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Case report

Magnetic resonance imaging criteria of immune checkpoint inhibitor-induced hypophysitis

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A B S T R A C T

Autoimmune hypophysitis is a rare complication of immune checkpoint inhibitors. Immune checkpoint inhibitors have been used for advanced stages of melanoma, renal cell carcinoma, and lung cancer. Multiple endocrinopathies, among them hypophysitis, could result as a reverse event from this therapy. MRI is the imaging modality of choice and usually demonstrates pituitary gland hypertrophy, irregular thickening of the pituitary infundibulum, and diffuse enhancement. We present a case of stage IV metastatic renal cell carcinoma complicated with hypophysitis secondary to combined nivolumab and ipilimumab therapy.

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A R T I C L E I N F O

Keywords: Autoimmune hypophysitis; Immune checkpoint inhibitors; MRI; pituitary gland

Introduction

Autoimmune hypophysitis is defined as a chronic pituitary gland inflammation due to lymphocytic over-activation resulting in dysfunction of 1 or more pituitary axes.[1] immunotherapy-induced hypophysitis is one of the rare autoimmune adverse event of immune check-point inhibitors.[2] The immune checkpoint inhibitors have 2 major classes including monoclonal

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antibodies to Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and programmed death 1 receptor and ligand (PD-1 and PD-L1).[2] We will present a case of immune-checkpoint inhibitor-induced hypophysitis in a patient received combined nivolumab and ipilimumab therapy for a stage IV metastatic renal cell carcinoma to lung.

Case report

A 58-year-old male presented with hematuria for a week time duration. The patient has been seen by a urologist who ordered an abdominal CT with contrast. CT discovered a suspicious right renal mass concerning of renal cell carcinoma for which right radical nephrectomy had been done. Postoperative surgical pathology resulted in clear cell type renal cell carcinoma, Fuhrman grade 2 with invasion of the renal sinus, perinephric adipose tissue but not beyond Gerota's fascia, and right renal vein wall. The patient underwent CT chest and abdomen as well as dynamic MRI abdomen for further staging of the disease. CT chest demonstrated multiple bilateral solid pulmonary nodules measuring up to 5 mm are concerning for metastasis. CT and dynamic MRI abdomen also showed segment VII focal hepatic lesion, in keeping with hemangioma that was confirmed with tissue sampling and pathologic evaluation. Patient was noted to have progressive enlargement of pulmonary nodules on surveillance CT scans. Biopsy of lung nodules was positive for metastatic clear cell renal cell carcinoma. A combination immunotherapy with ipilimumab (CTLA-4 monoclonal antibody) and nivolumab (PD-1 blocker) was initiated. Three weeks later, the patient presented with headache, bilateral leg muscle spasms, weakness, and fatigue. He denied nausea, vomiting, diarrhea, or weight loss. Immune-related adverse events of immune check-inhibitor therapy was suspect, laboratory testing and MRI of the brain for evaluation of the pituitary gland were ordered. The patient's labs showed decreased Hb 12.4, Albumin 3.8 (total protein 6.4), and mildly decreased Na 139 mmol/L. Biochemical testing of pituitary functions revealed adrenal insufficiency (cortisol 0.93 mcg/dL, and ACTH 36 pg/mL), primary hypergonadotrophic hypogonadism (LH 8.2 munit/mL, FSH 18.7 munit/mL High, free Testosterone 1.88 ng/dL, total Testosterone 75 ng/dL), normal thyroid functions (free Thyroxine 1.09 ng/dL), and normal prolactin 9.2 ng/mL. The MRI demonstrated global enlargement of the pituitary gland (black narrow arrows) with heterogeneous T2 hypointense signal (narrow and wide black arrows in Fig. 1b) and heterogeneous enhancement on postcontrast series (black narrow arrows). There was irregular thickening and enhancement of the pituitary infundibulum (wide black arrow in Fig. 1c and white arrow in Figured). The lab results and MRI findings were compatible with immune checkpoint-induced hypophysitis. The patient instructed to hold immunotherapy and started high-dose prednisone (1 mg/kg/d) therapy, which has been tapered slowly into 20 mg/d, then into prednisone 10 mg. The patient's clinical symptoms improved significantly and nivolumab maintenance had been started 1 month later.

