Hypophysitis from immune checkpoint inhibitors: challenges in diagnosis and management

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Purpose of review
This review will summarize the most recent and pertinent evidence regarding immune checkpoint inhibitor (ICI)-induced hypophysitis to describe diagnostic and management algorithm with the help of a case report.

Recent findings
Hypophysitis is the most common endocrine adverse event from CTLA-4 inhibitors and much less with PD-1/PD-L1 inhibitors. Its pathophysiology appears to be lymphocytic, predominantly affecting the anterior pituitary. The utility of high-dose glucocorticoids for treatment has been questioned, as they do not influence recovery of hypopituitarism and may reduce survival. A survival benefit with hypophysitis has been suggested.

Summary
The nonspecific nature of symptoms underlies the importance of clinical and hormonal monitoring especially in the first 6 months of CTLA-4 inhibitor cancer therapy. Adrenal insufficiency can be a diagnostic and management challenge, which persists in most cases; hence, a multidisciplinary team of oncologists and endocrinologists is essential for providing high-quality care to these patients. High-dose glucocorticoids should be reserved for mass effect or optic chiasm impingement. The ICI may need to be temporarily withheld but not discontinued. A survival advantage in cancer patients that develop ICI-induced hypophysitis may be a silver lining, especially as ICIs are being investigated for advanced endocrine malignancies.

Keywords
hypophysitis, hypopituitarism, immune checkpoint inhibitor, immune-related adverse events

INTRODUCTION

Lymphocytic autoimmune hypophysitis has traditionally been observed in women during pregnancy or postpartum [1], but has recently emerged as an immune-related adverse event (irAE) of the novel immune checkpoint inhibitors (ICIs) [2]. These are monoclonal antibodies (mAbs) that block immune checkpoints leading to enhanced T cell activation, proliferation and function [3,4] (Fig. 1). The Food and Drug Administration (FDA) approved ICIs include checkpoint cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitor ipilimumab; programmed cell death protein-1 (PD-1) inhibitors pembrolizumab, nivolumab and cemiplimab; and programmed cell death protein-ligand 1 (PD-L1) inhibitors atezolizumab, avelumab and durvalumab. The immune activation caused by ICIs is not only very effective for cancer cell destruction but also causes irAEs, including endocrine disorders such as hypophysitis [2,5–8], thyroiditis [2,9–13], diabetes mellitus [14–16], and much rarely adrenalitis [17–19] and autoimmune hypoparathyroidism [20,21].

Many observational studies have characterized ICI-induced hypophysitis [5–7,10,22▪▪,23,24,25▪,26▪]. A few society guidelines [27,28▪,29▪] and review articles from experts in the field [2,16,30–32,33▪,34▪▪] have also provided guidance on diagnosis and management. However, many unanswered questions remain pertaining to the patterns of hypopituitarism, pituitary abnormality on imaging, possibility of recovery, utility of high-dose glucocorticoids, and a possible association with survival in these cancer patients. The purpose of this review article is to summarize the most pertinent evidence in these aspects of

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KEY POINTS

- Hypophysitis is a common adverse event of CTLA-4 inhibitor or combination treatment, most frequently causing secondary adrenal insufficiency and central hypothyroidism.
- The nonspecific nature of symptoms and significant morbidity with delayed recognition underlie the importance of clinical and hormonal monitoring for hypophysitis.
- A normal pituitary appearance on MRI should not rule out hypopituitarism in the presence of clinical and biochemical evidence.
- High-dose anti-inflammatory glucocorticoids should be reserved for unrelenting mass effect or optic chiasm impingement.
- Multidisciplinary management and follow-up with a team including oncologist and endocrinologist improve the quality of care for hypophysitis.

ICI-induced hypophysitis and describe a diagnostic and management algorithm with the help of a case report.

PATHOPHYSIOLOGY

Immune checkpoints keep the over-activation of T-cells in check. Increased expression of the immune checkpoint CTLA-4 on T-cell membrane surface competes with CD28 for binding to B7 (newer nomenclature CD80 or CD 86) [3,4]. This represses T-cell activation and proliferation early in immune response, primarily in lymph nodes. Blocking CTLA-4 by mAbs enhances T cell activation and proliferation [3,4]. Activation of T cells also leads to increased expression of PD-1, which binds to its ligands (PD-L1, PD-L2) on peripheral tissues including cancer cells. This binding represses T-cell function. Blocking these immune checkpoints by mAbs enhances T-cell function [3,4]. This upregulation of T cells leads to cancer cell destruction but is also hypothesized to be the reason for irAEs.

