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Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights

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Abstract
Introduction Advances in immunotherapy have transformed the management of metastatic melanoma and generated encouraging results in the treatment of other malignancies. Autoimmune side effects from these agents, termed immune-related adverse events (IRAEs), are diverse and can include multiple endocrinopathies. Ipilimumab-induced hypophysitis (IH) is a recently recognized endocrine IRAE.
Methods This review summarizes published data and experience from our center on the incidence, presentation and management, and proposed mechanisms for immunotherapy-related hypophysitis, with a focus on patients treated with ipilimumab (Ipi).
Conclusion Hypophysitis occurs in a significant minority of patients treated with Ipi, in contrast to the relative rarity of idiopathic autoimmune hypophysitis or hypophysitis after treatment with other immunotherapies. Recently published cohorts have described the clinical presentation and management of IH and longitudinal outcomes in these patients. Additional studies with Ipi and other emerging agents have helped identify potential risk factors for the development of immunotherapy-related hypophysitis and possible underlying mechanisms for IH. Clarification of the mechanism(s) for IH may enhance our understanding of idiopathic autoimmune hypophysitis and could have potential therapeutic applications.

Keywords Ipilimumab · Hypophysitis · Hypopituitarism · CTLA-4

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Introduction

Recently developed immunotherapeutic agents have demonstrated substantial potential for the treatment of a variety of malignancies. Immune checkpoint inhibitors, which release constraints on immune cells to promote antitumor activity, have generated the most promising results. Ipilimumab (Ipi) was the first among these agents to be approved by the Food and Drug Administration (FDA) for the treatment of unresectable or metastatic melanoma. Following Ipi, pembrolizumab and nivolumab were approved in 2014 for treatment of melanoma, and nivolumab was also granted approval for metastatic squamous non-small cell lung cancer earlier this year. Numerous studies are evaluating the efficacy of these medications in other malignancies (Currently, ClinicalTrials.gov lists 118 open studies which include treatment with Ipi, 79 with pembrolizumab, and 51 involving nivolumab [1]).

Ipi is an IgG1 monoclonal antibody which binds and inhibits cytotoxic T-lymphocyte antigen-4 (CTLA-4). CTLA-4 is expressed on T cells following antigen stimulation and competitively inhibits B7/CD28 binding, thereby downregulating T cell activation and proliferation. Additional proposed mechanisms for CTLA-4 activity include constitutive inhibitory effects in regulatory T cells, cell extrinsic effects on antigen-presenting cells, and transendocytosis of B7 [2, 3].

CTLA-4 inhibitors such as Ipi act early in the process of immune activation to increase T cell proliferation and activity. Programmed cell death 1 (PD-1) modulates the immune response in a more peripheral fashion primarily at the tumor microenvironment. PD-1 is expressed on the surface of activated T and B lymphocytes and monocytes. Binding of PD-1 to its ligands, PD-L1 and PD-L2, inhibits the immune response of these cells. PD-L1 and PD-L2 are

normally expressed by antigen-presenting cells and may also be present on some tumors cells, possibly as a mechanism to evade immune surveillance. Nivolumab and pembrolizumab are IgG4 monoclonal antibodies which bind PD-1. (Pidilizumab is an IgG1 anti-PD-1 agent currently under study.) Multiple anti-PD-1L agents are also under development [4, 5].

In addition to their intended antitumor effects, immune checkpoint inhibitors can also trigger a wide range of autoimmune side effects, termed immune-related adverse events (IRAEs). Examples of IRAEs include colitis, dermatitis, hepatitis, pancreatitis and, more rarely, nephritis, polymyositis, uveitis, toxic epidermal necrolysis, DRESS syndrome, hemophilia A, Tolosa-Hunt syndrome, and Grave's ophthalmopathy [6]. These toxicities appear to be more frequent in patients receiving Ipi compared to PD-1/PD-L1 agents, possibly due to the latter's more peripheral site of activity [4]. The broad diversity of IRAEs has led some authors to conclude "since ipilimumab-induced irAES can virtually affect any organ system physicians have to consider all symptoms as potentially ipilimumab-associated" [6].

IRAEs affecting endocrine systems, such as hypophysitis, thyroiditis, and primary adrenal insufficiency have also been reported in patients treated with immune checkpoint inhibitors. This paper reviews the epidemiology, clinical presentation, treatment, and pathophysiology of hypophysitis in patients receiving immunotherapy, followed by a discussion of potential applications for this unintended side effect. Durable treatment responses have been observed in a subset of patients receiving immune checkpoint inhibitors, in contrast to most traditional cytotoxic regimens or targeted antitumor therapies [7]. The potential for long-term survival in patients treated with immunotherapy and the expanding applications for these medications underlines the significance of recognition and proper treatment of endocrine IRAEs.

