A Case of Acute Exacerbation of Chronic Adrenal Insufficiency Due to Ipilimumab Treatment for Advanced Melanoma

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Patient: Female, 50
Final Diagnosis: Adrenal insufficiency
Symptoms: Appetite loss • severe fatigue
Medication: —
Clinical Procedure: —
Specialty: Endocrinology and Metabolic

Objective: Unusual clinical course
Background: Ipilimumab is a therapeutic human monoclonal antibody that targets the T-cell inhibitory molecule, cytotoxic T-lymphocyte antigen-4 (CTLA-4), and is classified as an immune checkpoint inhibitor that has been shown to improve prognosis in patients with advanced melanoma. However, several immune-related adverse events have been reported to be associated with ipilimumab Treatment. A case of acute exacerbation of chronic adrenal insufficiency is presented that highlights that glucocorticoid dosage for patients undergoing steroid treatment at the time of ipilimumab treatment has yet to be established.

Case Report: A 50-year-old Japanese woman was diagnosed with malignant melanoma on the sole of her right foot. During her second course of ipilimumab treatment, she developed acute adrenal insufficiency caused by isolated adrenocorticotropic hormone (ACTH) deficiency, which required treatment with oral hydrocortisone. However, the symptoms of her adrenal insufficiency worsened, and she commenced treatment with 12 courses of nivolumab, a therapeutic human monoclonal antibody that blocks programmed cell death protein 1 (PD-1) on the surface of T-cells. She did not require corticosteroid support during nivolumab treatment.

Conclusions: This case report highlights the risk of exacerbating adrenal insufficiency during treatment with ipilimumab. The differences in clinical outcome in this patient between ipilimumab and nivolumab treatment might be explained by the different mechanisms between ipilimumab and nivolumab on immune function.

MeSH Keywords: Adrenal Insufficiency • CTLA-4 Antigen • Glucocorticoids • Melanoma • Programmed Cell Death 1 Receptor

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Background

Immune checkpoint inhibitors now include therapeutic monoclonal antibodies that target cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death receptor ligand 1 (PD-L1), and these emerging immune therapies have now been shown to be effective in the treatment of several types of advanced malignancy [1–3]. These breakthrough therapeutic checkpoint inhibitors target cells of the immune system and reduce immune tolerance of tumor cells also resulting in anti-tumor effects that benefit some patients with advanced malignancy [1–3].

Although treatment with immune checkpoint inhibitors can have beneficial effects in patients with malignancy, they are associated with specific immune-related adverse events, which involve the skin, gastrointestinal, liver, pulmonary, and endocrine systems [4–6]. A skin rash and colitis have been more commonly associated with human anti-CTLA-4 antibody treatment than anti-PD-1 and anti-PD-L1 antibodies [4]. Immune-related adverse event may be reversed with antihistamines, topical or systemic glucocorticoids, or anti-tumor necrosis factor-α (TNF-α) antibodies, especially for colitis, although adverse events associated with the endocrine system have been reported to be irreversible during treatment [6]. Because immune checkpoint inhibitors have a different impact on each patient, the type and degree of these immune-related adverse events might also be different for each patient. Several endocrinopathies are now categorized as immune-related adverse events from treatment with immune checkpoint inhibitors, including thyroid dysfunction [5], hypopituitarism [5,6], and primary adrenal dysfunction [5–7]. Most patients with irreversible adrenal insufficiency that suffer immune-related adverse events from immune checkpoint inhibitors might be able to continue with adequate corticosteroids replacement or, depending on the tumor response to treatment, a drug change or the use of combination therapy might be considered [8–10].

Several types of malignancy that show adrenal gland metastasis can result in primary adrenal insufficiency, and metastases to the pituitary gland can result in secondary adrenal insufficiency [11,12]. However, patients who have a history of long-term treatment with glucocorticoids due to chronic inflammatory or immunological disease are at risk of occult adrenal insufficiency. Although little is known about the influence of immune checkpoint inhibitors on the hypothalamic-pituitary-adrenal axis, care should be taken to diagnose adrenal insufficiency before commencing immune checkpoint inhibitor therapy, to prevent critical adrenal crisis.