Hypophysitis as an irAE appears to be lymphocytic, as Iwama *et al.* [35] showed lymphocytic infiltration into pituitary gland of mice who were given CTLA-4 blocking antibody. They also evaluated 20 ipilimumab-treated melanoma patients, of whom seven developed hypophysitis and had antipituitary antibodies, whereas 13 patients that did not develop hypophysitis did not have these antibodies [35]. The antibodies were directed against corticotroph

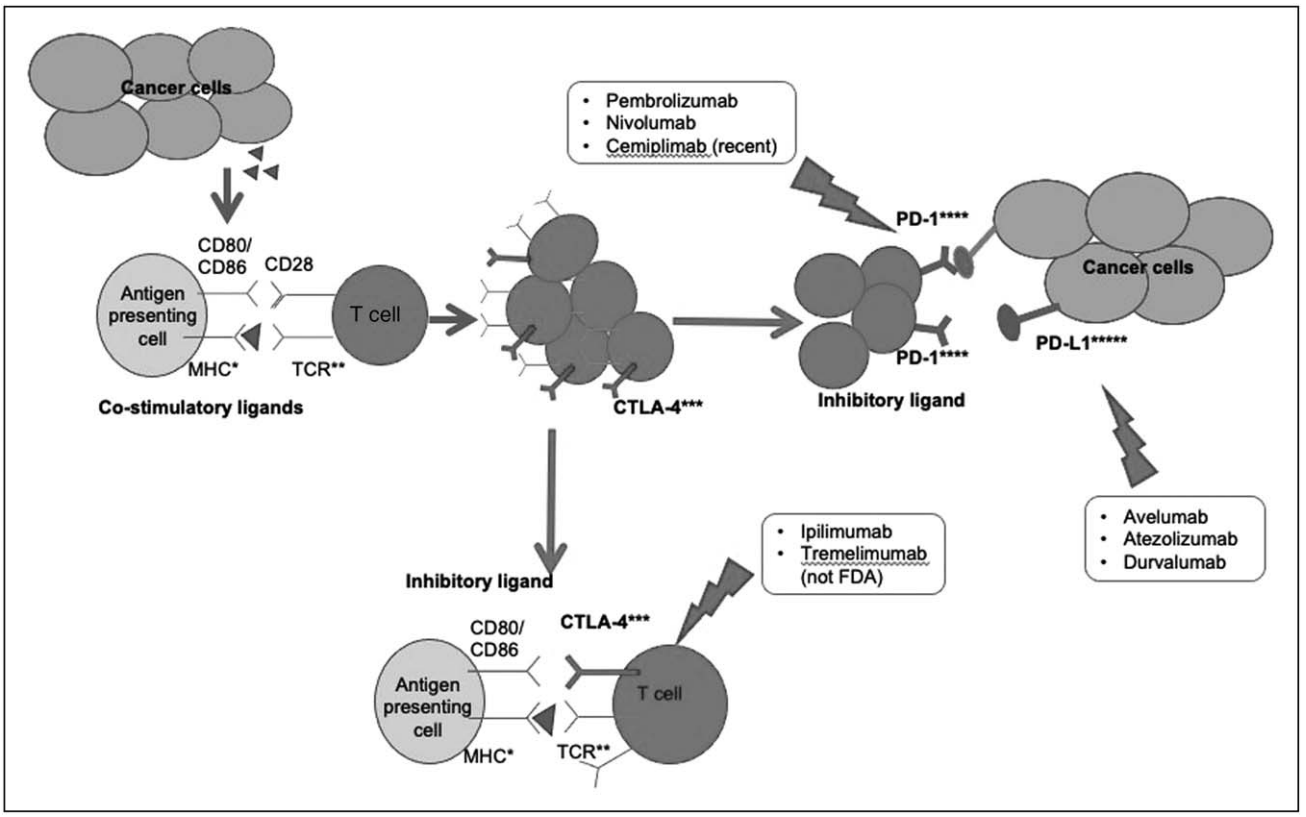

FIGURE 1. Schematic of mechanisms of immune checkpoints and their inhibitors. CTLA-4, cytotoxic T lymphocyte antigen-4; MHC, major histocompatibility complex; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein-ligand 1; TCR, T cell receptor.

