

Case Report

# Hypopituitarism and Ipilimumab, an Uncommon Disease, Uncommon Cause

Yasar A. Ahmed<sup>1\*</sup> and Kyle Taheny<sup>2</sup>

<sup>1</sup> Medical Oncology Department, Sligo University Hospital, Ireland

<sup>2</sup> Internal Medicine Department, Sligo University Hospital, Ireland

## Abstract

**Background:** Ipilimumab, a human monoclonal antibody that blocks cytotoxic T-Lymphocyte antigen CTLA-4 has demonstrated activity in patients with advanced (unresectable or metastatic) malignant melanoma. Up to 60% of patients treated with Ipilimumab develop immune-related adverse effects, usually occurring in the first twelve weeks. However, we present a case of hypopituitarism presenting over two months following final treatment with Ipilimumab, without radiological or clinical evidence of pituitary enlargement.

**Case presentation:** A 70 year old woman with a history of metastatic melanoma presented two months following complete response to treatment with Ipilimumab. She complained of increasing fatigue, extreme weakness, somnolence and confusion. Initial laboratory results revealed hyponatraemia and hypothyroidism.

**Conclusions:** While immune-related adverse effects are found in the majority of patients treated with Ipilimumab and cases of hypopituitarism are well documented, these are usually not acute and tend to progress sub-clinically. The onset of hypopituitarism observed in this patient, bearing in mind the lack of clinical and radiological evidence of pituitary enlargement, suggests that the auto-immune response induced by the anti-CTLA- 4 may additionally lead to clinical presentation even after a period from treatment cessation, without any clinically evident acute phase of inflammation. This may reflect the development of pituitary directed antibodies. Thus, we present a case of a previously unseen presentation of hypopituitarism secondary to Ipilimumab which will aid in its' diagnosis and management.

**Keywords:** melanoma; ipilimumab; hypopituitarism

**Academic Editor:** Xiaoning Peng, Hunan Normal University School of Medicine, China

**Received:** June 10, 2016; **Accepted:** July 30, 2016; **Published:** August 3, 2016

**Competing Interests:** The authors have declared that no competing interests exist.

**Consent:** Consent was taken from the patient for publication of this case report.

**Copyright:** 2016 Ahmed YA *et al.* This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**\*Correspondence to:** Yasar A. Ahmed, Medical Oncology Department, Sligo University Hospital, Ireland

