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Original paper

Secondary hypophysitis due to immune checkpoint inhibitors – case report and literature review

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Abstract

Traditionally considered a very rare condition, hypophysitis is likely to increase in burden the population as a consequence of use of immune modulatory therapy which are very effective against various malignancies, but can induce autoimmune endocrinopathies.

Recently developed immune checkpoint inhibitors (ICI) ipilimumab (CTLA4 antibody) and nivolumab (PD1 antibody) and combination therapies are being used for a number of metastatic malignancies. Hypophysitis is a recognized side effect of these agents. Pituitary inflammation with ICI -related therapies appears to have a higher incidence in males and the elderly.

We present the case of a 49 yrs. old man diagnosed with malignant melanoma and presumed secondary hypophysitis during a clinical trial with Ipilimumab and Nivolumab.

We discuss here the mechanism of action of ICI, their immune-related adverse events, and the management of secondary hypophysitis.

Keywords Hypophysitis, immune therapy, melanoma

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Introduction

Hypophysitis is a rare inflammatory condition of the pituitary gland that leads to hypopituitarism of various degrees, and is usually accompanied by swelling of the gland with mass effects or pituitary stalk thickening; the disease is highly heterogeneous in pathology and presentation. Hypophysitis can be classified as primary or secondary. Primary causes include lymphocytic hypophysitis, granulomatous hypophysitis and xanthomatoushypophysitis, while secondary causes include sellar diseases (egRathke's cleft cyst, craniopharyngioma), systemic disease such as lupus erythematous systemic, Langerhans's cell histiocytosis, neurosarcoidosis, Takayasu's disease, infectious disorders (bacterial, viral, fungal), IgG4-related hypophystis and, most recently immune-checkpoint inhibitors (ICI) M.N. JOSHI & al. [1]

The prevalence of the disease is low, with an incidence of all types of hypophysitis combined of 1 in 9 million per year, but this may be and underestimate, particularly since the advent of ICI. Neurosurgical centers report that hypophysitis represents less than 1% of sellar and suprasellar lesions referred for evaluation (0.24-0.88%) P. CATUREGLI & al. [2]

ICI are drugs that modulate immune checkpoint proteins which are expressed on the surface of T-lymphocytes, such as the cytotoxic T-lymphocyte antigen-4 receptor (CTLA4) and the programmed death-1 (PD-1) receptor pathway. These drugs have recently been approved for the treatment of malignant melanoma and certain types of lung cancer as they enhance the activity of regulatory T cells such that they can target tumor cells and produce an immune response against them. The aim of the immunotherapy is to develop an immune response against the tumor by interrupting tumor-induced immune tolerance. S.M. CORSELLO & al. [3]. Ipilimumab is the first developed antibody that blocks the cytotoxic T-lymphocyte antigen 4 (CTLA4) to bind its ligand B7, and as a consequence T-cell activation is reinforced. Ipilimumab is approved for use in patients with advanced melanoma, based on a significant improvement in overall survival. Nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab, all of which target either PD-1 or itsligand PD-L1, have been approved in various cancers (melanoma, renal cell carcinoma, non-small cell lung cancer, head and neck cancer, urothelial carcinoma, Hodgkin's lymphoma, Merkel cell carcinoma, as well as microsatellite instability-high or mismatch repair deficient solid tumors). However, despite such important clinical benefits, checkpoint inhibition is associated with a unique spectrum of side-effects termed immune-related adverse events (irAEs): IrAEs includedermatologic, gastrointestinal, hepatic, endocrine, and other less common inflammatory events. S. CHAMPIAT & al. [4]

Endocrine toxicities associated with the administration of ICI include thyroid abnormalities such as hypo/hyperthyroidism, primary adrenal insufficiency, hypopituitarism caused by hypophysitis and, less often, diabetes mellitus type 1. M. RYDER & al. [5]. We present a case report of a patient with immune-mediated hypophysitis in order to further emphasize the significance of this rare but life-threatening condition in the management of various cancers.