(produce adrenocorticotrophic hormone [ACTH]), thyrotroph (produce thyroid stimulating hormone [TSH]) and gonadotroph (produce luteinizing hormone, follicle-stimulating hormone) pituitary cells [35]. It has also been shown that single nucleotide polymorphisms in the *CTLA-4* gene are associated with autoimmune hypophysitis [30]. An autopsy study demonstrated variable expression of CTLA-4 by pituitary cells in six patients treated with CTLA-4 blockade, with highest expression in the patient that had hypophysitis whose pituitary also demonstrated T-cell infiltration and IgG-dependent complement fixation and phagocytosis in the anterior pituitary [36]. This study suggests that the susceptibility to development of hypophysitis may depend on the magnitude of pituitary expression of CTLA-4. Hypophysitis from PD-1 inhibitors is less frequent and less likely to cause significant pituitary gland enlargement as compared to CTLA-4 inhibitors [22▪▪]. An explanation for this difference is that the expression of CTLA-4 on pituitary gland [36] makes it more susceptible to be affected by CTLA-4 inhibitors, while another explanation is that CTLA-4 inhibitors ipilimumab and tremelimumab are IgG1 and IgG2 mAbs, respectively, which can activate the classic complement and antibody dependent cell-mediated cytotoxicity, whereas PD1 and PD-L1 inhibitors are IgG4 mAbs which are less effective in these pathways [34▪▪,37]. Recently, association with HLA DR15 has been demonstrated [38▪], which needs further exploration as a possible predictive marker. These studies demonstrate that research into the pathophysiology of ICI-induced hypophysitis is turning up some very surprising observations including a potential role for pituitary cell expression of CTLA4.

EPIDEMIOLOGY

A meta-analysis [39] has summarized the occurrence of endocrinopathies in clinical trials of ICIs, demonstrating that hypophysitis occurred in 6.4% with combination ICIs, 3.2% with monotherapy CTLA-4 inhibitors, 0.4% with PD-1 inhibitors and less than 0.1% with PD-L1 inhibitors. Observational longitudinal cohorts have demonstrated hypophysitis to occur at a higher frequency than that in the trials but with a similar pattern in terms of ICI class. In these studies, hypophysitis occurred in up to 14% with CTLA-4 inhibitor [2,5,10,23,24] but only 0–5% with PD-1/PD-L1 inhibitors [2,22▪▪]. It is possible that earlier studies of ICIs underestimated the frequency of pituitary dysfunction due to a higher reliance on clinical features, which can be nonspecific, as opposed to systematic hormonal evaluation; however, the latter is still not performed widely. We analysed a cohort of 91 PD-L1 inhibitor treated patients in whom hypophysitis did not occur during a median follow-up of 1 year [13]; however, few cases with PD-L1 inhibitor have been reported showing isolated ACTH deficiency [40].

As far as demographics, higher frequency in older men has been reported [5,26▪] as opposed to the classic autoimmune lymphocytic hypophysitis with a predilection for women [1]. However, this demographic difference may be influenced by the type of cancer being studied. The median time to onset is 2–4 months (range 1–19 months), with shorter time to onset after CTLA-4 inhibitor or combination as compared to PD-1/PD-L1 inhibitor [6,7,22▪▪,24,26▪,32,34▪▪,41].

PRESENTATION AND DIAGNOSIS

Case

A 40-year-old man with metastatic melanoma presented to our endocrinology clinic after two ipilimumab (CTLA-4 inhibitor) doses (12 weeks) with central headache, diplopia, nausea, low appetite, fatigue, muscle aches, diarrhoea and postural hypotension. He was diagnosed with secondary adrenal insufficiency and central hypothyroidism (Table 1). MRI before ipilimumab demonstrated normal pituitary gland (Fig. 2a), but at presentation demonstrated pituitary gland enlargement and contrast enhancement with optic chiasm impingement (Fig. 2b).