A case of adrenal insufficiency is reported in a patient who required emergency supplementation with high-dose glucocorticoid in hospital on the day of treatment with ipilimumab, the therapeutic monoclonal antibody to CTLA-4, which was not required when treatment was changed to nivolumab, a therapeutic human monoclonal antibody to PD-1, which supports differences between the immune response and anti-tumor mechanism of anti-CTLA-4 and anti-PD-1 antibodies [13]. This case of acute exacerbation of chronic adrenal insufficiency highlights that glucocorticoid dosage for patients undergoing steroid treatment at the time of ipilimumab treatment has yet to be established and that elucidating the mechanism of systemic reactions are required for successful therapy with immune checkpoint inhibitors.

Case Report

A 50-year-old Japanese woman was diagnosed with advanced melanoma arising from the right sole with multiple metastasis to regional lymph nodes, the skin and the lung (pT4b, N3, M1b) (stage IV). After surgical resection and chemotherapy with dacarbazine, the melanoma progressed, and nivolumab treatment was commenced. After 13 courses of nivolumab treatment, she was diagnosed with progressive disease (PD). In September 2015, ipilimumab was substituted for nivolumab. On the day of the second course of ipilimumab, she complained of loss of appetite and severe fatigue. Her plasma adrenocorticotropic hormone (ACTH) and cortisol levels were almost undetectable, and she was diagnosed with acute secondary adrenal insufficiency due to isolated ACTH deficiency (Table 1).

Following intravenous administration of hydrocortisone (200 mg/day), her general condition improved rapidly (Figure 1). Hydrocortisone was then gradually reduced to a maintenance dose of 20 mg/day. After glucocorticoid was replaced with 20 mg/day of hydrocortisone, ipilimumab was continued as therapy for advanced refractory malignant melanoma. On the third course of ipilimumab treatment, she showed symptoms similar to the previous event, including severe fatigue, loss of appetite, and she developed a fever of 39°C. Hyponatremia was present with a plasma sodium level of 136 mmol/L, elevated C-reactive protein (CRP), eosinophilia of 12.7%, and a white blood cell (WBC) count of 5670/μL, although plasma glucose and potassium levels were within the normal range. Her symptoms were relieved her CRP was reduced following treatment with 200 mg/day of hydrocortisone (Figure 1). On the fourth course of ipilimumab treatment, she required 200 mg/day of hydrocortisone. Also, 1 mg/day of dexamethasone and 20 mg/day of hydrocortisone were added on the same day as ipilimumab treatment, to prevent adrenal insufficiency.

In March 2016, computed tomography (CT) of her chest showed pulmonary metastases consistent with progressive disease, and treatment with nivolumab was restarted. At this time, she did not show signs of adrenal insufficiency and a low dose of
hydrocortisone (20 mg/day) was sufficient for glucocorticoid replacement to continue repeated nivolumab treatment (Figure 1).

### Discussion

This report has described the case of a patient with advanced (Stage IV) melanoma required treatment with hydrocortisone due to acute adrenal insufficiency caused by isolated adrenocorticotropic hormone (ACTH) deficiency, and who required additional glucocorticoid replacement therapy following treatment with the immune checkpoint inhibitor, ipilimumab. Two important clinical issues arose from the present case. Glucocorticoid reduction as an effect of treatment with ipilimumab, a therapeutic monoclonal antibody that targets the T-cell inhibitory molecule, cytotoxic T-lymphocyte antigen-4 (CTLA-4), might exacerbate adrenal insufficiency when administrated to a patient with underlying chronic adrenal insufficiency. The immune anti-tumor mediated effects due to treatment with ipilimumab and the therapeutic human monoclonal antibody that blocks programmed cell death protein 1 (PD-1), nivolumab, might result in different systemic effects.