Case report

A 49-year-old Caucasian male presented to the endocrinology outpatient clinic complaining of non-specific symptoms including fatigue, weakness, headache, nausea, asthenia, myalgia, arthralgia, confusion, memory loss and loss of libido. Medical history revealed malignant melanoma diagnosed in 2003 with wide local excision and sentinel lymph node biopsy, and 6 courses of carboplatin plus dacarbazine and 6 months of Interferon therapy, and then with no clinical evidence of recurrent disease for 11 years. However, he presented with local and lymph node recurrence in 2014, with a double resection followed by dacarbazine adjuvant therapy. A second recurrence was observed on an ^{18}FDG-PET/CT scan in the local lymph nodes two years later; these were excised and confirmed as metastatic melanoma. At this stage the patient was enrolled in a 49-week clinical trial with ICI (nivolumab 240 mg (every 2 weeks) plus ipilimumab 1 mg/kg (every 6 weeks), or nivolumab 480 mg (every 4 weeks) plus placebo. Two months within the trial he began to complain of moderate headache, asthenia, arthralgia and the oncologic team advised him to start prednisolone 4 mg/day. Once his symptoms had settled, the patient was taking prednisolone 4mg every 2-3 days. However, he presented to our team, as noted above, one month after completing the 49 weeks clinical trial.

Physical examination was unremarkable, except for the postoperative scar on his right leg. His blood pressure was 125/85 mmHg supine, 124/84 mmHg standing.

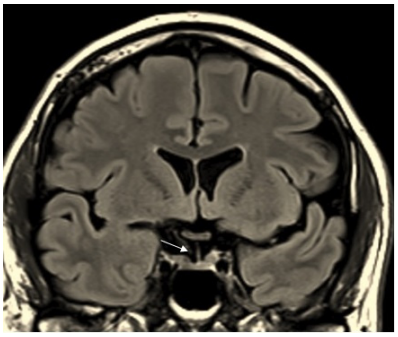
Hormonal assessment in our Endocrine department was performed by electrochemiluminescence immunoassay (ECLIA) for ACTH, plasma cortisol on a Cobas e601 automated analyser. Chemiluminescence immunoassay (CLIA) on an Access2 Immunoassay System or DxI 600 Beckmann Coulter was used for testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL). Thyroid function tests (thyroid stimulating hormone-TSH, free thyroxine-fT4, triiodothyronine-T3)

were performed also by CLIA on an Architect 2000i Abbot automated analyser. The results are presented in Table 1. Most significantly, his 9am serum cortisol was <1mcg/dL, with a subnormal serum T4 in the face of a normal level of serum TSH.

Table1
Hormonal assessment at presentation in Endocrine department

Hormone	Value	Normal values
Plasma Cortisol 8-9 am	0.06	4.82-19.5 mcg/dL
ACTH 8-9 am	1.54	3-66pg/mL
TSH	2.03	0.5-4.5 µIU/mL
Free T4	10.72	12-22pmol/lL
FSH	10.29	1.27-19.26 µlU/mL
LH	4.59	1.24-8.62 mlU/mL
PRL	6.69	2.64-13.13 ng/mL
IGF – 1	108.20	67 - 225 ng/mL
Testosterone	3.57	1.75 - 7.81 ng/mL

Thyroid ultrasound revealed a normal-sized thyroid gland, with a hypoechoic parenchymal pattern and two discrete hypoechoic nodules involving both the lobes. Magnetic resonance imaging (MRI) of the head with contrast showed small demyelinating lesions, probably microangiopathic changes, and a partial empty sella (Figure 1).


a)

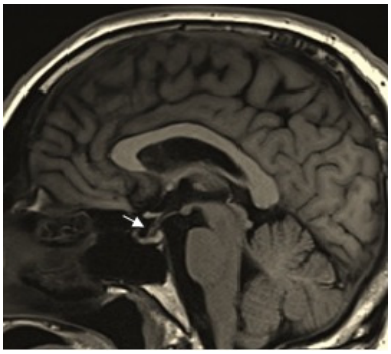

b)

Figure 1. MRI (T1) with coronal sections through the pituitary (**a**) revealing asymmetry of pituitary withhigher-left lateral segment and a sagittal section (**b**) demonstrating a thin pituitary stalk and a partial empty sella.

Discussions

Cancer therapy has rapidly evolved recently from conventional means of treatment such as surgery, chemotherapy and radiation, to alternative treatment strategies such as specific targeted therapies and immunotherapy. Immunotherapy uses the patient's own immune system to help target and destroy cancer cells, and a number of different techniques have been employed. H. ZHANG & al. [6]