The clinical presentation of hypophysitis relates to the extent of pituitary enlargement, which can cause mass effects such as central headache, diplopia and visual field deficits, but less in magnitude to other forms of hypophysitis [34▪▪,42]. The most common manifestations of hormone deficiency being fatigue, nausea, malaise, asthenia, anorexia, hyponatremia can be nonspecific [34▪▪,42]. The presence of hypotension or postural hypotension, vomiting, fever, confusion/delirium, hyponatraemia/hyperkalaemia/hypoglycaemia, AKI, hypovolemic shock should raise concern for adrenal crisis, which requires emergent management [43▪]. CTLA-4 inhibitor-induced hypophysitis usually causes multiple pituitary hormone deficiencies, and even though central hypothyroidism was noted to be the most frequent [5,10,23], recent studies have shown secondary adrenal insufficiency to be the most common hormone deficiency [31,44,45]. Hypophysitis from PD-1 inhibitors appears to be a separate entity [22▪▪], more commonly presenting with isolated secondary adrenal insufficiency [46]. Diagnosis may be delayed or missed due to nonspecific symptoms, which may overlap with those in malignancy. Some guidelines [27,28▪] and reviews [2] have

Table 1. Laboratory investigations in a patient who developed hypophysitis after ipilimumab therapy for metastatic melanoma

Laboratory investigations	Prior to ipilimumab	At presentation	At 3-month follow-up	Reference range
Thyroid-stimulating hormone (mIU/l)	3.2	0.1		0.3–4.2
Free thyroxine (ng/dl)	1.1	0.4	1.1	0.9–1.7
Total triiodothyronine (ng/dl)	–	85	–	80–200
Adrenocorticotrophic hormone (ACTH) (pg/ml)	35	<5	–	7–63
8 a.m. cortisol (μg/dl)	11	<1	2	7–25
Follicle-stimulating hormone (IU/l)	–	–	3	1.2 – 15.8
Luteinizing hormone (IU/l)	–	–	2.2	1.8 – 8.6
Total testosterone (ng/dl)	–	–	260	240 – 950
Bioavailable testosterone (ng/dl)	–	–	71	72–235
Prolactin (ng/dl)	–	1.2	–	2.6–13.1
Sodium (mmol/l)	138	128	140	135–145
Potassium	3.8	4.2	4	3.6–5.2

recommended monitoring morning serum adrenocorticotrophic hormone (ACTH) and cortisol levels during treatment with CTLA4 blockade given the potentially life-threatening outcome from adrenal insufficiency and its high incidence with anti-CTLA4 therapy. We recommend monitoring before start of CTLA-4 inhibitor, and if normal then before each infusion for the first 6 months, every 3 months for the next 6 months, and thereafter every 6–12 months or based on clinical suspicion (Fig. 3). Abnormal pituitary gland appearance on MRI should also prompt this monitoring; however, there are not enough data support MRI as a method of screening for hypophysitis [34▪▪].

Diagnosing secondary adrenal insufficiency is most critical because it is life-threatening if not treated in a timely manner. It is diagnosed with low or low normal 8 a.m. serum cortisol along with low or inappropriately normal ACTH (Table 1). In our opinion, 8 a.m. serum cortisol less than 5 mg/dl makes adrenal insufficiency likely, and borderline level 5–18 mg/dl still makes it possible if the suspicion is high (typical symptoms, CTLA-4 inhibitor use, MRI abnormality) in the absence of concomitant glucocorticoids. The patient's sleep-wake schedule should be taken into account when testing cortisol. If adrenal crisis is suspected, a random cortisol and ACTH could be drawn if time permits but emergent management should be initiated without waiting for these results. A high serum ACTH accompanied by hyperkalaemia suggests primary adrenal insufficiency, which is rare with ICIs, in which case testing for renin, aldosterone and suboptimal cortisol response to 250 μg ACTH