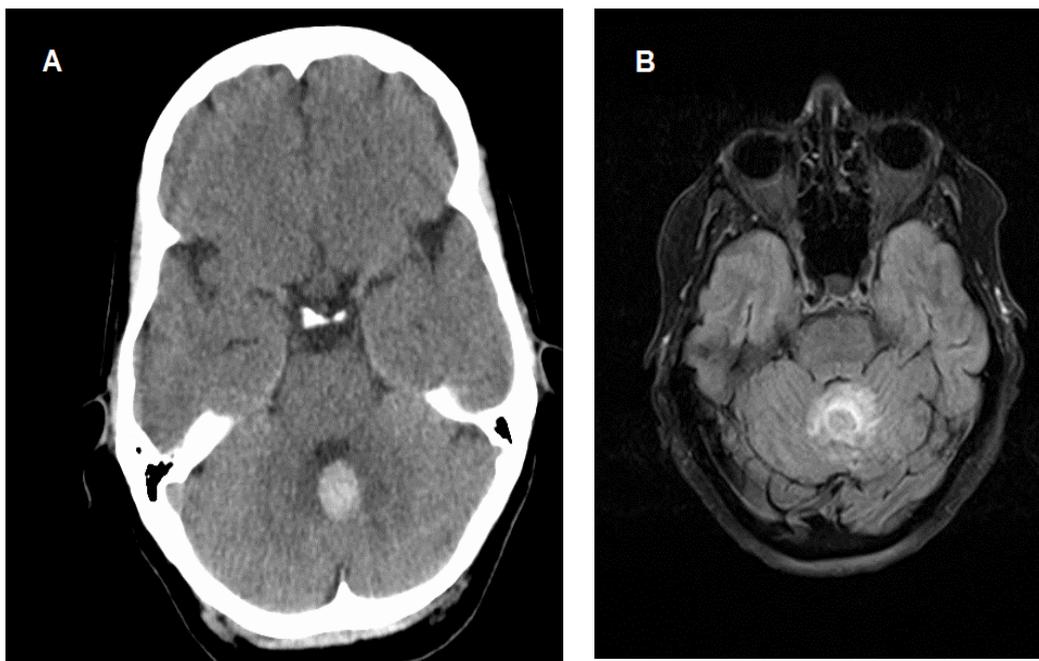
**E-mail:** drhammor@gmail.com

## Background

Ipilimumab, a human monoclonal antibody that blocks cytotoxic T-Lymphocyte antigen CTLA-4 has demonstrated activity in patients with advanced (unresectable or metastatic) malignant melanoma. Up to 60% of patients treated with Ipilimumab develop immune-related adverse effects, usually occurring in the first twelve weeks. However, we present a case of hypopituitarism presenting over two months following final treatment with Ipilimumab, without radiological or clinical evidence of pituitary enlargement.

## Case Report

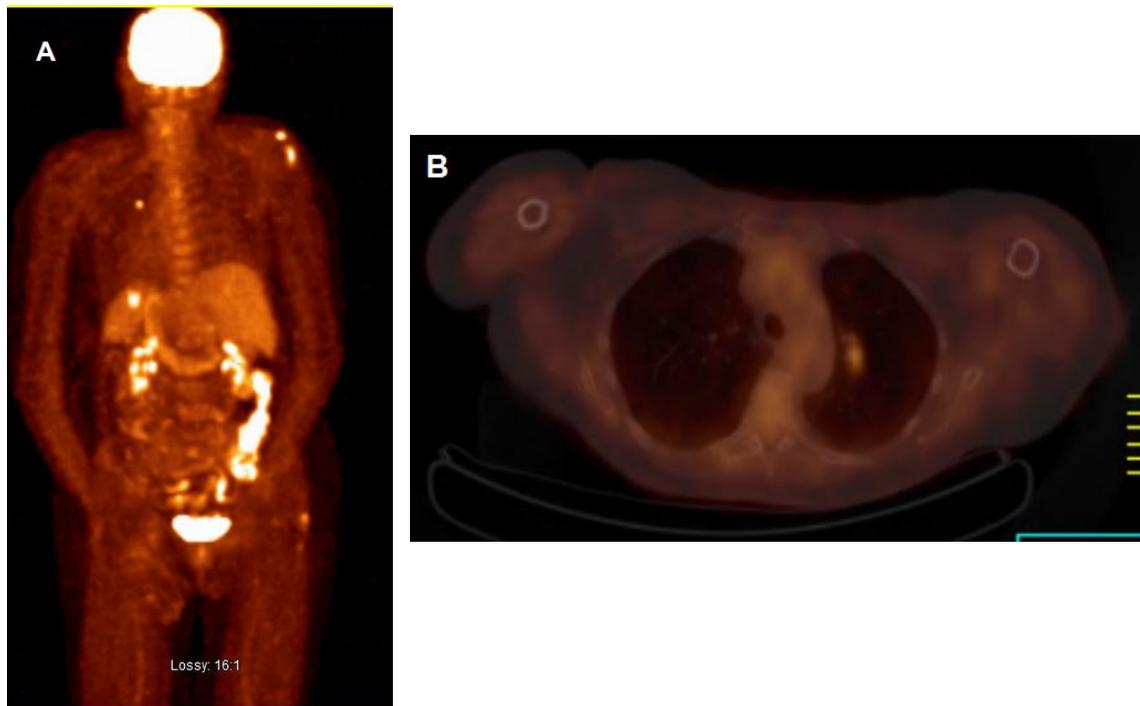
A 70-year-old Caucasian female with a history of a resected lentigo maligna melanoma 5 years earlier was admitted with cerebellar features. A Cerebellar vermis metastasis had been confirmed radiologically (Fig 1). Her baseline staging computed tomography (CT) revealed left pulmonary nodules and tiny non-specific liver lesion.



**Fig1A:** Contrast-enhanced CT brain reveal a 1.7 cm multiple hypodense lesion with surrounding oedema within the cerebellar vermis.

**Fig1B:** Axial T1-weighted MRI showing an enhancing lesion in the cerebellar vermis and also a lesion in the left parietal region.