Checkpoint inhibitors selectively block cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-1 or PD-L1, receptors on the surface of T-cells, resulting in immune cell activation, proliferation and an anti-tumor response (Figure 2). S.J. O'DAY & al. [7] PD1 is a transmembrane protein expressed on T cells, B cells and NK cells. It is an inhibitory molecule playing the role of a physiologic brake on cytotoxic T effector function when bound to the PD-1 ligand (PD-L1/B7-H1) or PD-L2/B7-H2. PD-L1 is expressed on the surface of multiple tissue types, including many tumor cells, as well as hematopoietic cells; PD-L2 is more restricted to hematopoietic cells. The interaction between PD-1 and PD-L1/2 directly inhibits apoptosis of the tumor cell and promotes peripheral T effector cell exhaustion. Cytokines such as IL-12 and IFN-gamma upregulate PD-1 and PD-L1/L2 to restrain cytotoxic T effector function, thus preventing the immune response from overshooting. S. SPRANGER & al. [8] Antibodies inhibiting PD-1 (pembrolizumab, nivolumab) and PD-L1 (atezolizumab, avelumab, durvalumab) have been approved for a number of clinical indications after demonstrating increased overall survival in phase III oncologic trials.

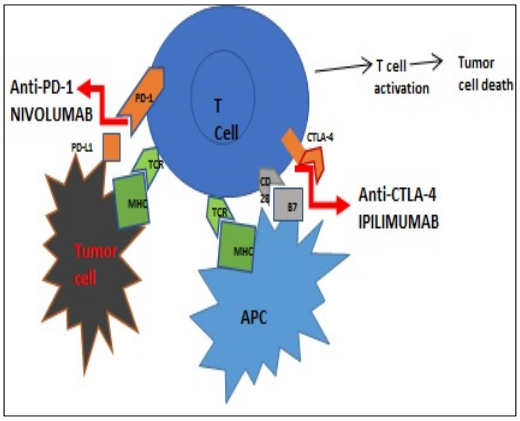


Figure 2. Mechanism of action of immune checkpoint inhibitors. PD-1 is expressed on activated T cells and when it binds to its ligand PD-L1 on tumor cells leads to T cell exhaustion. CTLA-4 competes with CD28 (co-stimulatory T cell molecule) for B7 ligands and upon activation decreases T cell proliferation as well as activity. Blockade of CTLA-4 (by anti-CTLA-4) and/or PD-1 or PD-L1 stimulates effector T cells to produce antitumor responses. MHC: major histocompatibility complex, TCR: T cell receptor.

CTLA-4 was discovered in 1987 and is part of the negative regulation of T cell activation. CTLA-4 exerts its effect when it is present on the cell surface of CD4+ and CD8+ T lymphocytes, where it binds to CD80(B7-1) and CD86 (B7-2) of the antigen-presenting cells (APCs) with higher affinity than the T cell costimulatory receptor CD28 (Figure 2). The expression of CTLA-4 is upregulated by the degree of T cell receptor (TCR) activation and cytokines such as IL-12 and IFN-gamma. CTLA-4 is part of the feedback inhibition loop on activated T effector cells. As a result, CTLA-4 can be broadly considered a physiologic "brake" on the CD4+ and CD8+ T cell activation that is triggered by APCs.

The anti-CTLA-4 antibody ipilimumab was the first immune checkpoint inhibitor to be approved by FDA in 2011, based upon its ability to prolong survival in patients with metastatic melanoma. Ipilimumab has also been approved as adjuvant therapy for high-risk melanoma as an alternative to IFN. D. SCHADENDORF & al. [9]. Three years later, nivolumab was approved for the treatment of unresectable or metastatic melanoma. L.A. RAEDLER & al. [10]

The irAEs induced by ICI affect not only the pituitary gland, but also thyroid, endocrine pancreas, and rarely adrenal and parathyroid glands. In a meta-analysis that included 7551 patients in 38 randomized trials, the overall incidence of clinically significant endocrinopathies is approximately 10% of all patients treated with checkpoint inhibitors. R. BARROSO-SOUSA & al. [11] Hypophysitis is the most common endocrine irAE associated with ipilimumab, occurring in 8%-11% of patients and less frequently encountered with with PD-1 and PD-L1 inhibitors (0%-5%). Secondary hypophysitis usually occurs 6-12 weeks after initiation of ipilimumab, but some cases have also been reported as late as 36 weeks. R. BARROSO-SOUSA & al. [11]. In our case, the symptoms of adrenocortical insufficiency occurred 12 weeks after initiation of immunotherapy, but the patient was only referred much later for endocrine review.

