Radiology Case Reports 13 (2018) 261–264

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RCR RADIOLOGY CASE REPORTS

Neuroradiology

Ipilimumab-induced hypophysitis involving the optic tracts and tuber cinereum evaluated using 3D fluid-attenuated inversion recovery

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ARTICLE INFO

Article history:
Received 27 September 2017
Received in revised form 10 November 2017
Accepted 13 November 2017
Available online 12 December 2017

Keywords:
Ipilimumab
Hypophysitis
Optic tract
3D FLAIR
Melanoma

ABSTRACT

Ipilimumab, a human monoclonal antibody against cytotoxic T-lymphocyte antigen 4, was approved by the U.S. FDA (Food and Drug Administration) in 2011 for the treatment of unresectable or metastatic malignant melanoma. Occurrence of hypophysitis, an immune-related adverse event due to ipilimumab use, has been frequently reported. We report a case of ipilimumab-induced hypophysitis involving the optic tracts and tuber cinereum, identified using 3D fluid-attenuated inversion recovery.

Introduction

Ipilimumab is an IgG1-type human monoclonal antibody (mAB) developed against cytotoxic T-lymphocyte antigen 4 (CTLA-4). Ipilimumab binding to CTLA-4 which is expressed on T-cells augments T-cell activation and proliferation, resulting in an antitumor response. Improved overall survival due to ipilimumab treatment in metastatic melanoma has been reported [1]. Several clinical trials using this agent in the treatment of other malignancies are ongoing. However, immune-related adverse events (irAEs) due to ipilimumab have also been frequently reported. In particular, the most common endocrinopathy caused by ipilimumab is hypophysitis with hypopituitarism. Recent studies suggest that approximately 10%-15% of patients receiving ipilimumab may develop hypophysitis [2,3]. Symptoms

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https://doi.org/10.1016/j.radcr.2017.11.007

affecting vision are rarely observed in ipilimumab-induced hypophysitis [4–6], because it is thought that pituitary lesions due to ipilimumab are not large enough to compress the optic chiasma, in contrast to lesions of autoimmune lymphocytic hypophysitis. Here we report a case of ipilimumab-induced hypophysitis with involvement of the optic tracts and tuber cinereum. We were unable to find a previous report like this case.

Case report

A 74-year-old woman was originally diagnosed with stage IIIA (pT2aN2aM0) melanoma of the right lower abdomen, and was later found to have multiple nodal metastases. She was commenced on a 3 mg/kg dose regimen of ipilimumab. After receiving the third course of ipilimumab 8 weeks after ipilimumab initiation for nodal metastases, she presented with complaints of headache, nausea, general fatigue, facial edema, but no polydipsia or polyuria. Goldman visual field testing showed bilateral nasal hemianopia and bitemporal superior quadrantanopia. During the fourth course, laboratory evaluations showed hypothyroidism (TSH 0.13 μIU/mL; reference range 0.35-4.94), FT4 0.58 ng/dL (0.70-1.48), adrenal insufficiency (ACTH 2.8 pg/mL; 7.2-63.3), cortisol 0.9 μg/dL, and hypogonadism (FSH 2.25 mIU/mL, LH 0.22 IU/mL). The prolactin level was low (PRL <0.60 ng/mL). She was negative for antithyroid antibodies and the IgG level was normal.

Magnetic resonance imaging revealed enlargement of the pituitary gland and stalk (Fig. 1). Postcontrast T1-weighted images showed heterogeneous enhancement of the pituitary lesion (Fig. 1B). Coronal 3D fluid-attenuated inversion recovery (3D FLAIR) showed high-signal intensity in the optic tracts and tuber cinereum (Fig. 1C), whereas coronal 2D T2-weighted images did not clearly show an intense signal in those regions (Fig. 1D). No enhancement of those regions was visible on postcontrast coronal T1-weighted images (Fig. 1E).

After steroid therapy for 11 weeks, follow-up magnetic resonance imaging demonstrated a decrease in size of the pituitary lesion (Fig. 2A) along with improvement in all symptoms. However, visual field constrictions were not fully recovered. The high-signal-intensity in the optic tracts and tuber cinereum seen with 3D-FLAIR did not disappear completely (Fig. 2B). Hormone data showed hypopituitarism, hypothyroidism, and adrenal insufficiency. The patient needed to continue hormone replacement therapy.

