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Case Report

Isolated Adrenal Insufficiency in a Patient with Melanoma on Nivolumab

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Abstract

Immune checkpoint inhibitors are widely used in the treatment of cancer. Though they are effective in many types of malignancies, purposeful over-activation of the immune system often results in many adverse effects. The PD-1 inhibitor nivolumab is particularly associated with endocrinopathies. Below we describe an elderly female with metastatic melanoma on nivolumab who developed adrenal insufficiency in absence of hypophysitis on MRI, suggesting an isolated process induced by the drug itself. More research is needed about this phenomenon, as the reported endocrinopathies associated with checkpoint inhibitor therapy appear to be irreversible, as was unfortunately the case for the patient described below.

Keywords: *Adrenal Insufficiency; Melanoma; Nivolumab*

Introduction

Immune checkpoint inhibitors are monoclonal antibodies to the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) and the programmed death protein 1 (PD-1). These therapies augment antitumor immune response and are becoming widely used in a variety of cancer types, most prominently melanoma, non-small cell lung cancer, and renal cell cancer. These agents have improved the prognosis of several malignancies and their use is becoming widespread [1]. However, non-specific activation of the immune system has resulted in immune-related adverse events (irAEs) that affect essentially any organ system. Nivolumab is a PD-1 inhibitor that is associated with a wide variety of irAEs, including several endocrinopathies. Nivolumab-induced thyroiditis has been frequently reported [3], as has as isolated ACTH deficiency [4] and hypophysitis [5], though the latter are scarcer. Endocrinopathies are inconsistently recognized and reported but can be highly symptomatic and potentially life threatening [6]. For this reason, we present below a case of isolated ACTH deficiency without pituitary enlargement in a patient with metastatic melanoma on Nivolumab.

Case Presentation

The patient is a 79-year-old female with a history of metastatic melanoma, who began taking Nivolumab three months prior to presentation. She began experiencing progressive fatigue and lightheadedness, associated with joint pains, decreased appetite, and short-term memory loss. She was ruled out for infection and had stable vitals, and her symptoms were thought to be due to immune mediated side effects of her nivolumab. Her oncologist prescribed her prednisone, 20 milligrams daily, which improved her symptoms. She was referred to endocrinology for evaluation of adrenal insufficiency.

She underwent a full battery of pituitary testing. Thyroid function tests, LH, and FSH were normal. Her prolactin was elevated to 49 ng/dL, however on repeat testing was normal (9 ng/dL). The ACTH level was < 5 pg/mL, and cortisol was 1.3 ug/dL but these tests were done after she had taken hydrocortisone so the results were not reliable. Pituitary MRI revealed no abnormality (Figure 1). She underwent an ACTH stimulation test with cosyntropin 250 mcg, which revealed cortisol < 0.8 ug/dL at 0 minutes, 1.5 ug/dL at 30 minutes, and 2.5 ug/dL at 60 minutes, indicating a secondary isolated ACTH deficiency, presumed to be due to the patient's treatment with nivolumab. The patient's ACTH level prior to starting Nivolumab, was 16 ng/dL and cortisol was 5.6 ug/dL.

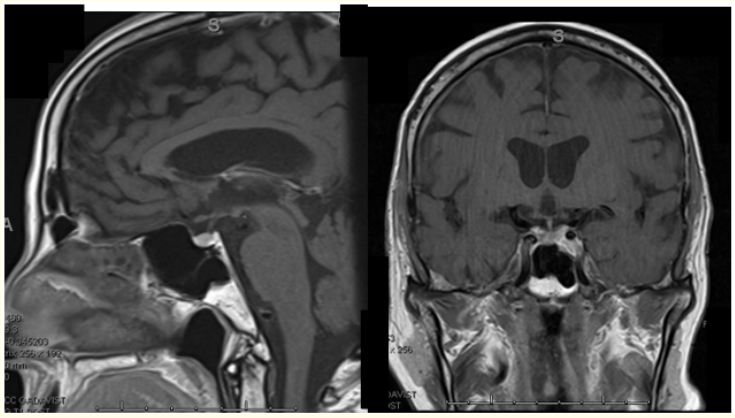

Figure 1: *Pituitary MRI demonstrating normal sized pituitary gland.*

She initially was started on hydrocortisone 20 mg every morning and 10 mg every evening. After the above results, she was tapered to 10 mg and 5 mg given recent DXA scans showed osteopenia. The patient missed her morning dose of hydrocortisone on one isolated later date and subsequently experienced nausea, vomiting and syncope later that day. Infectious workup was once again negative. She was started on stress dose steroids which improved her symptoms. She was gradually tapered and now remains on a stable dose of 15 mg in the morning and 10 mg in the afternoon with plans to further taper as tolerated. She continues to be on Nivolumab with close clinical follow-up.

