Recurrence of Hypophysitis After Immune Checkpoint Inhibitor Rechallenge

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Abstract

Immune checkpoint inhibitor (ICI)-induced hypophysitis is an immune-mediated pituitary inflammation that tends to cause long-term pituitary deficiency. Management of ICI-induced hypophysitis includes corticosteroids for acute inflammation and long-term hormone replacement due to irreversible pituitary cell damage. We report a case of recurrent hypophysitis following ICI rechallenge for metastatic melanoma. A 33-year-old woman with recurrent metastatic melanoma with adrenal, pelvic, and inguinal metastases developed recurrent hypophysitis during treatment with ipilimumab and nivolumab which recurred with rechallenge >5 years later. In both cases, headache was the most notable symptom and brain MRI showed pituitary enlargement and edema without evidence of metastases. Central adrenal insufficiency and symptoms caused by mass effect were treated with acute high-dose corticosteroids and long-term replacement corticosteroids. Based on recurrence and failure of symptomatic treatment with continued steroid treatment, ICI was discontinued. This case illustrates that hypophysitis may recur with ICI rechallenge, challenging traditional assumptions that chronic, irreversible irAEs are unlikely to recur or flare. The regenerative potential of pituitary cells after ICI-induced damage or additional damage to previously unaffected cells may be more conceivable than previously realized. Additional research on the potential for recurrent ICI-induced endocrinopathies are needed.

Introduction

Hypophysitis is an endocrine immune-related adverse event (irAE) from immune checkpoint inhibitor (ICI) therapies, though it is exceedingly uncommon outside this context. Hypophysitis occurs in between 1%-18%, with higher incidence with anti-CTLA-4-based regimens potentially related to the expression of CTLA-4 on the pituitary gland.1

Patients with hypophysitis often present with symptoms related to mass effect from pituitary gland enlargement or anterior pituitary hormone deficiencies. Hypophysitis has a 80%-100% chance of progressing to a chronic hormone deficiency due to irreversible destruction of the corticotrope, thyrotrope, or gonadotrope cells.2 Given this cellular exhaustion, the potential for hypophysitis flares with ICI rechallenge is unclear. Here, we describe a rare case of hypophysitis recurrence after rechallenge with anti-CTLA-4 and anti-PD-1 combination therapy.

Case Report

A 33-year-old woman initially presented in December 2015 with right thigh pain. Excisional biopsy of a right inguinal lymph node diagnosed metastatic melanoma. A subsequent PET scan demonstrated involvement of pelvic and inguinal adenopathy and adrenal metastases. Ipilimumab/Nivolumab combination therapy (dosed at 3 mg/kg, 1 mg/kg, respectively) was initiated.

After her second cycle, she began to experience joint pains, palpitations, and increasing daily headaches. Laboratory evaluation (Table 1) showed thyrotoxicosis with TSH <0.015 µU/mL (ref 0.35-3.60), T4 16 µg/dL (ref 4.0-11.0), T3 235 ng/dL (ref 58-160), for which atenolol was started. Her headache worsened over the next few days and MRI evaluation identified 9 x 12 mm pituitary gland enlargement with extension into the suprasellar space (Fig. 1A), consistent with hypophysitis, and no evidence of intracranial metastasis. Morning cortisol levels were normal at 10.8 µg/dL (ref 3.7-19.4). ICI treatment was held after the third cycle, and she was treated with prednisone 80 mg/day (1 mg/kg/day) tapered to 10 mg/day over 10 days with significant improvement in symptoms. After gradual prednisone taper to 2.5 mg daily, she began to experience increasing fatigue. Morning cortisol was undetectable, and she began maintenance hydrocortisone 15-25 mg daily in divided doses. Her thyroid function normalized within 8 weeks, (TSH 2.18 µU/mL, T4 5.7 µg/dL, and T3 111 ng/dL), and atenolol was discontinued. Notably, the patient had regular menstrual periods, suggesting normal HPG axis function. Radiographic evidence of hypophysitis resolved on subsequent MRI imaging (Fig. 1B). She continued maintenance nivolumab with ongoing partial response on PET scan until May 2017.

The patient developed recurrent melanoma in February 2022 with enlarging pelvic lymph nodes. Based on her previous long-term treatment response, combination Ipilimumab/Nivolumab was restarted. However, the patient reported fevers and arthralgias after cycle 1 and increasing headaches after cycle 2. Brain MRI showed a homogenously enhancing
mass lesion within the sella that extended into the suprasellar region measuring 13 mm in height (Fig. 1C), consistent with recurrent ICI-induced hypophysitis. Steroid treatment was promptly started and tapered with an improvement in headache symptoms.

With resolution of hypophysitis symptoms with prednisone followed by hydrocortisone replacement and an excellent response to 4 cycles of combination therapy, the patient resumed maintenance nivolumab. However, 1 week after the initial infusion, the patient experienced reoccurrence of headache along with eye pain, neck pain, and arthralgias; she was treated with a prednisone with plans to discontinue ICI treatment.

