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Case Report

A Case of Autoimmune Hypophysitis Induced by Ipilimumab/Nivolumab Combination Therapy for Metastatic Melanoma

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Abstract.

Ipilimumab and Nivolumab are immune checkpoint inhibitors used to treat patients with advanced melanoma to improve survival. However, they are commonly associated with immune-related adverse events, including endocrinopathies, colitis, dermatitis, and hepatitis. Here, we report a case of Autoimmune hypophysitis Induced by ipilimumab/nivolumab Combination Therapy, which is an increasingly recognised phenomenon. Prior to symptom onset, the patient's hormonal profile already suggested hypophysitis following initiation of ipilimumab/nivolumab, with a low thyroxine level and an inappropriately normal thyroid stimulating hormone level. The clinician was falsely reassured by a morning cortisol level within normal range, without performing low dose short synacthen test. Therefore, the diagnosis of hypophysitis was delayed. This case report serves as a reminder to suspect, diagnose, and treat immune checkpoint inhibitor Induced hypophysitis promptly, as the resulting hormonal insufficiency can be life-threatening.

Case history

An 83-year-old Chinese gentleman presented to the Accident and Emergency department in July 2021 for severe non-vertigo dizziness and fatigue. He is an ex-smoker and ex-drinker, with a past medical history of pulmonary tuberculosis in 2009.

10 months prior to presentation, in September 2020, he was diagnosed with BRAF-negative metastatic melanoma of scrotum with groin and external iliac lymph node metastasis. He was treated with 4 cycles of intravenous (IV) nivolumab 480mg every 4 weeks, an immune checkpoint inhibitor (ICPi), between November 2020 and February 2021. Routine thyroid function tests (TFTs) in January 2021 showed a secondary hypothyroid pattern, evidenced by a low free thyroxine (FT4) level of 10.8 pmol/L and an inappropriately normal thyroid stimulating hormone (TSH) level of 3.28 mIU/L. (Table 1) Anti-thyroglobulin and anti-thyroid peroxidase antibody levels were normal. Morning cortisol level was 160nmol/L, which was within normal range. The patient did not complain of symptoms related to hypothyroidism or hypophysitis at the time. Thyroxine replacement was started in March 2021 without further investigations for hypophysitis.

Physical examination identified disease progression of metastatic melanoma and the patient received 4 cycles of 4-weekly IV ipilimumab (3mg/kg)/nivolumab (1mg/kg) Combination Therapy since March 2021. After the fourth cycle, in July 2021, he complained of non-vertigo dizziness and fatigue, neurological examination was unremarkable, and his power was documented to be Medical Research Council (MRC) grade 5 over all four limbs. Postural hypotension was not present. Laboratory work up for hypophysitis revealed depleted adrenocorticotropic hormone (ACTH), inadequate low dose short synacthen test (LDSST) response, low Insulin-like growth factor 1 (IGF-1) and low TSH. FT4 was normal because the patient was on thyroxine replacement. Prolactin, luteinising hormone (LH) and follicle stimulating hormone (FSH) levels were elevated. Testosterone level was normal. The sodium (Na) level was borderline low and there was no evidence of cranial diabetes insipidus. Magnetic resonance Imaging (MRI) brain and pituitary gland in August 2021 showed normal pituitary gland enhancement with no focal mass lesion or suprasellar extension. Endocrinology was consulted and he was diagnosed with ipilimumab/nivolumab Induced hypophysitis based on these clinical and laboratory findings.

ICPis were suspended and oral prednisolone 1mg/kg daily was started with a plan to taper 5mg every week. However, during outpatient clinic follow up, morning cortisol level remains low, and the patient was inappropriately kept on medium dose glucocorticoid (defined as >7.5 mg, but ≤30 mg prednisolone per day or equivalent) for more than 3 months with cotrimoxazole as pneumocystis pneumonia prophylaxis. In October 2022, he suffered from Steven Johnson Syndrome with ocular involvement, which was suspected to be related to cotrimoxazole. Oral prednisolone was sequentially weaned off to oral hydrocortisone 10mg twice daily (physiological maintenance dose) in November 2022. Nivolumab 480mg every 4 weeks was resumed in January 2022. The latest morning cortisol level remained low in May 2022, 10 months after the diagnosis of hypophysitis.

