



## Immune Checkpoint Inhibitor Therapy- Related Hypophysitis: A Case Report

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### Abstract

*Hypophysitis due to programmed cell death protein-1 antibodies is not common. This condition may be life threatening. Diagnosis remain clinical and laboratory. Treatment requires pituitary hormones replacement.*

**Keywords:** Checkpoint inhibitors, Programmed cell death protein-1 inhibitor, Hypophysitis.

### Introduction

Immune checkpoints inhibitors including pembrolizumab, are effective treatments for advanced neoplasias. Pembrolizumab are monoclonal antibodies directed at the programmed cell death 1 (PD-1) pathway and was subsequently also approved for the additional treatment of renal carcinoma. Rare, but important adverse events include hypophysitis, requiring prompt diagnosis and treatment.

### Case History

A 67-year-old male was diagnosed with renal clear cell carcinoma of right kidney stage pT3aN0M0 and underwent exisional surgery. Two years later on whole-body computer tomography (CT) scan revealed metastases in the inferior lobe of the lung, bilateral hilar and mediastinal lymph node metastases in the C7 vertebrae, right humerus, both knees and ankles. The patient was started on anti PD-1 therapy with

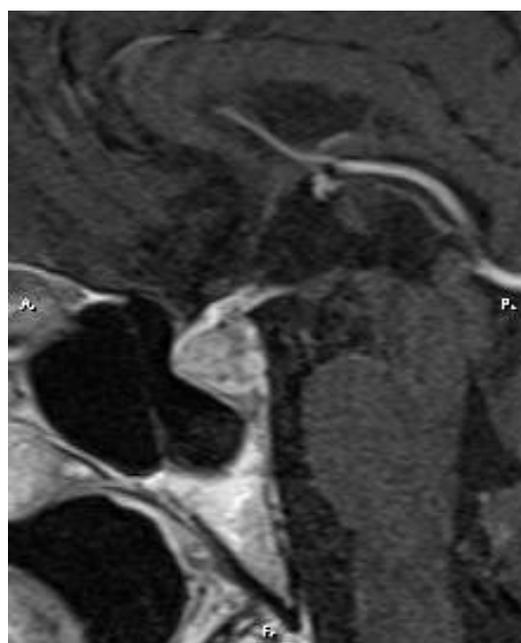
pebrozulimumab plus axitinib. After four months therapy, a CT showed a decreased size of pulmonary and lymph node metastases. About 5 months later, laboratory test showed THS 8.026 mU/l, (reference range: 3.350-4.940), fT4 10.9 pmol/l (reference range: 9-19), fT3 3.9 pmol/l (reference range: 2.68-5.7), consistent with post-axitinib hypothyroidism. After about 22 months of therapy, the patient presented to the hospital complaining of fatigue, nausea, vomitus, epigastric pain, diarrhoea. His laboratory test results were: Na 117 mmol/l, eosinophils  $2.6 \times 10^9$  /l (reference range: 0.0-0.5), cortisol 12.4 nmol/l (reference range: 263-724), ACTH 5.1 ng/l (reference range: 7.2-63.3), LH 0.5 U/l (reference range: 1.7-8.6), FSH 1.7 U/l (reference range: 1.5-12.4), testosterone 0.44 nmol/l (reference range: 10.0-34.0), GH, IGF1, PRL were normal. An magnetic resonance imaging (MRI) (fig.1) brain scan showed an enlarged hypophysis (10x14x16 mm), heterogeneous enhancement

with focal defects in T2-weighted images- figure 1. The diagnosis was grade 3 hypophysitis according to the CTCAE grading system (1). The patient was treated with dexamethasone 4 mg (qd), initially intravenous, then definitively switched to

20 mg hydrocortisone daily and as previously 75 ug levothyroxine daily. Axitinib was stopped after diagnosis of hypothyreosis and pembrolizumab was later stopped too.

### Figure 1: Hypophysitis on MRI

Sagittal and coronal sections of the pituitary. Swelling of the pituitary gland, thickening of the stalk with heterogenous enhancement signals



### Discussion

As of May 2017 pembrolizumab is approved for indications: advanced melanoma, non-small lung cancer, Hodgkin's lymphoma, urothelial cancer, renal cell carcinoma, head and neck cancer, Merkel cell carcinoma and tumors of any origin with high microsatellite instability (Baxi et al.).

PD-1 is expressed on the surface of activated T- and B- lymphocytes and monocytes and is upregulated by tumor cells, helping them avoid the immune response. Checkpoint inhibitors prevent this upregulation and allow the immune system to attack the cancer cell. Immune-mediated hypophysitis in relation to pembrolizumab is rare but important adverse event (0.2-1.2% (González-Rodríguez et al.)). The precise mechanism by which immune checkpoint inhibitors cause hypophysitis remains unclear. The condition may be life threatening because of adrenal insufficiency.

Diagnosis, after introducing pembrolizumab in treatment, is based on the clinical, laboratory and MRI picture, usually after 3.3-3.7 months of therapy (interval one day to 7.2 months) (Angelousi et al.). It requires prompt recognition and adequate management with hormone replacement (Lin et al.).

### Conclusion

Immune checkpoint inhibitors are effective therapeutic modalities but, their use also has many adverse side effects affecting the endocrine system. Therefore it is important to monitor any potential immune-mediated endocrinopathy while on PD-1 inhibitor therapy. To provide optimal care monitoring by an endocrinologist is recommended.

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