

Immunotherapy and Hypophysitis in the Clinical Practice: A Case Report

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Abstract

The reported frequency of ipilimumab-induced hypophysitis (IIH), a cytotoxic T-lymphocyte antigen 4 antibody, ranges from 0 to 17%, in contrast to the rarity of idiopathic autoimmune hypophysitis that has an estimated incidence of one in nine million people per year.

Here we present the case of a patient with ipilimumab-induced hypophysitis (IIH). After his third course of ipilimumab, the patient began to present worsening asthenia and severe headache. A brain MRI scan showed the mild swelling of the anterior pituitary gland and thickening of the stalk. Haematological reports were consistent with hypophysitis diagnosis: in fact, ACTH and cortisol levels were very low. Then ipilimumab was interrupted and therapy with a large dose of glucocorticoids (dexamethasone) was promptly started. A rapid symptoms improvement was obtained by this therapeutic approach. The dose of dexamethasone was gradually decreased over 4 weeks and hydrocortisone replacement was started.

Development of IIH is associated with the risk of acute adrenal insufficiency or adrenal crisis, so early recognition and therapeutic intervention are extremely relevant. Furthermore, in the absence of data demonstrating clinical benefit from high-dose glucocorticoid therapy, we wondered if, in absence of symptoms such as visual disturbances or other life-threatening simultaneous irAEs in other organs, there is the indication to start with hydrocortisone replacement therapy alone from the beginning. We also wondered if it was reasonable to administer ipilimumab during prolonged high-dose glucocorticoid therapy. Thus, guidelines for surveillance and management of IH are highly required.

Keywords: Metastatic melanoma; Ipilimumab; Hypophysitis; Secondary adrenal insufficiency; Glucocorticoids, Hydrocortisone replacement therapy

Introduction

Autoimmune hypophysitis (AH) is a rare immune mediated inflammatory disorder, characterized by cellular infiltration (activated lymphocytes) and inflammation of pituitary gland. It can be primary or secondary to systemic disease, local lesions or immunotherapies. It can impair the normal secretion of anterior and/or posterior pituitary hormones. Therefore, it can result in an adenohypophysitis with variable pituitary defects, in an infundibuloneurohypophysitis with diabetes insipidus, or in a pan-hypophysitis [1-9].

A new etiology of hypophysitis has recently been described in association with ipilimumab, a human MABs against the cytotoxic T-Lymphocyte antigen 4 (CTLA-4 Ab). T-Lymphocyte CTLA4 receptors enhance self-tolerance by downregulating the T-cell activation pathway and this can potentiate tumor growth. By blocking the CTLA4 receptor, ipilimumab enhances the innate immune response against tumors [1]. Ipilimumab was approved in 2011 by the US Food and Drug Administration (FDA) for the treatment of advanced melanoma and in 2015 FDA expanded the approved use of ipilimumab to include a new use as adjuvant therapy for patients with stage III melanoma, to lower the risk that the melanoma will return following surgery. Two recent phase-III studies have reported improved overall survival in metastatic melanoma [1,10-13]. Adjuvant ipilimumab significantly improved recurrence-free survival for patients with completely resected high-risk stage III melanoma [14]. However, it frequently causes several immune-related adverse events (irAEs) such as hypophysitis, enterocolitis, dermatitis, pneumonitis, peripheral neuropathy and hepatitis that are due to unrestrained T-cell activation [1,6,7]. A specific timing of occurrence after the initiation of therapy with ipilimumab was described for these irAEs: after 2-3 weeks for skin, later for gastrointestinal and hepatic irAEs, and >9 weeks for hypophysitis. The secretion of anterior pituitary hormones appears to be impaired in a typical order: the first

and the most frequent secretions impaired are the secretion of TSH and ACTH, then gonadotropins, prolactin, and GH secretions [1,6-9].