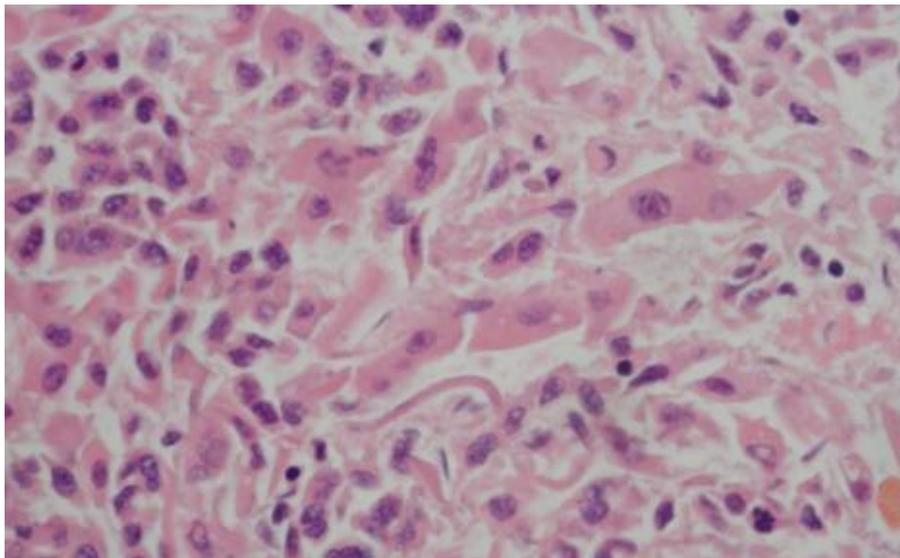
She had been treated with Whole Brain Radiotherapy (WBRT) for presumed metastatic melanoma. Furthermore, post WBRT a Positron-Emission Tomography- Computed Tomography (PET-CT) showed multiple suspicious lesions in both lungs as well as in spleen. In the liver solitary fluoro-2-deoxyglucose positron (FDG) avid lesion highly suspicious of metastatic focus was visible (Fig 2).



**Fig 2 A:** Coronal PET image shows the hypermetabolic splenic metastasis.

**Fig 2 B:** Lung metastases are demonstrated on axial PET.

Histopathological examination of an ultrasound-guided biopsy confirmed liver metastasis from a melanoma (Fig 3). Additional mutation analysis of the liver metastasis was not feasible due to insufficient material.



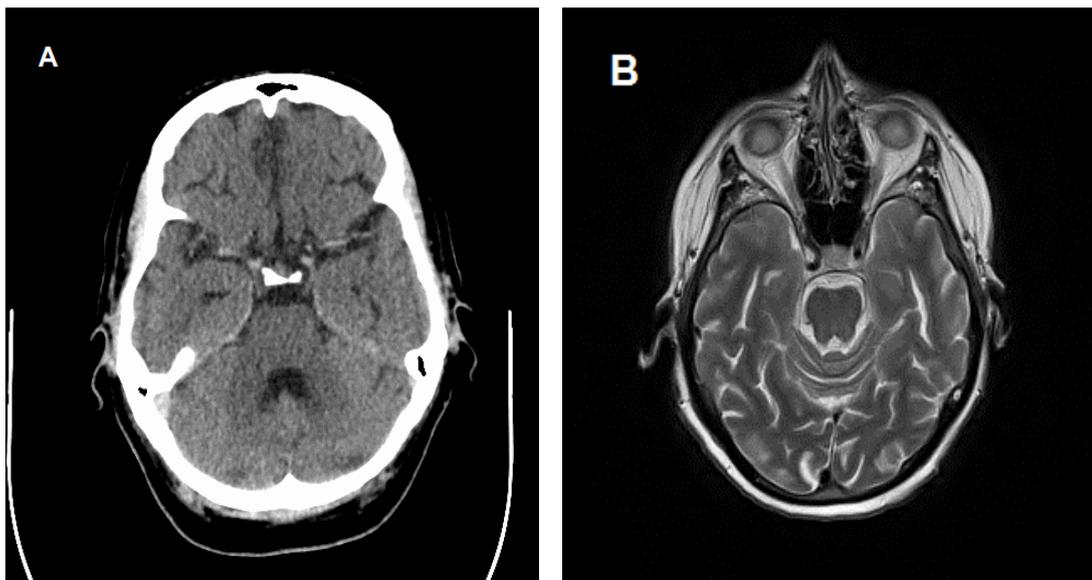
**Fig 3:** Histological examination indicates Large cells with pleomorphic vesicular nuclei, prominent nucleoli and large eosinophilic cytoplasm (hematoxylin and eosin, 400X)

The patient was treatment naïve, in very good performance status (Eastern Cooperative Oncology Group Performance Status of 1) and with normal organs function. She was considered for cytotoxic T-lymphocyte antigen 4 (CTLA4) blockade to treat the unresectable Stage IV melanoma. Four cycles of Ipilimumab 3 mg/kg were given without any substantial side effects and she achieved a complete clinical and radiological response.