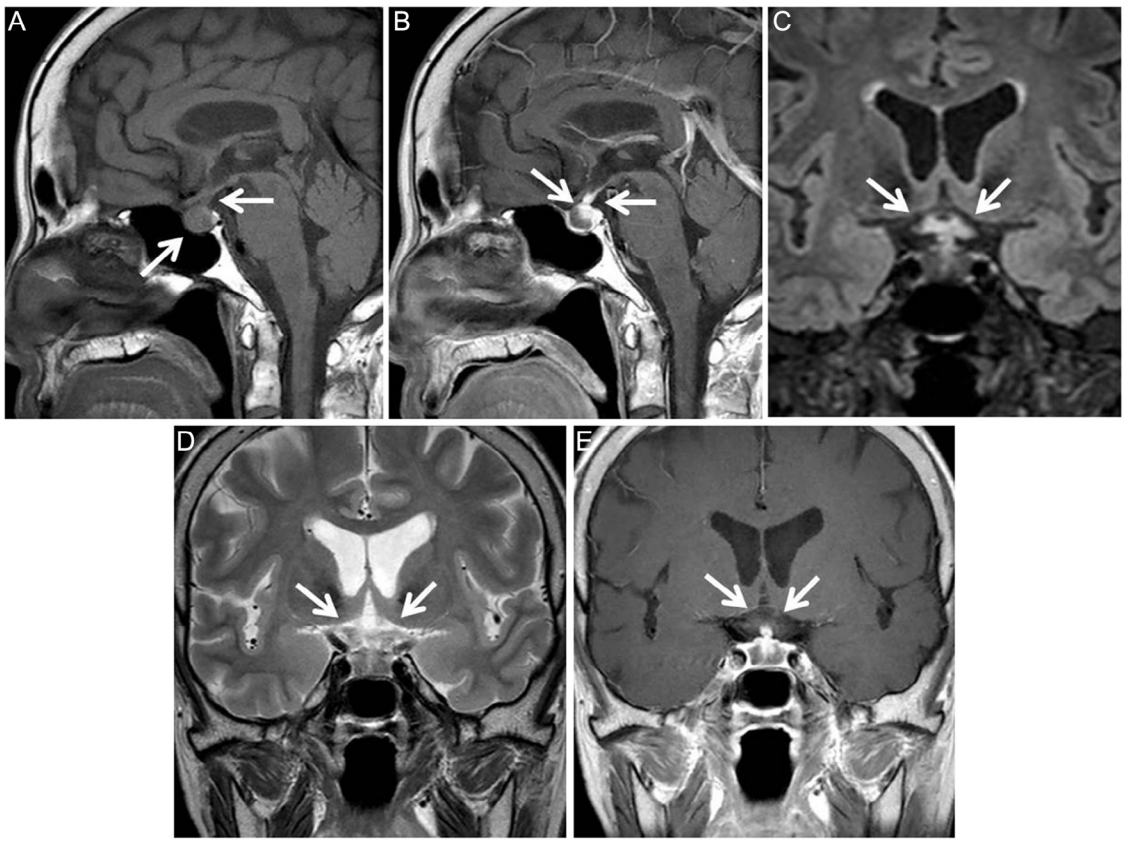

Fig. 1 – (A) Sagittal T1-weighted image showing enlargement of the pituitary gland and stalk (arrows). High-signal intensity in the posterior pituitary lobe is visible. (B) Sagittal postcontrast T1-weighted image showing heterogeneous enhancement of the pituitary lesion (arrows). (C) Coronal 3D FLAIR clearly showing high-signal intensity in the optic tracts and tuber cinereum (arrows). The pituitary gland is not large enough to compress the chiasm and tuber cinereum. (D) Coronal T2-weighted image showing no significant high-signal intensity in the optic tract and tuber cinereum (arrows). (E) Coronal postcontrast T1-weighted image showing no significant enhancement in the optic tract and tuber cinereum (arrows).

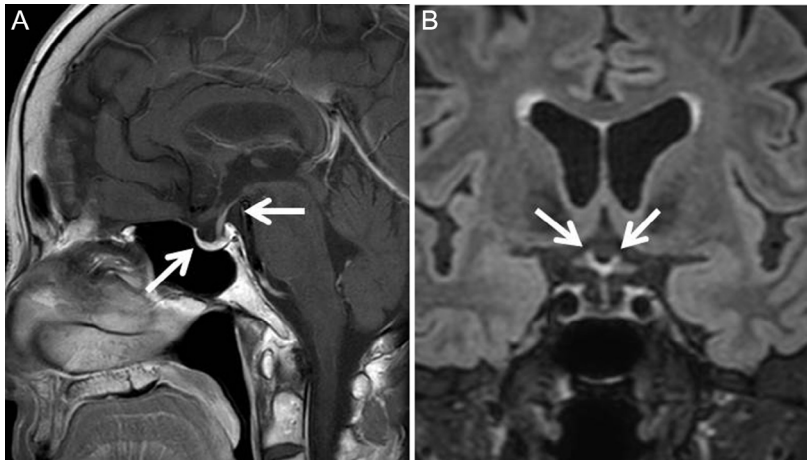

Fig. 2 – (A) Follow-up sagittal postcontrast T1-weighted image showing a decrease in the pituitary lesion after steroid therapy (arrows). (B) High-signal intensity in the tuber cinereum not completely eliminated on coronal 3D FLAIR imaging (arrows).