The exact pathogenic mechanism of anti-CTLA4 monoclonal antibody-induced hypophysitisis largely unknown. The presenting clinical features, MRI findings and hormone dysfunction resemble those seen in classic lymphocytic hypophysitis, therefore the pathogenic mechanism is suspected to be autoimmune with lymphocytic destruction of pituitary cells. Interestingly, hypophysitis has not been reported when ipilimumab is combined with cytotoxic chemotherapy, presumably due to lymphocyte depletion from cytotoxic agents. F. TORINO & al. [12]. Typical symptoms of hypophysitis include headache, fatigue and loss of libido. Our patient reported all of the symptoms but the diagnosis was only confirmed by obtaining full pituitary function investigations which showed hormone deficiencies on multiple axes.

Caturegliet al. have recently reported a number of clinical differences between immune checkpoint therapy (CTLA-4)-induced hypophysitis and primary (lymphocytic) hypophysitis. The incidence of visual disturbances and diabetes insipidus is extremely rare in secondary hypophysitis, while anterior pituitary hormones deficiencies are noted in more than 70% patients and include thyrotroph, gonadotroph and corticotroph insufficiency. P. CATUREGLI & al. [13] Our patient had no visual disturbances and only ACTH and slight TSH insufficiency. Recovery is very variable in most primary hypophysitis, while ACTH insufficiency is permanent in almost all CTLA-4-induced hypophysitis. P. CATUREGLI & al. [13].

Biopsies from CTLA-4 related hypophysitis revealed complement fixation, macrophage infiltration and lymphocyte activation. These findings suggest a type II and type IV hypersensitivity reaction that underlie the mechanism of CTLA- 4-related hypophysitis. Iwama *et al.* were the first to report to the presence of CTLA-4 Ag in pituitary tissue and suggest antibody-dependent

complement activation (ADCC) as the underlying model of immune activation. S. IWAMA & al. [14].

The radiological findings can precede clinical diagnosis by several weeks. However, CTLA-4-related hypophysitis has no distinctive radiological characteristics that could help differentiate it from primary hypophysitis. In such circumstances, the presence of an 'empty sella' has been considered secondary to atrophic response of the 'burnt-out' inflammatory process. H. GAO & al. [15]. In our case, cerebral MRI was performed approximatley 11 months after the onset of hypophysitis symptoms and revealed the presence of an empty sella, which can be secondary to atrophic response.

The management of immune checkpoint therapy-related hypophysitis depends on the severity of the clinical presentation. J. HAANEN & al. [16] In severe mass effect symptoms (throbbing headache, visual disturbance) or severe adrenal failure (hypotension, hyponatremia), ICI are withheld and i.v methyl-prednisolone 1 mg/kg can be initiated, together with advanced analgesia. MRI will be performed in order to exclude brain metastases and visual field assessment is necessary. After symptoms have reduced, the aim is to tapper the corticosteroid doses and to convert to 5 mg of oral prednisolone over the next 4 weeks. J. HAANEN & al. [16]. For other than severely symptomatic cases, pituitary function is assessed first, then replace cortisone and thyroxine as appropriate while immune checkpoint therapy can be continued and pituitary MRI performed. J. HAANEN & al. [16]

Recovery of the hypothalamic–pituitary–thyroid axis has been reported in 37%-50% of patients with gonadal axis recovery in 57% of men. The more severely affected hypothalamo–pituitary–adrenal axis is more persistent, with very few patients able to discontinue glucocorticoid replacement. Hypophysitis appears to be the only ipilimumab-induced irAE that persists long after exposure to the drug. A. JUSZCZAK & al. [17].

The long term treatment of pituitary insuficiency has the objective of adequately replace the hormones of the peripheral gland affected by the lack of tropic stimulation. Therefore, corticotroph deficiency is substituted by hydrocortisone which is administered in 20-25 mg/day tds or one morning dose of the longer acting prednisone 7.5 mg/day or prednisolone 5 mg/day. Patients on replacement doses of glucocorticoids should be instructed to eat a normal salt diet and to double/triple the doses of hydrocortisone when acute illness or physical stress or exercise occurs. Central hypothyroidism is treated by replacing levothyroxine only after adrenocortical replacement. It has been claimed that the development of irAEs such as hypophysitis is a favorable sign of efficacy of checkpoint inhibitors as they correlated with better tumor response in some trials. P. ATTIA & al. [18].

Conclusions

For all immune checkpoint inhibitors, a high index of suspicion for the incidence of hypophysitis is required. Symptoms of hypopituitarism are nonspecific and could mistakenly be attributed to comorbid conditions. Therefore, mixt teams of endocrinologists-oncologists should develop screening processes to ensure early detection of hypopituitarism which, if overlooked, and not treated adequately can be life-threatening.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by allauthors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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