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Table 1: *Blood test results before and after starting ipilimumab/nivolumab combination therapy.*

Lab Investigations	Baseline before ICPi treatment 11/2020	2 months after starting nivolumab 1/2021	4 months after starting ipilimumab/Nivolumab 7/2021	At 10 month follow up 5/2022	Reference Interval
TSH (mIU/L)	1.6	3.28	0.19 (L)	2.18	0.27-4.20
FT4 (pmol/L)	12.5	10.8 (L)	13.2	14	12.0-22.0
AM Cortisol (nmol/L)	185	160	142	12 (L)	133-537
ACTH (pmol/L)			<1.9 (L)		2.3-11.0
LDSST (nmol/L)			11 (0min) to 116 (30min)		≥376nmol/L at 30min
Prolactin (mIU/L)			359 (H)		86-324
IGF-1 (µg/L)			27 (L)		34-246
LH (IU/L)			26.1 (H)		1.7-8.6
FSH (IU/L)			23.4 (H)		1.5-12.4
Testosterone (nmol/L)			8.79		6.70-25.7
Sodium (mmol/L)	133 (L)	134	135 (L)	141	136-145
Potassium (mmol/L)	3.8	4.4	3.7	3.7	3.4-4.8

Discussion

Programmed death receptor-1 (PD-1) is expressed on the surface of activated T cells. T cells become inactivated if programmed death-ligand 1 (PD-L1), made by cancer cells, binds to PD-1. Nivolumab is an anti-PD-1 monoclonal antibody that blocks PD-L1 from binding to PD-1, allowing the T cells to function.

Cytotoxic T lymphocyte antigen 4 (CTLA4) is a protein receptor that serves as an immune checkpoint and down regulates T-cell activation and proliferation against cancer cells. Ipilimumab, an anti-CTLA4 monoclonal antibody, blocks CTLA4 which leads to enhanced T-cell activation and antitumor effects.

Nivolumab and ipilimumab are ICPis which have improved survival in patients with advanced melanoma but are commonly associated with immune-related adverse events (irAE), including endocrinopathies, colitis, dermatitis and hepatitis. (1) Autoimmune hypophysitis, also known as lymphocytic hypophysitis, is a rare condition which has now emerged as a relatively common irAE of ICPis, with many case reports describing this phenomenon. (2-5) A recent multi-centre retrospective review conducted by Faje et al reported 13.6% and 0.5% of patients treated with ipilimumab and anti-PD-1 (nivolumab or pembrolizumab) respectively to have developed hypophysitis. (6)

Hypophysitis can affect only the anterior pituitary (adenohypophysitis), infundibulum and posterior pituitary (infundibulo-neurohypophysitis), or the entire pituitary gland (panhypophysitis). The anterior pituitary gland produces and releases ACTH, FSH, LH, Growth hormone, prolactin and TSH, while the posterior pituitary gland is connected to the hypothalamus through the infundibulum, releasing oxytocin and vasopressin produced in the hypothalamus.

Patients with hypophysitis commonly present with symptoms including headache, fatigue, nausea, dizziness, altered mental status, myalgia, and low blood pressure. The diagnosis of ICPi Induced hypophysitis is established by the presence of low levels of pituitary hormones mentioned above, following treatment with ICPis, with or without radiographic pituitary enlargement. (6) It is important to note that primary adrenal insufficiency may also be an irAE of ICPi. The differentiation between primary and secondary adrenal insufficiency relies on the ACTH level in the setting of low cortisol level. A high ACTH level suggests primary adrenal insufficiency while a low ACTH level suggests secondary adrenal insufficiency. Our patient's ACTH level was low, which is compatible with a diagnosis of secondary adrenal insufficiency due to hypophysitis.

Here we have reported a case of adenohypophysitis following treatment of metastatic melanoma with ICPis. Our patient was initially treated with nivolumab monoTherapy. Before symptom onset, he was already found to have abnormal TFTs suggestive of secondary hypothyroidism 2 months after starting nivolumab. The morning cortisol level was 160nmol/L at the time. The patient was started on thyroxine replacement and no further pituitary hormone tests were carried out.