Discussion

Ipilimumab-induced hypophysitis usually involves the anterior lobe, resulting in central hypothyroidism, central adrenal insufficiency, and hypogonadism. Prolactin levels are often low in patients with ipilimumab-induced hypophysitis [3]. On the other hand, involvement of the posterior lobe is uncommon, and diabetes insipidus is also rare. The mechanism of ipilimumab-induced hypophysitis has not been fully understood. Iwama et al. have recently reported that CTLA-4 is expressed in the pituitary gland, predominantly in thyroid stimulating hormone- and prolactin-producing cells [7]. This suggests that CTLA-4 may utilize type IV or type II immune mechanisms [7,8]. This also explains lesser occurrence of hypophysitis with other immunotherapies such as the anti-programmed cell death protein 1/programmed cell death ligand 1 (anti-PD-1/PD-L1) compared to anti-CTLA-4 therapies. However, the expression level of CTLA-4 varies between individuals [8]. An elevated level of CTLA-4 expression is known to cause an aggressive and necrotizing form of hypophysitis.

The most common imaging finding in ipilimumab-induced hypophysitis is mild to moderate diffuse enlargement of the pituitary gland with variable enhancement. In some cohorts, symmetrical enlargement of the pituitary gland has been reported in 12%–88% of patients with ipilimumab-induced hypophysitis [9,10]. Pituitary enlargement rarely causes compression of the optic apparatus [10]. Steroid therapy results in resolution of pituitary enlargement and chronic persistent enlargement of the pituitary is uncommon [2]. Furthermore, involvement of the posterior pituitary is extremely rare, being reported in only one out of 15 ipilimumab-induced hypophysitis cases [11]. Stalk thickening was reported in 10 out of 17 patients in another cohort [10].

This patient presented with bilateral nasal hemianopia and bitemporal superior quadrantanopia. Those findings are not typically seen in patients with pituitary mass, but the characteristic visual field defect caused by pituitary mass with suprasellar extension is bitemporal hemianopsia. Ophthalmologic complications from ipilimumab therapy are rare, occurring in less than 1% of patients, but generally manifest as uveitis [6]. In our case, 3D FLAIR clearly showed high-signal lesions in optic tracts and tuber cinereum, which were considered related to her visual symptoms. 3D FLAIR eliminates inflow artifacts in the basal cistern and reduces CSF signals completely, producing high-resolution images with thinner slices [12]. Therefore, 3D FLAIR could clearly identify tiny lesions in optic tracts in this case. Because the pituitary lesion was not large enough to compress the optic chiasma, the optic tract and tuber cinereum lesions may suggest inflammation due to hypophysitis. 3D FLAIR might be useful in patients with ipilimumab-induced hypophysitis with visual field constrictions.

REFERENCES

[1] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.
[2] Faje A. Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights. Pituitary 2016;19:82–92.
[3] Joshi MN, Whitelaw BC, Palomar MTP, Wu Y, Carroll PV. Immune checkpoint inhibitor-related hypophysitis and endocrine dysfunction: clinical review. Clinical Endocrinol 2016;85:331–9.
[4] Kaehler KC, Egberts F, Lorigan P, Hauschild A. Anti-CTLA-4 therapy-related autoimmune hypophysitis in a melanoma patient. Melanoma Res 2009;19:333–4.
[5] Bertrand A, Kostine M, Barnetche T, Truchetet ME, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. BMC Med 2015;13:211.
[6] Wilson MA, Guld K, Galetta S, Walsh RD, Kharlip J, Tamhankar M, et al. Acute visual loss after ipilimumab treatment for metastatic melanoma. J Immunother Cancer 2016;4:66.

[7] Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med 2014;6:230ra45.
[8] Cturegli P, Di Dalmazi G, Lombardi M, Grosso F, Larman T, Taverna G, et al. Hypophysitis secondary to cytotoxic T-lymphocyte-associated protein 4 blockade: insights into pathogenesis from an autopsy series. Am J Pathol 2016;186:3225–35.
[9] Mahzari M, Liu D, Arnaout A, Lochnan H. Immune checkpoint inhibitor therapy associated hypophysitis. Clin Med Insights Endocrinol Diabetes 2015;8:21–8.
[10] Faje AT, Sullivan R, Lawrence D, Tritos NA, Fadden R, Klibanski A, et al. Ipilimumab-induced hypophysitis: a detailed longitudinal analysis in a large cohort of patients with metastatic melanoma. J Clin Endocrinol Metab 2014;99:4078–85.
[11] Albarel F, Gaudy C, Castinetti F, Carre T, Morange I, Conte-Devolx B, et al. Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. Eur J Endocrinol 2015;172:195–204.
[12] Naganawa S. The technical and clinical features of 3D-FLAIR in neuroimaging. Magn Reson Med Sci 2015;14:93–106.