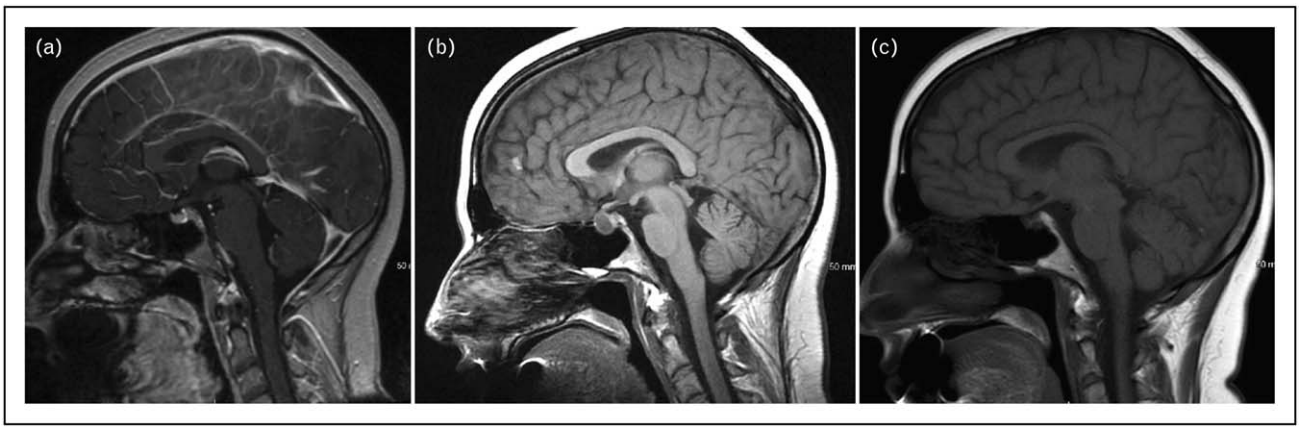

FIGURE 2. (a) MRI with gadolinium contrast of sella turcica sagittal view before ipilimumab demonstrating normal appearance of pituitary gland with concave upper margin. (b) MRI with gadolinium contrast of sella turcica sagittal view at the time of presentation with hypophysitis demonstrating pituitary gland enlargement with convex upper margin and optic chiasm impingement. (c) MRI with gadolinium contrast of sella turcica sagittal view at 3-month follow-up demonstrating a small pituitary gland with an almost empty sella appearance.