Discussion

Hypophysitis is usually classified into primary or secondary (Table 1).[1] Immune check-point inhibitor-induced hypophysitis is a rare cause of secondary hypophysitis which results from immune-related complications of check-point inhibitor immunotherapy.[3-6] Nivolumab and ipilimumab are monoclonal antibodies which block immune check points releasing T cells to attack cancer cells.[2,7] These agents are readily effective in treatment of several cancers including lung cancer, renal cell carcinoma, and melanoma.[2,3,5] Diagnosis of immune checkpoint inhibitor-induced hypophysitis is challenging, as it presents as subtle imaging findings on MRI. High clinical suspicion is required.[3]

Hypophysitis commonly manifests with nonspecific symptoms, for example, fatigue, headache, weakness, endocrinopathy, visual changes, and/or hyponatremia.[3,6] The diagnosis is confirmed by the development of new anterior and/or posterior pituitary dysfunction, that is, acute hypothyroid hormones, ACTH, FSH, LH, or prolactin.[3,6]

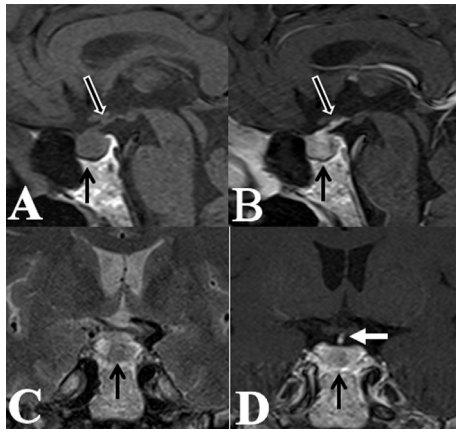

Fig. 1. Immune checkpoint inhibitor-induced hypophysitis in a 58-year-old male. Sagittal T1-weighted images (a) show global enlargement and globular morphology of the pituitary gland (black narrow arrow) with mild thickening of the pituitary infundibulum (black wide arrow). Coronal T2-weighted image (b) demonstrates heterogeneous T2 hypointense signal of the enlarged pituitary gland (arrows). Sagittal (c), and coronal (d) postgadolinium administration T1-weighted images show heterogeneous enhancement of the enlarged pituitary gland (black arrows) and nonuniformly thickened pituitary infundibulum (black wide arrow in c, and white arrow in d).

Table 1
Causes of hypophysitis.[1]

Primary	Secondary
Lymphocytic hypophysitis – Lymphocytic adenohypophysitis – – Lymphocytic infundibulo-neurohypophysitis – – Lymphocytic panhypophysitis	Systemic diseases: – Sarcoidosis – Langerhans cell histiocytosis – Granulomatous hypophysitis – Takayasu's disease – Crohn's disease – Inflammatory pseudotumor
IgG4-related hypophysitis	
Necrotizing hypophysitis	Infectious: Bacterial, viral, fungal disease
Xantomatous hypophysitis	Drugs:
Mixed	– Immune check-point inhibitor induced hypophysitis; cytotoxic T- lymphocyte antigen 4 (CTLA-4), and programmed cell death protein 1 (PD-1) antibodies – Interferon

Biochemical testing and imaging should be done to reach diagnosis.[2] Measurement of pituitary and target tissue hormones is important.[2,4,5] Radiolographically, hypophysitis secondary to immune checkpoint inhibitors is usually accompanied by subtle and nonspecific MRI findings.[2] MRI features include hypertrophy of the pituitary gland and infundibulum with loss of the normal neurohypophysis bright spot on noncontrast T1 images.[4] Contrast-enhanced MR images may demonstrate diffuse enhancement of the pituitary gland and pituitary infundibulum.[1,2,4] A normal MRI does not exclude the diagnosis.[2] Baseline MRI of the pituitary before starting immune checkpoint inhibitor therapy is now recommended.[5]

The management of immune checkpoint inhibitor-induced hypophysitis depends on the severity.[2] The treatment usually includes discontinuation of immunotherapy, initiation of corticosteroids, and long-term supplementation of the deficient hormones.[2-4] Following immunotherapy discontinuation and/or corticosteroid treatment, the pituitary MR morphology as well as clinical manifestations usually normalize.[8]

Conclusion

Autoimmune hypophysitis is a rare adverse event of immune checkpoint inhibitor therapy. A normal MRI does not exclude this possibility. MRI characteristics include hypertrophy of the pituitary gland, loss of neurohypophysis bright spot, with enhancement of pituitary gland and infundibulum.[7]

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