Transformative Medicine (T-Med)

Volume 2 | Number 1 Article 2

March 2023

Delay in diagnosis of PD-1 Inhibitor induced Secondary adrenal Insufficiency

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Recommended Citation

Oladunjoye O, Oke I, Garrahy I, Oladunjoye AO, Macaulay K, Ellis J. Delay in diagnosis of PD-1 Inhibitor induced Secondary adrenal Insufficiency. *Transformative Medicine (T-Med)*. 2023; 2(1):6-9. doi: https://doi.org/10.54299/tmed/xcah6223.

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Cover Page Footnote

Manuscript was prepared while Olubunmi Oladunjoye was a resident at Department of Internal Medicine, Reading Hospital-Tower Health, West Reading, PA

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Case Report

Delay in Diagnosis of PD-1 Inhibitor Induced Secondary Adrenal Insufficiency

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Published March, 2023

ABSTRACT

INTRODUCTION: Immune checkpoint inhibitors including PD-1 inhibitors, were initially approved for the treatment of metastatic melanoma but are now increasingly being used for different types of solid organ malignancies. Despite the important clinical benefits, they are associated with immune-related adverse events. The most critical endocrinopathy associated with PD -1 inhibitor is adrenal insufficiency (AI), which requires prompt diagnosis and management to avoid fatality.

CASE PRESENTATION: We present the case of a 78-year-old woman with colon adenocarcinoma treated with Nivolumab (PD-1 inhibitor) after her pulmonary metastases progressed on chemotherapy. She presented to the hospital with progressive generalized weakness, fatigue, headache, lightheadedness, nausea, myalgia, reduced oral intake. She had 2 prior hospitalizations on account of similar symptoms with workup negative for cancer progression or gastrointestinal obstruction. Her laboratory values showed Na 128mmol/L, K 3.4mmol/L, Cr 0.52mg/dL and blood sugar 42mg/dL. Morning cortisol was low at 2.2µg/dL and ACTH stimulation test was positive. She was diagnosed with AI secondary to Nivolumab use and was started on Hydrocortisone while Nivolumab was discontinued.

CONCLUSION: Immune checkpoint inhibitors have a unique side effect profile of immune-related adverse events, the most critical of which is AI. However, the non-specific manifestations of AI can lead to misdiagnosis or delay in diagnosis. Therefore, it is important for physicians to have high index suspicion for AI in acutely ill patients on PD-1 inhibitors for prompt recognition, diagnosis and treatment of AI which is important to prevent life-threatening adrenal crisis.

KEYWORDS: PD-1 inhibitor, Adrenal insufficiency, checkpoint inhibitors

INTRODUCTION

Immune checkpoint inhibitors were initially approved for the treatment of metastatic melanoma but are now increasingly being used for many different types of solid organ malignancies. These immune checkpoint inhibitors include cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, programmed cell death protein1 (PD-1) inhibitors and programmed cell death1 ligand 1 (PD-L1) inhibitors[1-4]. Despite the important clinical benefits in cancer treatment, they are associated with a spectrum of side effects referred to as immune-related adverse events. These include dermatologic, gastrointestinal, hepatic, and endocrine diseases. Endocrinopathies result from inflammation of the pituitary, thyroid, or adrenal glands[5-7]. The incidence of endocrinopathies associated with immune checkpoint inhibitors has been reported to be about 8-13%[6,8-10]. The most critical endocrinopathy is adrenal insufficiency (AI) which requires prompt diagnosis and management to avoid significant morbidity and even mortality[6]. It's incidence ranges from less than 1-2% in those on monotherapy and 4-9% in patients on combination therapy[11,12]. However, given the non-specific nature of the symptoms of AI and its mimic of other conditions, it's diagnosis can be delayed or even missed. Therefore, we present a clinical case of delayed diagnosis of secondary AI following treatment with immune checkpoint inhibitor.

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Disclosure Statement: The authors have no conflicts of interest to declare.

CASE PRESENTATION

We present the case of a 78-year-old woman with a history of gastric bypass, alcohol use and initially stage III (T3N1bM0) colon adenocarcinoma status post hemicolectomy and adjuvant capecitabine. Later she developed metastasis to the lungs on chemotherapy. She was eventually started on Nivolumab after she had failed 6 cycles of chemotherapy. About 10 months into treatment, she was hospitalized (Admit 1) on account of dry heaving, reduced oral intake and fatigue. Vital signs at this hospitalization showed BP 97/57mmHg, pulse 75/min, temperature 36.6°C. Her laboratory values showed hyponatremia with serum sodium 128 mmol/L (ref: 135-145 mmol/L), hypokalemia 3.3mmol/L (ref 3.6-5.3 mmol/L), hypomagnesemia 1.5 mg/dl (ref 1.8 -2.2 mg/dl) and blood sugar 91 mg/dL (ref: 70-90 mg/dL). Clinical examination did not reveal any significant finding. Esophagogastroduodenoscopy was done to rule to gastric obstruction, computerized tomography scan of the abdomen excluded cancer progression and MRI of the brain did not show any evidence of metastatic disease or hemorrhage. She was started on antiemetics and proton pump inhibitor and then discharged home. However, she presented again at the hospital 2 months later (admit 2) with similar symptoms. Blood pressure was 122/71mmHg with normal pulse and temperature. Labs again showed hyponatremia, hypokalemia, and blood sugar of 77 mg/dl. She was placed on Olanzapine and dexamethasone (for 5 days) for possible cancer related nausea. Nivolumab was discontinued and was discharged home after a few days. She presented a third time 2 months after second admission (Admit 3) with generalized weakness, fatigue, headache, nausea and reduced oral intake. Her vitals at this admit showed blood pressure 171/88mmHg, pulse 83/minute, temperature 36.4 °C and oxygen saturation of 98% in room air. Her laboratory values showed Na 128mmol/L, K 3.4mmol/L, Cr 0.52mg/dL and blood sugar 42mg/dL. Her chemotherapy was withheld. Hypoglycemia workup included serum insulin, proinsulin, c-peptide and TSH were all within normal limits. Morning cortisol was low at 2.2µg/dL (ref: 6.7 -12.0 µg/dL). A diagnosis of AI possibly secondary to Nivolumab use was made. Adrenocorticotropic hormone (ACTH) stimulation test was also done in which cortisol level was measured before and after ACTH injection. The result showed cortisol <18µg/dL at 60 minutes (baseline cortisol 1.4µg/dL, 7.0 µg/dL at 30 minutes and 9.7µg/dL at 60 minutes). She was started on Hydrocortisone 15 mg in the morning and 10 mg in the evening. A repeat ACTH test done at follow-up was consistent with secondary AI with baseline cortisol <1.0 µg/dL, Cortisol 4.5µg/dL at 30 minutes, Cortisol 5.7µg/dL at 60 minutes and ACTH 2.8pg/mL. She was continued on hydrocortisone with eventual resolution of symptoms at subsequent follow-up visits.