Epidemiology of hypophysitis in patients receiving immunotherapy

Older immunotherapy agents, such as interleukin 2 and interferon, have well-described effects on thyroid autoimmunity and function [8], but case reports of potential hypophysitis are very rare [9–13]. In contrast, hypophysitis appears to be the most common endocrine IRAE in patients receiving Ipi. Early studies involving Ipi reported a low incidence of hypophysitis. In a phase 3 trial of Ipi, hypophysitis was diagnosed in only 4 of 540 patients (0.7 %) [14]. No case of hypophysitis or endocrine IRAE was reported in another large phase 3 trial where 250 patients received Ipi plus dacarbazine [15]. Incidence rates in these studies contrast sharply with more recent cohorts described after hypophysitis became a recognized side effect of Ipi. Recent studies suggest that approximately 10–15 % of patients receiving Ipi may develop hypophysitis [16–18]. Clinical recognition appears to be an important, if not predominant, factor that affects the reported incidence rates of Ipi-induced hypophysitis (IH). In our hospital we have encountered 29 cases of IH among 228 melanoma patients treated with Ipi (12.7 %). Four cases of IH were diagnosed in 65 patients treated with Ipi prior to FDA approval in 2011 (6.1 %). Twenty-five cases of IH were diagnosed in 163 patients who received Ipi after FDA approval (15.3 %, $p = 0.07$). Descriptions of endocrine IRAEs in oncology trials also suffer from inconsistent and imprecise classification. In a recent trial of Ipi plus nivolumab, for example, endocrine IRAEs appeared to be categorized separately and also in a partially overlapping fashion into the following groups: hypophysitis, adrenal insufficiency, hyperthyroidism, blood TSH decreased, hypothyroidism, and thyroid disorder [19]. Some trials have grouped "hypopituitarism" and "hypophysitis" separately [14]. Assessment of adrenal function, gonadal steroid levels, and thyroid function tests can be affected by exogenous glucocorticoid administration, acute or chronic illness, and other factors. Estimated incidence rates for endocrine IRAEs such as IH become ambiguous in the absence of precise and consistent definitions or proper clinical context. Data from the cohorts summarized in Table 1 appear to be the most reliable estimates of the incidence of IH.

The relatively high incidence of IH is impressively unique. With the exception of tremelimumab (an anti-CTLA-4 monoclonal antibody which failed to gain FDA approval), hypophysitis appears to be an extremely rare event in patients treated with other immune checkpoint inhibitors. In 10 studies totaling approximately 2000 patients treated with nivolumab, pembrolizumab, or anti-PD-L1, only 18 cases of "hypophysitis" were described [19–28]. In 13 of these cases, the patients received concurrent or prior therapy with Ipi. Only 5 cases of hypophysitis have been reported in patients receiving monotherapy with a PD-1 or PD-L1 agent; the details of these cases were not described [22, 23, 28].

The incidence of thyroid function abnormalities after treatment with anti-PD-1 or anti-PD-L1 agents is more common than hypophysitis and occurs in approximately 5–10 % of patients [20–28]. Ipilimumab may also affect thyroid function and has been associated with primary adrenal insufficiency, though the former occurs less frequently than hypophysitis and the latter appears to be very rare [14–17, 29].

Idiopathic autoimmune hypophysitis is generally diagnosed more frequently in women compared to men [30,

Table 1 Longitudinal case cohorts of ipilimumab-induced hypophysitis

	Faje et al. [17]	Min et al. [18]	Albarel et al. [16]	Total
Cohort size (male/female)	154 (99/55)	187 (118/69)	87–131[a] (–)	428–472
Hypophysitis (n, %)	17, 11.0 %	25, 13.3 %	15, 11.4–17.2 %	57, 12.0–13.3 %
Hypophysitis (male/female)	15/2	19/6	10/5	44/13
Hypophysitis mean age (y)	68.2	–	55.5	–
Dosage (3, 10 mg/kg)	13, 4	17, 8	2–4, 11–13[a]	32–34, 23–25
Median time to diagnosis after Ipi initiation (wks)	8.4	9	9.5	–
Radiographic pituitary enlargement	17/17	15/25[b]	12/14[b]	44/56[b]
Visual defects	0/17	0/25	0/15	0/57
Hyponatremia	8/14	14/25	–	22/39
Most common presenting symptoms	HA (14/17), fatigue (10/17)	–	HA (13/15), fatigue (11/15)	HA (27/32), Fatigue (21/32)
Hypopituitarism at diagnosis				
Thyroid	17/17	22/25	13/15	52/56
Adrenal	7/14	22/25	11/15	40/54
Gonadal	15/15	15/20	12/14	42/49
Growth hormone (IGF-1)	1/6	3/7	2/8	6/21
Prolactin (elevated, low)	0/13, 12/13	1/9, 4/9	1/9, 3/9	2/31, 19/31
Diabetes Insipidus	0/17	0/25	0/15	0/57
Resolution of pituitary enlargement	17/17	11/11	12/12	40/40
Hypopituitarism at most recent followup				
Thyroid	13/17[c]	8/25	2/15	23/57
Adrenal	14/17[c]	22/25	13/15	49/57
Gonadal	13/15	8/25	2/15	23/57
Growth hormone (IGF-1)	–	–	1/11	1/11
Prolactin (elevated, low)	–	–	1/11, 1/11	1/11, 1/11