Case Report

A 68-year-old man referred to our oncology clinic in June 2015 after the diagnosis of metastatic BRAF V600E mutated melanoma. ECOG performance status was 0; no comorbidities. For his melanoma, he was treated surgically in June 2011. In May 2015, he underwent a CT-scan that displayed pulmonary metastases and conglomerated pathological lymph nodes in left axilla of around 8 cm. In June 2015, after adequate screening, he began Ipilimumab. In August 2015, he referred to our Institution with a 1 week history of headache following his third course of Ipilimumab. He denied nausea, vomiting, visual symptoms, loss of libido, polydipsia or polyuria. As metastatic brain disease or hypophysitis was suspected, he underwent a brain MRI that showed a pituitary swelling consistent with hypophysitis (Figure 1). Hormonal investigations demonstrated hypopituitarism: morning cortisol 0.7 mcgr/dl (reference range 8 to 25), with a low-normal LH and FSH, TSH 0.208 Uui/ml (0.250 to 4.5). There was no diabetes insipidus, his prolactin and IGF-1 were normal. He was started on dexamethasone 4 mg every 6 h; 5 days later levothyroxine 50 mcg daily was added and gradually increased to 100 mcg once a day, because his

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Received September 06, 2016; Accepted September 24, 2016; Published September 30, 2016

Citation: Gambale E, Tinari C, Carella C, Di Paolo A, De Tursi M (2016) Immunotherapy and Hypophysitis in the Clinical Practice: A Case Report. J Clin Case Rep 6: 861. doi: [10.4172/2165-7920.1000861](https://doi.org/10.4172/2165-7920.1000861)

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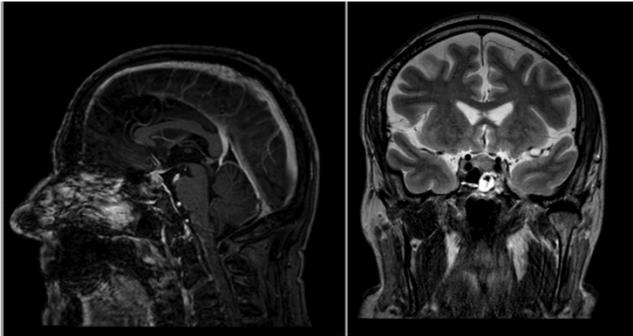


Figure 1: Sagittal and coronal sections of the pituitary gland on magnetic resonance imaging (MRI) scans. Swelling of the pituitary gland and thickening of the stalk with homogenous enhancement on MRI scan performed on August 2015 1-A:T1 Weighted sequence 1A:T2 Weighted sequence.

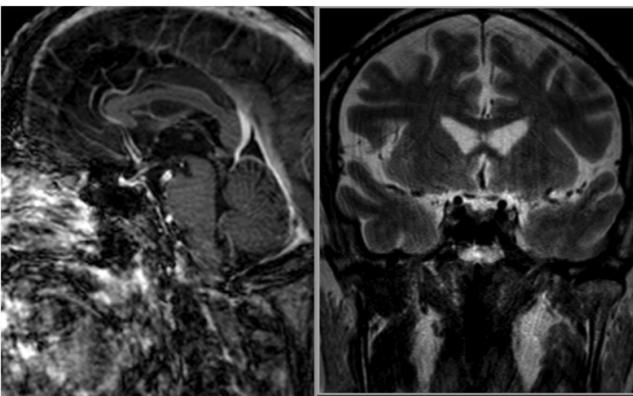


Figure 2: The swelling of the pituitary gland and thickening of the stalk improved in T1-weighted images on a plain MRI scan performed on October 2015 1-B:T1 Weighted sequence 1-B:T2 Weighted sequence.

TSH and free T_4 continued to decrease and it resulted in a thyrotrophic deficiency (TSH=0.011 uUI/ml and free T_4 =0.50 ng/dl reference range: 0.70 to 1.70). A rapid resolution of his symptoms was observed. The dose of dexamethasone was gradually decreased over 3 weeks and then replaced with physiological hydrocortisone replacement of 20 mg in divided doses (15 mg at 8 a.m. and 5 mg at 4 p.m.). Two months later, in November 2015, the patient recovered normal thyrotrophic function and levothyroxine was stopped. He had not received his fourth course of ipilimumab because he presented liver toxicity: AST 160 U/L (15 U/L to 46 U/L) and ALT 350 U/L (11 U/L to 66 U/L). Ipilimumab was found to be effective for the conglomerated pathological lymph node in left axilla on a follow-up CT-scan performed on August 2015, with a stable pulmonary disease. A brain MRI performed two months later, on October 2015, revealed improvements in the enlargement of the pituitary gland (Figure 2). The follow-up chest CT-SCAN of November 2015 showed progressive disease, but, in reason of a pseudo-progression, we waited to start a new therapy. The CT-scan performed in January 2016 confirmed progression disease. Therefore, the patient began therapy with daily oral dabrafenib 300 mg and trametinib 2 mg. The last total body CT-SCAN, performed on July 2016, has shown progression disease and the patient is waiting to begin nivolumab.