Several case studies have reported that treatment with ipilimumab was associated with hypopituitarism due to hypophysitis [14–16]. However, no previous study has reported how to determine the glucocorticoid replacement dose during immune checkpoint inhibitor treatment of patients with adrenal insufficiency. The present case showed an acute exacerbation of adrenal insufficiency each time the patient received ipilimumab therapy, although she continued being treated with hydrocortisone (20 mg/day). The patient’s C-reactive protein (CRP) levels were elevated each time ipilimumab was adminstered, although she showed a rapid recovery from adrenal insufficiency on receiving an increased dose of hydrocortisone. The closed circle with a solid line represents the proportion of eosinophils in the total white blood cell (WBC) population. The open circle with the broken line represents the values of C-reactive protein (CRP).
depletion in glucocorticoids due to glucocorticoid resistance associated with systemic inflammation, which is an effect that was not found to be associated with treatment with nivolumab in this case.

Anti-tumor immune therapy with ipilimumab and nivolumab is likely to occur due to different mechanisms, which might also be different in degree with different systemic effects. Severe side effects have previously been reported more frequently for ipilimumab, and other forms of CTLA-4 antibody therapy when compared with PD-1 blockade therapy, including PD-1 antibody therapy and programmed cell death receptor ligand 1 (PD-L1) antibody therapy [18–20]. The CTLA-4 and PD-1 immune checkpoint pathways are thought to operate at different stages of the immune response. CTLA-4 is thought to block autoreactive T-cells at the initial stage of naïve T-cell activation, typically in the lymph nodes [21,22]. However, PD-1 pathway agents regulate previously activated T-cells at the late stages of the immune response, primarily in peripheral tissues [21]. Studies in CTLA-4 knock-out mice have shown the development of lymphoproliferative disorders with multiorgan infiltration of polyclonal T-cells, resulting in murine mortality by between 3–4 weeks of age [23,24] whereas PD-1 deficiency induced localized and mild autoimmune diseases [25] such as rheumatoid arthritis, glomerulonephritis or cardiomyositis that caused dilated cardiomyopathy, and PD-1 knock-out mice survived [26]. In contrast to CTLA-4 blockade, PD-1 blockade has been shown to function predominantly within the tumor microenvironment, where its ligands are commonly overexpressed by tumor cells as well as infiltrating leukocytes [27]. In this context, CTLA-4 antibody therapy might be more likely to affect systemic immune reactions through the induction of large numbers of effector T-cells and/or reduction of regulatory T-cells, when compared with PD-1 antibody therapy. These differences in immune reactive pathways might also explain the differences observed in the effects on glucocorticoid depletion between the two drugs.

As this case report has demonstrated, it is important to note that ipilimumab may induce adrenal insufficiency when administered to patients with underlying abnormalities in the function of the hypothalamic-pituitary-adrenal axis. The current National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Insights and recent clinical studies have identified the preferred therapeutic effect of nivolumab therapy followed by ipilimumab, and combination therapy of ipilimumab and nivolumab, or optionally recommend single-agent ipilimumab for first-line, second-line, and subsequent treatment, depending on the tumor type and patient response [8–10]. When ipilimumab is used, it is important to identify patients with adrenal insufficiency, including patients with pituitary or adrenal metastasis, and those receiving chronic steroid therapy, as these patients may be more likely to develop immune-related adverse events. The present case indicated that the risk of unexpected symptoms of adrenal insufficiency might be associated with systemic inflammation (CRP levels), and should be assessed relative to the timing of ipilimumab treatment even when nivolumab is well tolerated. Also, when adrenal insufficiency is diagnosed, adequate doses of hydrocortisone should be administered.

Conclusions

This case report highlights the risk of exacerbating adrenal insufficiency during treatment with ipilimumab. The differences in clinical outcome in this patient between ipilimumab and nivolumab treatment might be explained by the different mechanisms between ipilimumab and nivolumab on immune function. Different systemic effects by immune checkpoint inhibitors may be different, including effects mediated by the hypothalamic-pituitary-adrenal axis, which indicate that careful follow-up of symptoms of adrenal insufficiency must be taken into account for successful treatment with immune checkpoint inhibitors.

Department and Institution where work was done

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Conflict of interest

None.

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