[a] Some patient data remained blinded, and these subjects were treated with Ipi (3 vs. 10 mg/kg) or placebo

[b] Imaging obtained after the diagnosis of IH was delayed or performed following glucocorticoid treatment in some patients. Authors also did not report whether pre-Ipi MRIs were available for comparison in patients without overt pituitary enlargement

[c] Results were updated after initial publication

31]. IH, in contrast, appears to occur more frequently in men [18, 29], even after adjustment for the male predominance in melanoma treatment cohorts [17, 32]. The incidence of melanoma increases with advancing age [32], and older age may also be a risk factor for the development of IH [17]. The impact of Ipi dosage (3 vs. 10 mg/kg) on the incidence of IH is unclear. Although the risk of other IRAEs appears to be dose-dependent [33, 34], the case for IH dose-dependency is less established. An early and more recent dose-escalation study suggested that higher dosages of Ipi may increase the risk of hypophysitis [34, 35]. It is important to note, however, that Ipi dosages were escalated rapidly in these protocols, and IH typically occurs after several cycles of Ipi (regardless of dosage). Therefore, IH would naturally be expected to occur more frequently in these protocols after patients received higher Ipi dosages. Additionally, the diagnosis of IH may have been somewhat delayed in the earlier study by Maker et al. due to the initial lack of familiarity with this side effect. In our experience the cumulative Ipi dosage and/or use of high dose (10 mg/kg) versus standard dose (3 mg/kg) do not appear to be risk factors for the development of IH [17]. This pattern remains unchanged in an updated review of 228 patients treated with Ipi at our hospital. The incidence of IH did not differ in patients receiving 10 or 3 mg/kg (16 and 12.4 %, respectively, $p = 0.54$) (unpublished data). Other large series of IH patients did not specifically examine this topic [16, 18]. Further prospective data gathered from recent patient cohorts (i.e., after the broad recognition of IH as a common IRAE) would help clarify the relationship between Ipi dosage and IH.

Whether concurrent or sequential treatment with other agents (cytotoxic regimens, targeted therapy, immunotherapy, or radiation) alters the risk of IH is not well-

defined. Some data suggests that radiation therapy may help boost the effectiveness of immunotherapy, and abscopal effects from radiation have been demonstrated in melanoma patients [36–38]. It seems plausible therefore that radiation treatment could alter the risk of IH, but this possible effect has not yet been examined. It has previously been suggested that IH may be more frequent after combination treatment with Ipi and bevacizumab [29], but phase I study results do not appear to support such an association [39]. The risk of IH does not appear to be elevated in patients who are also treated with traditional chemotherapy or targeted therapies [15, 40–43]. Although limited data are available (and with the interpretative caveats that were previously discussed), the incidence of IH does not appear to be significantly elevated in patients receiving combination treatment with nivolumab [19, 25] or recombinant granulocyte macrophage colony-stimulating factor [44].

Diagnosis and clinical presentation of IH

The diagnosis of IH is presumptive and generally based on the presence of new hypopituitarism (without an alternative etiology) and reversible radiographic pituitary enlargement after treatment with Ipi. No pituitary histologic specimen has been described in human cases of IH, but focal infiltration of lymphocytes and macrophages were observed in the pituitary glands of mice treated with an anti-CTLA-4 antibody [45].