Two months after the final treatment, the patient presented with complaints of increasing fatigue, extreme weakness, somnolence and confusion. She denied nausea, vomiting, visual symptoms, polydipsia or polyuria. She did not have other co-morbidities or family history of endocrine problems or malignancy.

Initial laboratory evaluation revealed low sodium of 125[133-145] mmol/L and inappropriately low free T4 < 5.2 [9-19] pmol/L with normal TSH 0.52 [0.35-4.94] uIU/ml. Previous thyroid function studies obtained before Ipilimumab were normal.

CT of the head (Fig 4 A).followed by contrast-enhanced magnetic resonance imaging (MRI) showed interval improvement of the previously noted lesion in the vermis. (Fig 4 B).There was no swelling of the pituitary gland.



**Fig 4A:** Contrast-enhanced CT brain revealed a complete resolution of the previously noted vermis lesion.

**Fig 4B:** MRI brain showing normal brain enhancement and normal appearance of pituitary gland.

A more complete assessment of pituitary function was undertaken by Endocrinology team, and the biochemical findings confirmed central hypocortisolism (random cortisol 16 nmol/L [reference range 180-620] and hypothyroidism, FSH 4.8 mIU/ml, LH 0.4 mIU/ml. Oestradiol Serum <92 pmol/L.

There was no diabetes insipidus; her prolactin was 10.2 [5.18-26.53] ng/ml and the serum IGF-1 was normal [13.5nmol/L, normal range 10.5-35 nmol/L].

A glucagon stimulation test was carried out initially. [Table 1] This proved an adult growth hormone deficiency was present.

**Table 1 Glucagon Stimulation Test**

	0 mins	60 mins	120 mins	180mins
Cortisol	18	20	19	21
Growth Hormone	<0.3	0.4	0.4	<0.3

A Synacthen Test was then carried out [Table 2] which was positive for adrenal insufficiency.

**Table 2 Synacthen Test**

	0 mins	30 mins
Cortisol	<b>18</b>	<b>173</b>

She was diagnosed with hypopituitarism, secondary to Ipilimumab treatment. She was commenced on dexamethasone 0.75 mg twice daily and three days later Levothyroxine 100mcg daily was added. These resulted in rapid resolution of the hyponatremia and gradual improvement of her cognitive function. Follow-up eight and sixteen weeks later showed full resolution of symptoms, with the patient to remain on maintenance dose of steroids and levothyroxine.

## Discussion

Advanced melanoma is characterized by disseminated metastatic disease which carries very poor prognosis with a median survival of 8–9 months. In those patients the estimated 3-year survival rate of less than 15% [1]. It has high propensity of metastasize to the central nervous system and is the third most common solid tumor causing cerebral metastases, after lung and breast cancers [2].

Melanoma brain metastases (MBM) is the most devastating event in the course of melanoma carries that is responsible for 20–54% of deaths in patients with melanoma [1]. The prevalence of MBM is about 20–40% in clinical series and up to 75% in autopsy series [2]. The conventional management of MBM remains challenging due to the limited treatment options. It consists of surgical resection, whole brain radiotherapy and stereotactic radiotherapy to achieve local disease control [2, 3].

Prior to 2011, dacarbazine (DTIC) and interleukin-2 (IL-2) immunotherapy were the only two systemic therapeutic agents available, however, traditionally melanoma has been resistant to treatment with conventional chemotherapy.

Most recently Clinical results from the development of immunotherapy agents such as Ipilimumab and targeted therapies such as dabrafenib and vemurafenib suggest that systemic therapy may have a role in carefully selected patients with MBM [4].

Ipilimumab, a human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen CTLA-4 helps regulate the balance between immune activation and tolerance, has demonstrated activity in patients with advanced melanoma. Clinical trial data suggest that Ipilimumab has activity in patients with brain metastases [4].

Since its approval in 2011 by the Food and Drug Administration and the European Medicines Agency, Ipilimumab, has become a standard treatment option for patients with advanced (unresectable or metastatic) malignant melanoma.