Discussion

Our case illustrates a diagnosis of isolated ACTH deficiency, presumed to be an irAE associated with Nivolumab treatment for metastatic melanoma. Though their use is increasing exponentially, PD-1 inhibitors are relatively new medications and their side effect profiles are not fully understood. This contrasts the well-studied immune checkpoint inhibitor, ipilimumab, whose effects are well characterized. Sznol., *et al.* (2017) report that endocrinopathies caused by immune checkpoint blockade are often irreversible [7], however, their data refers primarily to ipilimumab. There is a lack of research on the reversibility of endocrinopathies associated with PD-1 inhibitors. Our patient remains dependent on exogenous glucocorticoids; however, she also remains on active treatment with Nivolumab.

The precise mechanism of checkpoint inhibitor-mediated endocrinopathies is not well understood, and once again much data is extrapolated from what is known about ipilimumab. It has been postulated that hypophysitis due to CTLA-4 blockade from ipilimumab may be due to T-cell mediated pituitary destruction, versus ectopic CTLA-4 expression within the pituitary itself, resulting in complement activation and subsequent inflammation after the drug itself binds to endocrine cells [7,9]. In cases of hypophysitis, one could expect adrenal insufficiency related to downstream effects in the target organ. However, in the case described above, there was no hypophysitis observed on MRI. This case therefore represents an isolated ACTH deficiency. No research describes this mechanism, specifically related to PD-1 inhibitors rather than ipilimumab.

There is a growing amount of reportable cases of isolated ACTH deficiency related specifically to Nivolumab. However, many cases of mild adrenal insufficiency likely go unreported, especially those which do not require endocrine referral for assistance with management. While the effects of ipilimumab range from isolated deficiency to multiple hormone deficiency [10], thus far nivolumab is primarily reported as causing isolated target gland deficiencies. Kitano., *et al.* [11] reported nine cases of hypopituitarism associated with nivolumab in patients with advanced melanoma; in all cases, hypopituitarism manifested as isolated ACTH deficiency. Pituitary MRI was either normal or not performed; in one case there was slight pituitary swelling. This same phenomenon was observed by Kitajima., *et al.* [4], who propose a nivolumab-induced autoimmune mechanism behind isolated ACTH syndrome, though admit that the details of the pathogenesis are not understood. Because the adrenal glands are in the abdominal cavity, direct destruction of the gland by its proximity to the PD-1 inhibitors target, the tumor itself, may be the reason for the isolated deficiency, but this has been merely theorized, and does not apply in cases where patients do not have abdominal tumors or metastases [7].

Treatment with nivolumab may continue with low grade endocrine toxicity [8], which was fortunately the case for the patient described above. However, there is minimal data to inform whether her ACTH deficiency due to nivolumab is reversible. While other inflammatory syndromes related to checkpoint inhibitor therapy are reversible (such as hepatitis, pancreatitis, colitis), endocrinopathies associated with their use are felt to be permanent [7]. As the use of PD-1 inhibitors becomes more widespread, both randomized prospective studies and awareness are needed; the former to elucidate the mechanism of the phenomenon of isolated ACTH deficiency, and the latter given the general, non-specific, but sometimes life-threatening symptoms of adrenal insufficiency in patients with metastatic cancer.

Conclusions

This case adds to an ever-growing body of rare irAEs in patients on checkpoint inhibitors. PD-1 inhibitors are relatively new medications and their endocrine related side effect profiles are mostly extrapolated from studies on CTLA-4 inhibitors. Specifically, our case demonstrates that isolated ACTH deficiency in patients treated with Nivolumab is an unelucidated process, yet one that will likely to grow in incidence. Most importantly, symptoms consistent with adrenal insufficiency are easily overlooked in an otherwise chronically ill population, and providers should be acutely aware of the importance of checking the function of the HPA axis, specifically ACTH and cortisol, for their patients on PD-1 inhibitors.

Declaration

Ethics approval and consent to participate: Ethics approval was not required for this case report. The patient involved in the case above gave full consent for her information to be reviewed for the purposes of this report.

Consent for Publication

The patient involved in the case above gave full consent for publication of this case report.

Availability of Data and Material

The data obtained for purposes of this case report is available entirely within the electronic health record at this patient's treating institution, for those who have access.

Competing Interests

The authors declare that they have no conflict of interest.

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Authors' Contributions

Each author contributed to this report. Drs. Wilson and Agrawal cared for the patient and edited this manuscript. Dr. Newman reviewed the patient's chart, performed the literature review, and drafted the manuscript.

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