



# IMMUNE CHECKPOINT-INHIBITOR-RELATED HYPOPHYSITIS IN RENAL CELL CARCINOMA

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## Introduction

Use of immune checkpoint inhibitors is increasingly common in the treatment of advanced cancers and is first-line therapy for some lung cancers. Endocrinopathies are a known side effect of checkpoint inhibitors due to increased autoimmunity. While hypophysitis has a higher reported incidence with the CTLA-4 inhibitor ipilimumab, incidence is much lower with the PD-1 inhibitor pembrolizumab. We present the case of a patient with pembrolizumab-induced hypophysitis.

## Case Description

A 54-year-old male with metastatic renal cell carcinoma on pembrolizumab presented with weakness and dyspnea. He was admitted for septic shock and was treated with antibiotics, fluids, and eventually vasopressors. He remained persistently hypotensive. Random cortisol level was found to be 1.1 mcg/dL. The patient had never been treated with steroids. ACTH was inappropriately normal at 8.6 pg/mL. ACTH stimulation test was positive; cortisol levels were 0.9 mcg/dL at baseline, 3.6 mcg/dL after 30 minutes, and 3.7 mcg/dL after 60 minutes. The patient had a cardiac arrest later that day and was admitted to the ICU after resuscitation. He was started on stress-dose hydrocortisone. Concern was raised for checkpoint-inhibitor-related hypophysitis in the absence of other obvious causes of secondary adrenal insufficiency.

## Case Description, cont'd

The patient had last been treated with pembrolizumab five weeks earlier. Due to clinical instability, MRI of the pituitary gland was not initially obtained. Treatment for presumed hypophysitis was started with 100mg IV hydrocortisone every eight hours (equivalent to 0.5mg/kg prednisone). Thyroid function tests were abnormal with TSH of 8.882 mcU/mL and free T4 of 0.9 ng/dL, likely reflecting nonthyroidal illness. Testosterone level was low at 22.3 ng/dL and FSH was low-normal at 2.1 mU/mL, further supporting the diagnosis of hypophysitis. Abnormal hormone levels are summarized below in Figure 1. The patient's hemodynamic status and mentation improved significantly with steroids. He was transitioned to an equivalent dose of prednisone prior to discharge.

Hormone	Patient's Value	Reference Range
ACTH	8.6 pg/mL	0-46 pg/mL
Baseline cortisol	0.9 mcg/dL	3.4-22.5 mcg/dL
Cortisol 30min post-Cosyntropin stimulation test	3.6 mcg/dL	>18.0 mcg/dL
Cortisol 60min post-Cosyntropin stimulation test	3.7 mcg/dL	>18.0 mcg/dL
TSH	9.127 mcUnits/mL	0.350-5.000 mcUnits/mL
FT4	0.9 ng/dL	0.8-1.5 ng/dL
Testosterone level	22.3 ng/dL	280.0-1100.0 ng/dL
FSH	2.1 mUnits/mL	1.4-18.1 mUnits/mL
LH	5.6 mUnits/mL	1.5-9.3 mUnits/mL
Prolactin	10.3 ng/dL	2.1-17.7 ng/dL

Figure 1. Results of hormone levels obtained during hypophysitis workup. Abnormal levels are highlighted in red. FSH level was borderline low and is highlighted in orange.

## Discussion

Hypophysitis is a rare but serious side effect of checkpoint inhibitor immunotherapy. It is important for clinicians to obtain baseline hormone profiles in patients starting these chemotherapies and to monitor for development of endocrinopathies. This case highlights the importance of keeping checkpoint-inhibitor-related hypophysitis and adrenal insufficiency high on the differential in hospitalized patients; failure to recognize these syndromes and initiate high-dose steroids can be fatal. As immunotherapy becomes more standard in cancer treatment, it is important for oncologists and endocrinologists to be proactive in monitoring for and treating serious endocrinopathies such as hypophysitis.

## References

- Barroso-Sousa, Romualdo, et al. "Endocrine Dysfunction Induced by Immune Checkpoint Inhibitors: Practical Recommendations for Diagnosis and Clinical Management." *Cancer*, vol. 124, no. 6, 3 Jan. 2018, pp. 1111-1121., doi:10.1002/cncr.31200.
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