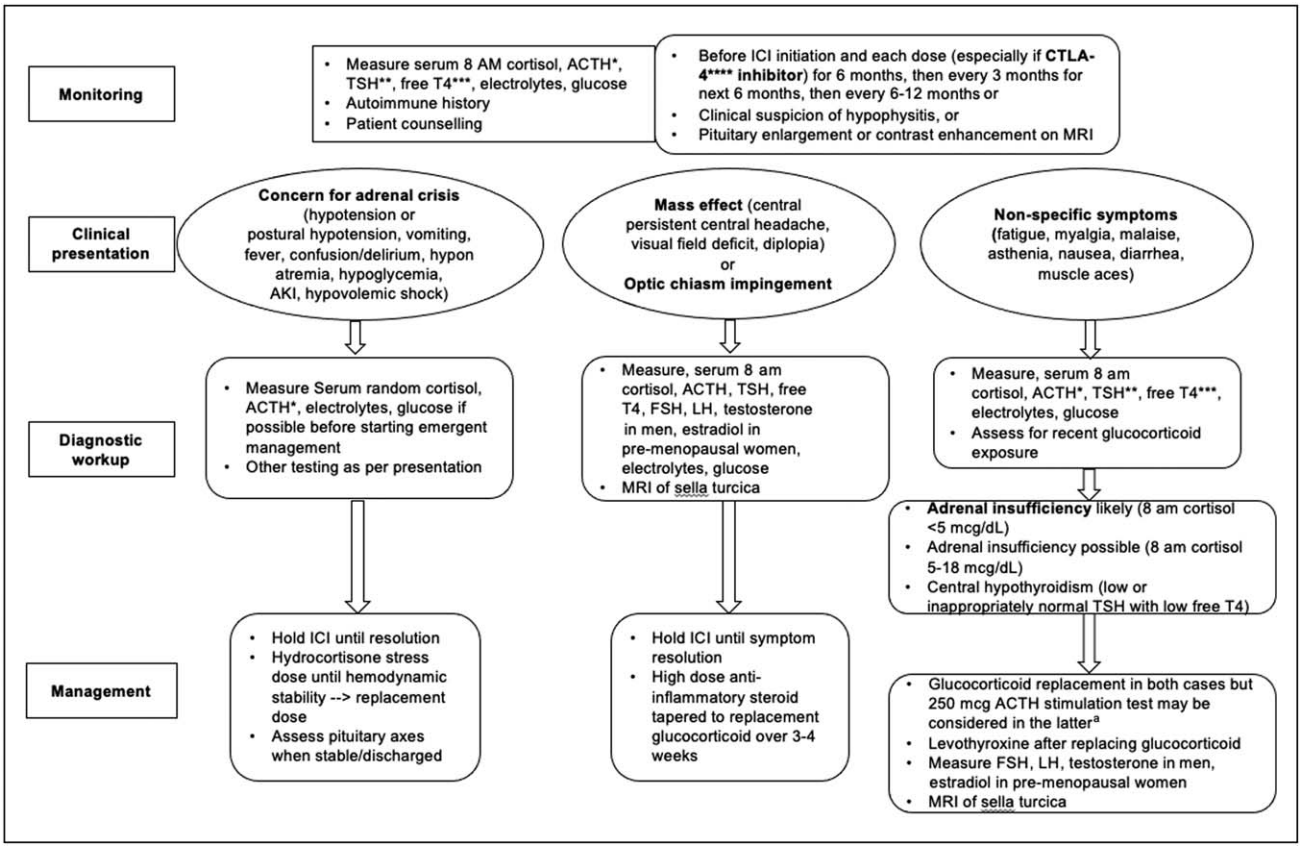

FIGURE 3. Algorithm for monitoring, diagnosis and management of immune checkpoint inhibitor-induced hypophysitis. ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; T4, thyroxine; TSH, thyroid-stimulating hormone; . [a]Normal 250 μg ACTH stimulation test does not exclude recent onset secondary adrenal insufficiency.

stimulation aid in diagnosis. A 250 μg ACTH stimulation test is not helpful in diagnosing early secondary adrenal insufficiency because in initial pituitary injury, the adrenal glands may respond to ACTH stimulation normally, as they have not yet atrophied from the chronic absence of ACTH stimulation. Hence, the clinician should not be falsely reassured by a cortisol response to more than 18 μg/dl in this setting. Another, complicating aspect of diagnosis is exposure to exogenous glucocorticoids which can suppresses the hypothalamic-pituitary-adrenal (HPA) axis and also mask hypophysitis, hence can precipitate secondary adrenal insufficiency when discontinued abruptly.

Central hypothyroidism is characterized by low free T4 along with low or inappropriately normal TSH (Table 1, Fig. 3). Interestingly, an early reduction in TSH in some studies [34▪▪,42,47], while a reduction in free T4 and TSH index in another [48▪▪] have been shown to precede hypophysitis; however, this pattern could also be from nonthyroidal illness and high-dose glucocorticoids. Secondary adrenal insufficiency and/or hypothyroidism can cause syndrome of inappropriate antidiuretic hormone (SIADH) leading to hyponatremia, which resolves after hormone replacement [5,24,41] (Table 1).

Testing for central hypogonadism (low estradiol or testosterone, low or inappropriately normal gonadotropins) can be performed 2–3 months after diagnosis. Prolactin level may be high due to stalk effect or low in setting of hypopituitarism. It should be tested in setting of central hypogonadism to rule out hyperprolactinemia but does not change management in the initial setting. Growth hormone replacement is contraindicated in active malignancy; hence, testing is usually not helpful. Posterior pituitary involvement causing central diabetes insipidus is rare, with only three cases reported to date [49–51], so its occurrence should also raise concern for pituitary metastases especially if the pituitary enlargement on MRI persists for longer than 3 months.

Gadolinium contrast MRI focusing on sella turcica should be performed if hypophysitis is suspected or biochemically evident to characterize the pituitary gland enlargement and exclude other causes of hypopituitarism such as pituitary mass (adenoma or metastases), abscess or apoplexy. In

most cases of hypophysitis, MRI demonstrates enlargement and contrast enhancement of the pituitary gland, with sometimes enlargement of the pituitary stalk (Fig. 2b), which usually resolves in 2–3 months after which MRI demonstrates a small pituitary or an empty sella (Fig. 2c) [24,34▪▪,42]. MRI evidence of pituitary enlargement usually occurs concurrently or preceding the hormone deficiency [7,42]. However, it should be noted that MRI imaging of pituitary can be normal in up to 23% of CTLA-4 inhibitor-induced hypophysitis [36] and even more frequently with PD-1/PD-L1 inhibitors [7,22▪▪, 44,52], hence a normal appearing pituitary on MRI in the setting of clinical suspicion and laboratory confirmation of hypopituitarism does not rule out hypophysitis.