One year later, the last hormonal investigations, performed on 11 August 2016, have demonstrated low ACTH level (4.9 U/ml-reference range: 7.2 U/ml to 63.3 U/ml), normal morning cortisol levels (9.1 mcgr/dl-reference range 8 mcgr/dl to 25 mcgr/dl) and normal thyrotrophic

function with normal TSH levels (0.65 uUI/L-reference range 0.25 uUI/L to 4.50 uUI/L) and normal free T_4 levels (0.97 ng/dl- reference range: 0.7-1-7). The patient continues therapy with hydrocortisone of 20 mg in twice daily doses.

Discussion

Hypophysitis occurs in a significant minority of ipilimumab-treated melanoma patients. Its reported frequency in the literature ranges from 0% to 17% [1,9]. The initial symptoms are related to the hormonal deficiencies. Indeed, worsening asthenia and headache are the most frequent initial symptoms of ipilimumab-induced hypophysitis [1-9]. Patients very often show a swelling of the pituitary gland by MRI, without optic chiasm compression due to an enlarged pituitary gland with consequently absence of symptoms related to mass effect, like visual disturbances [1,3-8]. Male gender and older age can be risk factors for ipilimumab-induced hypophysitis, in contrast to the autoimmune hypophysitis that is reported to be more commonly observed in young women, with a strong association with pregnancy [1,3-8]. Most patients present their first symptoms after third infusion, at a mean time of about 9 weeks after starting ipilimumab [1-12,15-22].

The involvement of the posterior pituitary gland is extremely rare, with only one case of diabetes insipidus described in the literature during treatment with Ipilimumab [1].

Thyrotrophic function may recover in 37% to 50% of patients and gonadotropic function in 57% of men, but recovery of adrenotropic function rarely occurs [1,6].

There is significant morbidity associated with development of IH and early recognition and therapeutic intervention are fundamental. Although in absence of a prospective randomized study conducted to evaluate the long-term efficacy and safety of high-dose glucocorticoid therapy in patients with ipilimumab-induced hypophysitis, its effectiveness to resolve enlargements in the pituitary gland in the acute phase has been empirically appreciated [6,7]. About the concerns that high-dose of dexamethasone can decrease the function of activated T cells is not inhibited by glucocorticoids [6]. Moreover, despite the administration of high-dose glucocorticoid therapy, hormonal deficiencies persisted in most cases [6]. High-dose of systemic glucocorticoid treatment appears in fact not to be associated with a better outcome of IIH [6]. According to these considerations, if visual disturbances, other life threatening irAEs (pneumonitis for example) and hyponatremia are absent, it is reasonable to administer a conservative treatment and to start on hydrocortisone from the beginning [6].

About nivolumab, a human antibody against programmed death 1, an inhibitor receptor expressed by activated T cells, the incidence of nivolumab-induced hypophysitis appears to be lower (<1%) [1,10]. These great different incidences may be attributed to functional differences in the processes of T cell activation and the ectopic expression of CTLA-4 in the human pituitary gland that may be targeted by ipilimumab [6,10-12]. Furthermore, about patients treated with nivolumab who had progressed after ipilimumab, like our patient, who is ipilimumab-refractory, prior grade 3-4 immune-related adverse effects from ipilimumab were not indicative of nivolumab toxicities [23].

In summary, hypopituitarism as a consequence of IIH, if not promptly recognized, can lead to potentially fatal events, such as adrenal insufficiency. Therefore, oncologists and endocrinologists should be familiar with the key aspects of this condition. More studies

to develop screening protocols and therapeutic intervention algorithms should be performed to decrease morbidity related to IIH. A precise monitoring of ACTH, cortisol, TSH, and free T4 levels as well as the suspicion of hypophysitis based on patient symptoms like headache, asthenia, hypotension, hyponatremia and a history of having received at least three doses of Ipilimumab will lead to an earlier diagnosis and appropriate treatment [1,6,12].

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