DISCUSSION

This is a case of delayed diagnosis of secondary AI in a patient on PD-1 inhibitor for treatment of colon cancer. She had represented with non-specific symptoms of nausea, fatigue, loss of appetite and weight loss, low blood pressure on the first admit, hyponatremia, hypokalemia, and borderline-low blood sugar level but diagnosis of AI was not made until the third hospital admission.

Given our patients history of alcohol use and metastatic colon cancer other diagnosis like cancer progression, gastritis, gastric outlet obstruction were ruled out. She also received treatment for syndrome of inappropriate antidiuretic hormone secretion in the setting of hyponatremia without consideration for AI. The diagnosis of AI was delayed due to the non-specific symptoms which can be easily disregarded if physicians do not high index of suspicion for side effects of immune checkpoint inhibitors. Also, our patient had hypokalemia which is not the usual pattern in AI. Hyperkalemia is usually

https://scholarcommons.towerhealth.org/t-med/vol2/iss1/2
DOI: https://doi.org/10.54299/tmed/xcah6223

seen in primary AI but potassium can be normal or near normal in secondary AI given the preservation of the mineralocorticoid axis (aldosterone). Our patient may also have had hypokalemia due to nutritional deficiency in the setting loss of appetite, dry heaving and alcohol use.

Both primary and secondary AI can occur with Check point inhibitors[13,14] and can occur from one to several months following the initiation of treatments9. Primary AI occurs due to inflammation of the adrenal glands while secondary AI results from the inflammation of the anterior pituitary gland (hypophysitis). de Filette et al in a systematic review and meta-analysis reported incidence of primary AI to be 5.2 – 7.6% and that of secondary AI (hypophysitis) to be 8.8 – 10.5%. The incidence of hypophysitis varies with type of immune checkpoint inhibitor and whether patient is on monotherapy versus combination therapy. The incidence is higher for those on CTLA-4 than those on PD-1 inhibitors, and also for those on combination therapy compared with those on monotherapy[3,12]. Our patient was on a PD-1 monotherapy.

Despite this established side effect of immune checkpoint inhibitors, there is still no recommendation for routine laboratory monitoring (e.g. random AM cortisol) but physicians should have a high index of suspicion for AI as adverse effect profile of checkpoint inhibitors are less predictable than general chemotherapy. In the setting of acute illness, standard work up for AI to confirm abnormal cortisol (basal and/or stimulated) should be considered. In ACTH stimulation test, cortisol level is measured before and after ACTH injection. It is expected there will be an increase in cortisol after stimulation with ACTH. The post stimulation blood cortisol should be greater than 18µg/dL in normal tests. Our patient's cortisol was cortisol <18µg/dL at 60 minutes. If abnormal, exogenous steroid use should be ruled out and ACTH level should be checked to differentiate primary from secondary AI. In secondary AI, the pituitary gland does not make adequate ACTH leading to low ACTH as was seen in our patient.

As regards treatment, the immune checkpoint inhibitor should be held once AI is suspected. The treatment approach is based on the severity of the patient's presentation. Patient should then be treated with corticosteroid (especially hydrocortisone). Oral administration (Hydrocortisone 15-25 mg/day in 2-3 doses or the equivalent) can be considered if the symptoms are mild, but if severe and life threatening (adrenal crisis) patient should receive intravenous hydrocortisone and fluid resuscitation[15,16.] The dose can then be titrated according to the patient's symptoms[14]. The treatment with immune checkpoint inhibitors can be resumed after resolution of symptoms.

CONCLUSION

Immune checkpoint inhibitors have a unique side effect profile of immune-related adverse events, the most critical of which is AI. However, the non-specific manifestations of AI can lead to misdiagnosis or delay in diagnosis. Therefore, it is important for physicians to have high index suspicion for AI in acutely ill patients on PD-1 inhibitors. This will aid prompt recognition, diagnosis and treatment of AI in order to prevent life-threatening adrenal crisis.

TAKE HOME POINT

Immune checkpoint inhibitors can cause primary or secondary adrenal insufficiency. Acutely ill patients on immune checkpoint inhibitors should have their cortisol level checked. If you think adrenal failure: make sure to exclude it and if in doubt treat it.

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