MANAGEMENT

Case continued

Due to significant mass effects and optic chiasm impingement, prednisone 60 mg daily was initiated and tapered over 3 weeks to hydrocortisone 15 mg in a.m. and 5 mg in p.m. Levothyroxine was initiated for central hypothyroidism. At the 3-month follow-up, he was diagnosed with mild hypogonadotropic hypogonadism and MRI demonstrated an empty sella appearance (Fig. 2c). On follow-up over 2 years, he has not recovered form hypopituitarism, and continues to require hydrocortisone, levothyroxine and testosterone replacement.

The Common Terminology Criteria for Adverse Events (CTCAE) has been used to characterize irAEs [29▪], but its utility for endocrine irAEs is limited due to the nonspecific nature of symptoms and limited utility of high-dose anti-inflammatory glucocorticoids for endocrine irAEs [2,34▪▪]. Recent evidence [6,24] has questioned the utility of high-dose glucocorticoids for treating hypophysitis. Min *et al.* [24] reported neither improvement nor worsening of survival with high-dose glucocorticoids. Faje *et al.* [6] reported reduced survival with use of high-dose glucocorticoids even after adjusting for age, sex and tumour status. Although the acute course of hypophysitis was mitigated, no patient was successfully tapered off their hormone replacement therapy during the follow-up duration, regardless of the pituitary axis affected or use of initial high-dose glucocorticoid therapy [6,24]. Hence, in our opinion, high-dose glucocorticoids should be administered only for significant mass effect (severe headache, diplopia or visual field defect) or optic chiasm impingement in order to reduce the inflammation. This can be with methylprednisolone or prednisone 1–2 mg/kg/day or Dexamethasone 4 mg every 6–8 hours until symptom resolution, then rapidly tapered to physiologic replacement over 3–4 weeks (Fig. 3).

Glucocorticoid replacement should be done before thyroid hormone replacement, as the latter can precipitate or worsen underlying adrenal insufficiency. Glucocorticoid substitution is initially with hydrocortisone 20 mg when the patient wakes up and 10 mg 6–8 h later, which can be tapered to 15–20 mg/day in two to three divided doses (Fig. 3). Prednisone 5–7.5 mg once daily is a second-line option in cases of poor adherence. Adrenal crisis requires emergent management with fluid resuscitation and intravenous hydrocortisone 100 mg followed by 50 mg every 6–8 hours or until the patient is hemodynamically stabe, then tapered to physiologic replacement (Fig. 3). Levothyroxine starting at 0.8–1.6 μg/kg/day [2,29▪] for central hypothyroidism should be titrated to target fee T4 in mid-upper normal range. Testosterone or estradiol replacement should be considered if hypogonadism persists for 3–6 months after diagnosis because initial hypogonadism may recover.

ADDITIONAL CONSIDERATIONS

Recovery of hypopituitarism may be tested every 3–6 months for the first year and every 6–12 months thereafter. Recovery can occur in up to 50% for central hypothyroidism and hypogonadism [42], however, secondary adrenal insufficiency is permanent in most cases [5,7,10], with only a few cases of recovery reported [53]. This underlies the importance of long-term follow-up and patient education regarding 'sick-day rules' for glucocorticoid replacement in times of significant illness and hospitalization. The ICI should be temporarily withheld for mass effect or adrenal crisis but can be resumed once the acute presentation has resolved even if the initial presentation was categorized as CTCAE 4, highlighting the limitation of this grading for endocrine irAEs [2,34▪▪]. Interestingly, improved survival has been demonstrated with the occurrence of ICI-induced hypophysitis in some studies [5–7,25▪] but not in another [26▪]. Even though the data are not very strong, the survival benefit suggests that hypophysitis may be a biomarker for better cancer response to the ICI, and also supports exploration of ICIs for aggressive pituitary carcinoma as has been demonstrated in a case [54].

CONCLUSION

Hypophysitis is a common adverse event of CTLA-4 inhibitor or combination treatment causing secondary adrenal insufficiency, which can be life-

threatening if not identified and treated in a timely manner. The nonspecific nature of symptoms highlights the importance of clinical and biochemical monitoring, and follow-up with a multidisciplinary team. Pituitary enlargement occurs in most cases and resolves in a few months hence persistence should raise concern for metastases, whereas absence of enlargement should not exclude hypopituitarism if there is clinical and biochemical evidence. High-dose glucocorticoids are reserved for adrenal crisis or mass effects with optic chiasm impingement. A survival advantage with hypophysitis needs further investigation, especially as these therapies are being investigated for advanced endocrine malignancies.

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Conflicts of interest

There are no conflicts of interest.

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