In randomized, controlled phase 3 trials, Ipilimumab significantly improved overall survival (OS) in both pretreated and treatment-naïve patients with metastatic melanoma [5,6]. Also, intracranial antitumor activity of Ipilimumab has been demonstrated in a multicenter Phase II study [6].

Immune-stimulatory therapy, predictably generates autoimmunity causing immune-related adverse events (IRAE) in the majority of patients. In the phase III trial that demonstrated an increase in survival, IRAE occurred in approximately 60 % of patients treated with Ipilimumab [5]. The most common serious manifestations include enterocolitis, hepatitis, dermatitis, and endocrinopathy. IRAE occur during the first 12 weeks and the median time to resolution is approximately 6 weeks for grade 2 IRAE and 8 weeks for grade 3 and 4 IRAE [7].

The incidence of IRAE endocrinopathy in Ipilimumab phase II and III trials of 1498 patients was <5%, with <3% being grade 3 or higher [8]. The most common endocrinopathy was hypophysitis with hypopituitarism in 0–17%, followed by hypo- and hyperthyroidism secondary to thyroiditis in 2.7 and 0.3% respectively, and adrenal insufficiency in 2.1% [8]. Usually, the clinical onset of these endocrine IRAE is not acute and they progress subclinically [9].

Hypopituitarism is thought to be an infrequent disease, with an incidence of 4.2 cases per 100,000 per year & Hypophysitis is among the rarest causes of hypopituitarism [10]. Autoimmune hypophysitis (AH), often referred to as lymphocytic hypophysitis is characterized by dense diffuse lymphocytic infiltration of the pituitary and usually is confined to the anterior pituitary [9].

Patients who experience anti-CTLA-4 Autoimmune hypophysitis usually present with nonspecific symptoms such as headache, visual impairment, fatigue, weakness, confusion, memory loss, erectile dysfunction and loss of libido, anorexia, labile moods, insomnia, temperature intolerance, subjective sensation of fever, and chills [9]. Most patients developed relevant symptoms after a median time of 9.4 weeks (range 6-12 weeks) suggesting a possible cumulative effect [5].

In contrast to other forms of AH Levels of ACTH, cortisol, TSH and/or free T4, GH, prolactin, IGF-1, FSH, LH, and testosterone are variably altered, indicating different degrees of hypopituitarism [9,10]. A rare presentation of hyponatremia due to the syndrome of inappropriate anti-diuretic hormone (SIADH) secretion was reported in a single case [11]. There is also a single case report describing diabetes insipidus [12].

It is unclear why the anterior pituitary is particularly susceptible to Ipilimumab therapy. In the published literature, the posterior pituitary function remained normal in most of the cases, suggesting a possible predilection of Ipilimumab for corticotrophic and probably thyrotrophic cells [6,9,12–15].

In contrast to most cases of lymphocytic hypophysitis which are accompanied by uniform pituitary enlargement [9,16,17], MRI in this case showed a normal sized pituitary gland without evidence of pathological post contrast enhancement. This is in keeping with what is previously reported in about 20 % of patients with hypophysitis following Ipilimumab [9,17]. The typical MRI hypophysitis enlargement usually resolve in 4-6 weeks [17], however, it has been reported to resolve after 3 months [18].

The onset of anterior lobe hypopituitarism we observed in this patient and given the lack of clinical and radiological evidence of pituitary enlargement suggests that the auto-immune response induced by the anti-CTLA-4 may additionally lead to clinical presentation even after a period from the treatment cessation, without a clinically evident acute phase of inflammation. This could reflect the development of pituitary-directed antibodies. It is generally accepted that the hypophysitis is not reversible. Long-term or even lifelong hormone therapy will be frequently required [9,12,18].

Several issues concerning anti-CTLA-4 –autoimmune hypophysitis are still unknown .The exact incidence of this and other EIRAEs and the role of CTLA-4 gene polymorphisms, which are known to correlate with certain autoimmune endocrinopathies such as Graves disease and Hashimoto thyroiditis, need to be better clarified in larger studies.

Also the correlation between tumor response and the incidence and severity of IRAEs needs to be defined using an appropriate analytical approach. The development of IRAEs appears to be associated with antitumor response and longer survival in some studies. Having said that disease survival and benefits with Ipilimumab were similar among patients with or without IRAE.