**Discussion and Conclusion**

Here we report a rare case of recurrent ICI-induced hypophysitis. Our patient presented with classical clinical and imaging characteristics associated with hypophysitis at both junctures.1 The patient experienced primary thyroiditis at both initial presentation and recurrence and had persistent secondary adrenal insufficiency throughout her clinical course; gonadal function remained intact. Several common imaging findings include nonspecific pituitary gland and stalk enlargement or geographic hypoenhancement in the anterior lobe.1 On brain MRI, our patient had homogenously enhancing pituitary gland enlargement at initial presentation which resolved after steroid treatment. Upon rechallenge, imaging showed similar pituitary gland enlargement. Of note, focal enhancement of the pituitary gland in the setting of hormone deficiencies are more consistent with hypophysitis, while brain metastases commonly involve gray-white matter junctions and border zones between major vascular territories. Management consisted of a brief course of high-dose corticosteroids to mitigate acute inflammation (targeting pituitary enlargement and mass effect) and additional hormone replacement for endocrinopathies.4 ICI therapy was held in the acute setting, but continued shortly after clinical symptom management. Of note, high-dose steroids do not appear to

| Characteristics                      | Initial irAE                                                                 | Recurrence                                      |
|--------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------|
| Clinical symptoms                    | Headaches, jitteriness, skin tingling, palpitations, and fatigue             | Headaches, nausea, arthralgia, extraocular pain, and tachycardia |
| Notable laboratory findings          | TSH: <0.015* µu/mL. T4: 16.0* ng/dL. T3: 235* ng/dL. Cortisol: <0.8* µg/dL     | TSH: 0.019* µu/mL. Free T4: 1.69* ng/dL. T3: 94 ng/dL. Cortisol: 5.7 µg/dL |
| MRI findings                         | Pituitary enlargement 9 × 12 mm with extension into the suprasellar space without displacement of pituitary stalk | Pituitary enlargement 13 mm within the sella and extending into the suprasellar region |
| Time after ICI initiation            | 64 days                                                                      | 33 days                                         |
| Response to treatment                | Partial response                                                             | N/A                                             |
| irAE treatment                       | Hyperthyroidism: 50 mg atenolol                                               | Hypophysitis: prednisone 60 mg/day tapered to 10 mg over 10 days to 10 mg/day for 7 days |
| Outcome                              | Acute symptoms resolved and maintained on hydrocortisone 15 mg daily         | Acute symptoms resolved with steroid taper and continued baseline hydrocortisone 15 mg daily; flared with nivolumab monotherapy |

*Refers to values outside of normal reference range.
Abbreviation: N/A, not available.

![Figure 1. Postcontrast T1-weighted MR images (A) during initial hypophysitis evaluation after ICI initiation (5/17/16), (B) after steroid treatment and resolution of acute hypophysitis (12/10/18), and (C) after ICI rechallenge and recurrence of hypophysitis (3/22/22).](image-url)
improve pituitary function although may improve compressive symptoms.\textsuperscript{4,5} Rather, treatment consists of hormone replacement, allowing for ICI continuation.

While the precise pathophysiology of ICI-induced hypophysitis is largely unknown, recent studies have suggested the roles of the antibody-dependent cell-mediated cytotoxicity and complement pathways in anti-CTLA-4-related hypophysitis.\textsuperscript{6} Anti-pituitary antibodies may target different cell types including thyrotrophs, corticotrophs, and gonadotrophs by binding to CTLA-4 antigen expressed on pituitary endocrine cells.\textsuperscript{7} This case supports the hypothesized mechanistic predisposition of anti-CTLA-4 therapies for the development of hypophysitis.\textsuperscript{6,7} Shortly after the first initiation of combination therapy and reinitiation for disease recurrence, hypophysitis occurred. Recurrence of either the same initial irAE or de novo irAE are not rare with ICI rechallenge and occurs in one quarter to one-half of cases.\textsuperscript{8} However, irreversible irAEs, such as hypophysitis, are not known to reoccur based on the chronic, exhaustive nature of ICI-associated endocrinopathies.\textsuperscript{2} Chronic irAEs often require baseline immunosuppression or hormone replacement, potentially decreasing the risk of recurrence.

The current case highlights the possibility for ICI-induced hypophysitis to recur with rechallenge. Conventionally, many have considered that many endocrinopathies (including hypophysitis) result in “burned out” organ, with ablation of target hormone producing cells. However, this case challenges this assumption, as clinical and radiologic features were consistent with highly symptomatic hypophysitis flare. Thus, it seems clear that at least some “target” cells in the pituitary remained to drive inflammation upon rechallenge. Preserved gonadal and thyroid function perhaps signaled that residual pituitary tissue was present and might be a risk factor for recurrence. There have also been reports of thyrotroph, gonadotroph, and rarely, adrenocorticotroph recovery.\textsuperscript{9,10} Hypophysitis recurrence may indicate the potential for the recovery of a subset of hormone-secreting cells damaged by the inflammatory process. As more reports emerge of pituitary function recovery after ICI-induced hypophysitis, additional work is necessary to study the potential for pituitary gland recovery and recurrence of endocrinopathies with ICI rechallenge.

Conflict of Interest

Douglas B. Johnson: BMS, Catalyst Biopharma, Iovance, Janssen, Mallinckrodt, Merck, Tevo, Targovax, Mosaic, ImmunoEngineering, Novartis, Oncosec, Pfizer, Targovax, Tevo (CA), BMS, Incyte (RF), Patents pending for use of MHC-II as a biomarker for immune checkpoint inhibitor response and for abatacept as treatment for immune-related adverse events (IP). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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