It was speculated that the attending clinician was falsely reassured by a morning cortisol of 160nmol/L, which was within the reference interval (133-537nmol/L). Cheung et al suggested that for outpatients who were ambulatory and not under stress, a morning cortisol of ≤124 nmol/L indicated adrenal insufficiency, and a value of ≥428 nmol/L signaled adequate adrenal reserve. (7) In other words, when the morning cortisol level falls between the gray area of >124nmol/L and <428nmol/L, proceeding to confirmatory tests such as LDSST to diagnose adrenal insufficiency is recommended if the clinical suspicion is high.

Our patient subsequently received 4 cycles of ipilimumab/nivolumab due to disease progression of metastatic melanoma. After the fourth cycle, he developed symptoms of hypophysitis and blood tests revealed low TSH, IFG-1 and ACTH. Prolactin, LH, FSH and testosterone levels were either normal or raised. ICPi Induced hypophysitis does not necessarily affect all pituitary axes. Faje et al reported that Anti-PD-1 monoTherapy patients often only had isolated central adrenal insufficiency while deficiencies in other pituitary axes were observed more often in the ipilimumab monoTherapy and Combination Therapy

groups. (6) ICPi Induced hypophysitis commonly affects anterior pituitary gland and rarely affects the infundibulum and posterior pituitary causing DI. (8) Faje et al did not report cranial diabetes insipidus in any patient in a cohort study of 106 ipilimumab or anti-PD-1 Induced hypophysitis cases. (6)

MRI of our patient showed normal pituitary gland enhancement with no focal mass lesion or suprasellar extension. Faje et al reported pituitary gland enlargement in 98% of patients with ipilimumab Induced hypophysitis. In contrast, only 28% of patients treated with Anti-PD-1 monoTherapy were reported to have pituitary enlargement. Optic chiasm compression was not found in any patient with ipilimumab or nivolumab Induced hypophysitis. (6)

The American Society of Clinical Oncology (ASCO) guideline suggests ICPi Induced hypophysitis to be graded 1-4 according to their severity. Hypophysitis with none or mild symptoms are grade 1; moderate symptoms with the ability to perform activities of daily living (ADL) are grade 2; and severe symptoms with medically significant or life-threatening consequences plus loss of ability to perform ADL are grade 3-4. (9)

Holding ICPi for grade 1-2 hypophysitis can be considered, and secondary adrenal insufficiency should be replaced by physiological maintenance dose hydrocortisone (15-20mg daily in divided dose). Our patient had severe symptoms affecting his ADL, therefore his hypophysitis was graded 3-4 according to the ASCO guideline, which suggests these patients to receive stress dose IV hydrocortisone (50-100mg every 6-8 hours) and taper it down to physiological maintenance dose hydrocortisone over 5-7 days and hold ICPi until the patient is stabilised on hormonal replacement. For those with significant pituitary swelling on MRI, severe headache, optic chiasm changes or visual changes, a pulse dose treatment of oral prednisolone 1-2mg/kg daily (or equivalent) tapered over at least 1-2 weeks to physiological maintenance dose is suggested (9)

In most patients with ICPi Induced hypophysitis, long term hormonal supplement is usually required as anterior pituitary function recovery is uncommon. Discontinuing ICPi in mild hypophysitis is not necessary and one study found the incidence of hypophysitis may positively predict survival in melanoma patients treated with Ipilimumab. (10) Our patient inappropriately received medium dose glucocorticoid for more than 3 months. According to clinical notes, his low spot morning cortisol level was falsely interpreted as an indication to continue medium dose glucocorticoid.

In conclusion, Autoimmune hypophysitis is increasingly recognised as an irAE of ICPis. Clinicians should suspect, diagnose, and treat this condition promptly as the resulting adrenal insufficiency can be life-threatening. Morning cortisol levels should be interpreted carefully, with consideration of confirmatory tests when its result is >124nmol/L and <428nmol/L. Anterior pituitary hormone production is usually affected, and recovery is uncommon, therefore patients usually require long term hormonal supplement. A low morning cortisol level while on physiological maintenance dose hydrocortisone is not an indicator to increase glucocorticoid dose. Pituitary gland enlargement on imaging may or may not be present with hypophysitis. The management of ICPi Induced hypophysitis should be guided by its severity grading according to the ASCO guideline. (9)

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