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CASE REPORT

# Immunotherapy Induced Adrenal Insufficiency: An Underdiagnosed Cause of Persistent Hypotension in Cancer

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**Abstract**

**Endocrinopathies following immunotherapy have infrequently been documented in the literature. Adrenal insufficiency is a rare consequence of pembrolizumab immunotherapy, with incidence reported to be between 0.98 and 1.3%. We present the case of a 34-year-old female with triple negative breast cancer on chemotherapy who presented with generalized weakness with tachycardia, tachypnea and hypotension unresponsive to fluids. Despite initial improvement with intravenous hydrocortisone and midodrine, the patient continued to be symptomatically hypotensive following discharge and required re-admission. AM cortisol level was found to be < 0.5 ug/dl and ACTH was <1.5 pg/dL, consistent with secondary adrenal insufficiency. CT abdomen and pelvis was unremarkable for adrenal pathology. Patient had been initiated on pembrolizumab (Keytruda) 4 months prior to presentation as part of neoadjuvant chemotherapy. The patient was provided supportive treatment with discharge on fludrocortisone, prednisone, and midodrine. This case reports an unusual consequence of immune checkpoint inhibitors, in which early diagnostic testing, identification, and management is critical.**

*Keywords:* Pembrolizumab, Keytruda, Adrenal insufficiency, Secondary adrenal insufficiency, Endocrinopathy

## 1. Introduction

Pembrolizumab (Keytruda) is a IgG4 monoclonal antibody against programmed death receptor-1 (PD-1) first approved by the US Food and Drug Administration in 2014 for cancer immunotherapy. It is currently approved for the treatment of malignancies including triple negative breast cancer,[1,2] non-small cell lung cancer,[3] head and neck squamous cell carcinoma, renal cell carcinoma, and most recently cervical cancer.[4] Combinations of anti-PD-1 agents paired with chemotherapy have also shown improved response rates and survival in these cancer types.[5]

While immune checkpoint inhibitors have revolutionized the landscape of cancer therapy, immune-related adverse effects (irAEs) have been observed with varying clinical presentations depending on the organ involved. Immunotherapy-induced endocrinopathies are an uncommon but potentially life-threatening consequence, and may involve the thyroid, pituitary, adrenals, and pancreatic islet beta cells.

## 2. Case report

A 34-year-old woman with a 6-month history of triple negative breast cancer presented for generalized weakness. She had received her most recent dose of chemotherapy and immunotherapy 1 week before presentation, which consisted of pembrolizumab, doxorubicin, and cyclophosphamide. Upon admission, patient was tachycardic, tachypneic, and hypotensive at 92/61 mmHg. Significant myelosuppression was evident, with an absolute

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neutrophil count of 120 and platelets of 44,000. Patient was started on empiric cefepime and vancomycin for concern of sepsis in the setting of neutropenia. Despite multiple fluid boluses of 30 mL/kg resulting in some symptomatic improvement, the patient remained hypotensive.

Subsequent infectious work-up was grossly negative, unremarkable for lactic acid, procalcitonin, or urinalysis. Patient remained afebrile with no localizing signs, and blood cultures returned negative after 4 days. Antibiotics were ultimately discontinued for low likelihood of infection.

Cardiogenic causes for persistent hypotension were investigated, with EKG upon admission revealing sinus tachycardia with QT interval prolongation. CT angiogram was negative for pulmonary embolism. Echocardiography was grossly unremarkable, with normal left ventricular (LV) systolic and diastolic function, normal ventricular sizes, and only trace regurgitation of mitral and tricuspid valves. CT were abdomen and pelvis showed no acute abnormalities.

Given a negative infectious and cardiogenic workup, her persistent hypotension was treated with supportive measures, and the patient responded well to midodrine. After an inpatient stay of 4 days, she was discharged with blood pressure having returned to baseline. Less than 12 h later, however, the patient returned due to re-emergence of generalized weakness and near-syncope. She was once again found to be hypotensive at 83/52 mm Hg. An 8am serum cortisol was drawn and found to be < 0.5 μg/dL. ACTH was found to be < 1.5 pg/dL (Table 1). Cosyntropin stimulation test was abnormal, showing lack of cortisol response to ACTH stimulation. CT abdomen was unremarkable for adrenal gland pathology. Pituitary MRI was contraindicated due to the presence of tissue expanders secondary to breast reconstructive surgery. Patient was ultimately discharged with prednisone 15 mg daily, fludrocortisone 0.1 mg daily, and midodrine 5 mg daily.

