.83	1.88
Free T4 (ng/dL)	1.70	1.23

Abbreviations: ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone

Nivolumab-induced secondary adrenal insufficiency caused by isolated ACTH deficiency. After hydrocortisone replacement therapy, he quickly recovered and was discharged on hospital day 11.

DISCUSSION

Nivolumab is a new immune checkpoint inhibitor, and general physicians are not familiar with it. However, adverse events caused by Nivolumab, especially adrenal insufficiency, can lead to serious outcomes if overlooked. We should recognize Nivolumab-induced adrenal insufficiency and administer a glucocorticoid in cancer patients treated with immune checkpoint inhibitors.

Nivolumab is an approved drug that has recently been used for the treatment of many types of advanced cancer. However, visits to emergency departments by cancer patients suffering from acute adverse effects of Nivolumab may become more frequent. Immune checkpoint inhibitors activate T-cells. Therefore, if excessive immune stimulation occurs, the adverse effects of immune checkpoint inhibitors can include a wide spectrum of autoimmune manifestations including dermatologic, gastrointestinal, hepatic, endocrine, renal, ocular and pulmonary toxicities. The most serious adverse events include Stevens-Johnson syndrome, toxic epidermal necrosis, colitis, hypophysitis, adrenal crisis, hepatitis and pneumonitis.³⁻⁴⁾ If these toxicities are not managed appropriately, they may lead to serious outcomes and result in discontinuation of effective anti-cancer therapy.

Among these adverse events, adrenal insufficiency is a rare event that occurs in less than 1% of patients and usually occurs about 2 months after initiation of treatment.^{3,5)} The common manifestations of adrenal insufficiency are fatigue, headache, hyponatremia, confusion and hypotension.⁶⁻⁸⁾ Some of these manifestations are non-specific, and adrenal insufficiency may be overlooked if adverse effects of an immune checkpoint inhibitor are not suspected. In fact, our patient did not have hyponatremia, and we were not able to start treatment for adrenal insufficiency until the serum cortisol and ACTH levels had become clear. If adrenal insufficiency is suspected in a cancer patient treated with immune checkpoint inhibitors, serum cortisol and ACTH levels should be immediately measured and a stress-dose glucocorticoid (e.g., hydrocortisone succinate sodium at 100 mg intravenously) should be administered.⁶⁾ If adrenal insufficiency is not treated appropriately, it may become a life-threatening adrenal crisis and result in death. In addition, they often have concomitant other endocrine dysfunction, so pituitary function, thyroid function and glucose metabolism should be checked.^{3,4,6)}

In conclusion, Nivolumab is a new immune checkpoint inhibitor and general physicians are not familiar with it. However, adverse events caused by Nivolumab, especially adrenal insufficiency, can lead to serious adverse outcome if overlooked. Not only oncologists but also general physicians should recognize Nivolumab-induced adrenal insufficiency and administer a glucocorticoid immediately in cancer patients treated with immune checkpoint inhibitors. Like immune checkpoint inhibitors, new drugs will be approved in various medical fields, and visits to emergency departments by patients suffering from adverse effects of new drugs may become more frequent. General physicians should be aware of new drugs and their adverse effects and communicate with other specialists about the latest trends in their area of expertise.

CONFLICT OF INTEREST

None declared.

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