It is still unclear whether the effects result from T cells specifically acting against antigens shared by tumour and normal cells or from the concomitant activation of multiple T cells populations with separate anti-host and tumour activity

While immune-related adverse effects are found in the majority of patients treated with Ipilimumab and cases of hypopituitarism are well documented, these are usually not acute and tend to progress subclinically. The onset of hypopituitarism observed in this patient, bearing in mind the lack of clinical and radiological evidence of pituitary enlargement, suggests that the auto-immune response induced by the anti-CTLA- 4 may additionally lead to clinical presentation even after a period from treatment cessation, without any clinically evident acute phase of inflammation. This may reflect the development of pituitary directed antibodies. Thus, we present a case of a previously unseen presentation of hypopituitarism secondary to Ipilimumab which will aid in its' diagnosis and management.

## Reference

1. Tas F, Tas F. Metastatic Behavior in Melanoma: Timing, Pattern, Survival, and Influencing Factors, Metastatic Behavior in Melanoma: Timing, Pattern, Survival, and Influencing Factors. *J Oncol J Oncol*. 2012, 2012:e647684
2. Giglio P, Gilbert MR. Neurologic Complications of Cancer and its Treatment. *Curr Oncol Rep*. 2010, 12(1):50–59
3. Marcus DM, Lowe M, Khan MK, Lawson DH, Crocker IR, Shelton JW, et al. Prognostic Factors for Overall Survival After Radiosurgery for Brain Metastases From Melanoma. *Am J Clin Oncol*. 2014, 37(6):580–584
4. Olszanski AJ. Current and future roles of targeted therapy and immunotherapy in advanced melanoma. *J Manag Care Spec Pharm*. 2014, 20(4):346–356
5. 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, 19;363(8):711–723
6. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol*. 2012, 13(5):459–465
7. Marlier J, Cocquyt V, Brochez L, Van Belle S, Kruse V. Ipilimumab, not just another anti-cancer therapy: hypophysitis as side effect illustrated by four case-reports. *Endocrine*. 2014, 47(3):878–883
8. Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. *J Clin Oncol*. 2015, 2014.56.2736
9. Torino F, Barnabei A, De Vecchis L, Salvatori R, Corsello SM. Hypophysitis Induced by Monoclonal Antibodies to Cytotoxic T Lymphocyte Antigen 4: Challenges from a New Cause of a Rare Disease. *The Oncologist*. 2012, 17(4):525–535

10. Schneider HJ, Aimaretti G, Kreitschmann-Andermahr I, Stalla G-K, Ghigo E. Hypopituitarism. *The Lancet*. 2007, 369(9571):1461–1470
11. Barnard ZR, Walcott BP, Kahle KT, Nahed BV, Coumans JV. Hyponatremia associated with Ipilimumab-induced hypophysitis. *Med Oncol Northwood Lond Engl*. 2012, 29(1):374–7
12. Dillard T, Yedinak CG, Alumkal J, Fleseriu M. Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes. *Pituitary*. 2010, 13(1):29–38
13. Juszczak A, Gupta A, Karavitaki N, Middleton MR, Grossman AB. Ipilimumab: a novel immunomodulating therapy causing autoimmune hypophysitis: a case report and review. *Eur J Endocrinol Eur Fed Endocr Soc*. 2012, 167(1):1–5
14. Marlier J, Cocquyt V, Brochez L, Van Belle S, Kruse V. Ipilimumab, not just another anti-cancer therapy: hypophysitis as side effect illustrated by four case-reports. *Endocrine*. 2014, 47(3):878–883
15. Chodakiewitz Y, Brown S, Boxerman JL, Brody JM, Rogg JM. Ipilimumab treatment associated pituitary hypophysitis: clinical presentation and imaging diagnosis. *Clin Neurol Neurosurg*. 2014, 125:125–130
16. Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR. Autoimmune Hypophysitis. *Endocr Rev*. 2005, 26(5):599–614
17. Carpenter KJ, Murtagh RD, Lilienfeld H, Weber J, Murtagh FR. Ipilimumab-Induced Hypophysitis: MR Imaging Findings. *Am J Neuroradiol*. 2009, 30(9):1751–1753
18. Juszczak A, Gupta A, Karavitaki N, Middleton MR, Grossman AB. Ipilimumab: a novel immunomodulating therapy causing autoimmune hypophysitis: a case report and review. *Eur J Endocrinol Eur Fed Endocr Soc*. 2012, 167(1):1–5