*Table 1. Endocrinology work-up for persistent hypotension.*

| | Unit | Value | Reference range |
|---|---|---|---|
| Cortisol, fasting | ug/dL | **< 0.5** | 4.2–22.4 |
| ACTH | pg/dL | **< 1.5** | 7.2–63.3 |
| Cosyntropin stimulation test | | | |
| - Cortisol, baseline | ug/dL | **5.4** | 4.2–22.4 |
| - Cortisol, 1 h | ug/dL | **4.5** | 4.2–22.4 |
| Adrenal antibodies | ng/dL | Negative | 2–70 |
| Potassium | mmol/L | **3.4** | 3.5–5.3 |
| DHEA-SO4 | mcg/dL | **6.0** | 31–274 |
| Renin | ng/mL/hr | 0.37 | 0.25–5.82 |
| TSH | uIU/mL | 2.506 | 0.45–4.5 |
| T4 | ng/dL | 0.96 | 0.76–1.46 |

During her post-hospitalization course, the patient was transitioned from prednisone to hydrocortisone at physiologic dosing. Fludrocortisone was ultimately discontinued due to presence of hypokalemia and normal renin. Her clinical course has been stable since.

Altogether, these findings appear most consistent with secondary adrenal insufficiency in the setting of pembrolizumab.

## 3. Discussion

Here, we report a case of adrenal insufficiency, likely secondary to immunotherapy with pembrolizumab (Keytruda), an immune checkpoint inhibitor. Various autoimmune-induced endocrino pathies have been reported in the literature following immunotherapy. Clinical trials of immune checkpoint inhibitors have identified hypothyroidism/hyperthyroidism and hypophysitis to be the most prevalent manifestations of endocrinopathies.[6]

Adrenal insufficiency is a rare consequence of immune checkpoint inhibitor therapy. In a phase three trial with 1174 triple-negative breast cancer patients randomly assigned to pembrolizumab-chemotherapy or placebo-chemotherapy, adrenal insufficiency was noted in 1.3% of the patients receiving concurrent immunotherapy.[2] Similarly, other case reports have documented adrenal failure following the use of ipilumab, tremelimumab, and nivolumab in various cancers.[4] The etiology of these immunotherapy-related endocrinopathies has yet to be elucidated. The immune checkpoint blockade induced by immunotherapy has been linked to increased T-cell infiltration, T-cell dysfunction, and upregulated pre-existing autoantibodies.[6] Secondary adrenal insufficiency has also been proposed to be related to a type II hypersensitivity reaction, as some studies have shown the presence of autoantibodies and lymphocytic infiltration in the pituitary.[5]

Symptom onset in immunotherapy-related adrenal insufficiency has been observed to typically occurs within 3–4 months of treatment with anti-PD1/PD-L1 therapy.[5] Common symptoms typically include nausea, vomiting, hypotension causing dizziness or fainting, and signs of hypoglycemia. Secondary adrenal insufficiency may also cause symptoms mimicking signs of neuro-compression, including headache, diplopia, and visual field defects.[5]

A thorough evaluation is warranted in the setting of suspected immunotherapy-induced adrenal insufficiency, include measurements of morning cortisol and ACTH levels, cosyntropin/ACTH

stimulation testing, and radiologic imaging. Patients with confirmed adrenal insufficiency should be treated with replacement dose glucocorticoids with mineralocorticoids if indicated.[5] Generally, patients may continue anti-PD-1/anti-PD-L1 therapy while receiving treatment for adrenal insufficiency, as endocrinopathies related to immunotherapy are often irreversible and would not change management of the malignancy.[5]

## 4. Conclusion

Although uncommon, adrenal insufficiency is a severe and life-threatening consequence of immune checkpoint inhibitor therapy. As medications like pembrolizumab become a mainstay of treatment for malignancy, physicians must have a high level of suspicion in such patients who present with persistent hypotension or other symptoms suggestive of endocrinopathy. Swift diagnosis and management of immunotherapy-induced adrenal insufficiency can prevent complications and improve overall quality of life.

## Conflicts of interest

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## Consent for the publication

Consent for the publication of all patient photographs and medical information was provided by the authors at the time of article submission to the journal, stating that all patients gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

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