Table 1 summarizes data from the largest and most detailed longitudinal cohorts of patients with IH that have been reported to date. Patients are typically diagnosed with IH approximately 2–3 months after the initiation of Ipi, though delayed presentations have also been described [46]. New relative pituitary enlargement after treatment with Ipi is a sensitive and specific indicator for IH (Table 1) [17]. Radiographic evidence of IH may precede biochemical hypopituitarism or the onset of symptoms [17, 47]. Gland enhancement may be homogeneous or heterogeneous with IH (Fig. 1) and be accompanied by stalk thickening in some patients. Pituitary enlargement can be quite mild and may not be readily apparent without comparison to a prior imaging study (Fig. 2). Pituitary enlargement also rapidly resolves in some cases of IH. We observed complete resolution of pituitary enlargement in one patient after only 12 days of glucocorticoid therapy, and another group reported reduction of pituitary size in 1 week [48]. Chronic persistent pituitary enlargement appears to be uncommon in IH. We observed resolution of pituitary enlargement in all patients with IH, including 7/7 patients within 40 days. Similar findings were reported by other groups (Table 1). Min et al. reported that 5/11 patients had resolution of pituitary enlargement within 3–8 weeks after the diagnosis of IH. Since pituitary enlargement is transient and often mild in patients with IH, it seems likely that the incidence of pituitary expansion may be underestimated by some groups, especially if imaging is delayed after the diagnosis of IH or if a prior magnetic resonance imaging (MRI) study is unavailable for comparison.

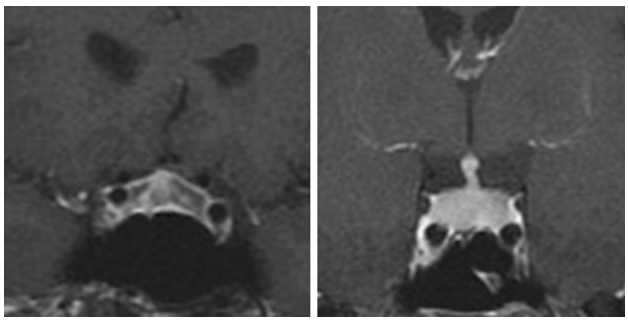

Fig. 1 Pituitary glands may exhibit heterogeneous or homogeneous enhancement in patients with IH, and stalk thickening occurs in some patients

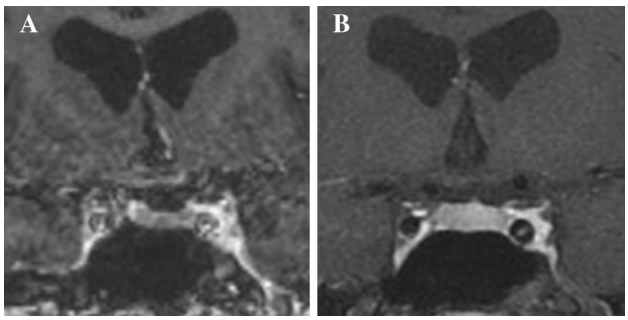

Fig. 2 Pituitary enlargement in IH can be mild and evident in some patients only after comparison with imaging obtained prior to treatment with Ipi. **a** Depicts a coronal post-contrast T1-weighted image of the pituitary prior to treatment with Ipi. Mild relative pituitary gland enlargement is visible after the diagnosis of IH (**b**)

Patients with IH frequently present with symptoms of headache and fatigue or weakness (Table 1). In contrast to lymphocytic hypophysitis, visual defects are extremely rare in patients with IH since the degree of gland enlargement is typically mild. Again, in contrast to other forms of hypophysitis, diabetes insipidus (DI) is also very rare in patients with IH. Only one case of IH with confirmed "partial" diabetes insipidus has been reported [49]; one other patient with a clinical diagnosis of DI has also been described [50]. Most patients with IH have multiple anterior pituitary hormone deficiencies, and secondary hyponatremia can also occur. Central hypothyroidism appears to be the most frequent hormone deficiency; central adrenal insufficiency and hypogonadotropic hypogonadism are also common. Interestingly, the growth

hormone axis appears to be relatively spared. Hyperprolactinemia is also uncommon; prolactin levels are often low in patients with IH (Table 1). The manufacturer's package insert for Ipi recommends that thyroid function tests be checked prior to each treatment cycle [51]. Our experience demonstrates that levels of thyroid stimulating hormone (TSH) often decline prior to the diagnosis of IH and the development of overt central hypothyroidism (Fig. 3). Declining TSH levels, much like asymptomatic radiographic pituitary enlargement, can occur prior to the diagnosis of IH and onset of clinical symptoms. Patients receiving combination therapy with Ipi and anti-PD-1 agents also have a significant risk of primary thyroid dysfunction (20, 26), and we have encountered such patients with new concurrent primary thyroid dysfunction and hypophysitis. In patients receiving Ipi and agents that target PD-1 or PD-L1, it is important to measure both TSH and free thyroxine (FT4) levels with each treatment cycle.

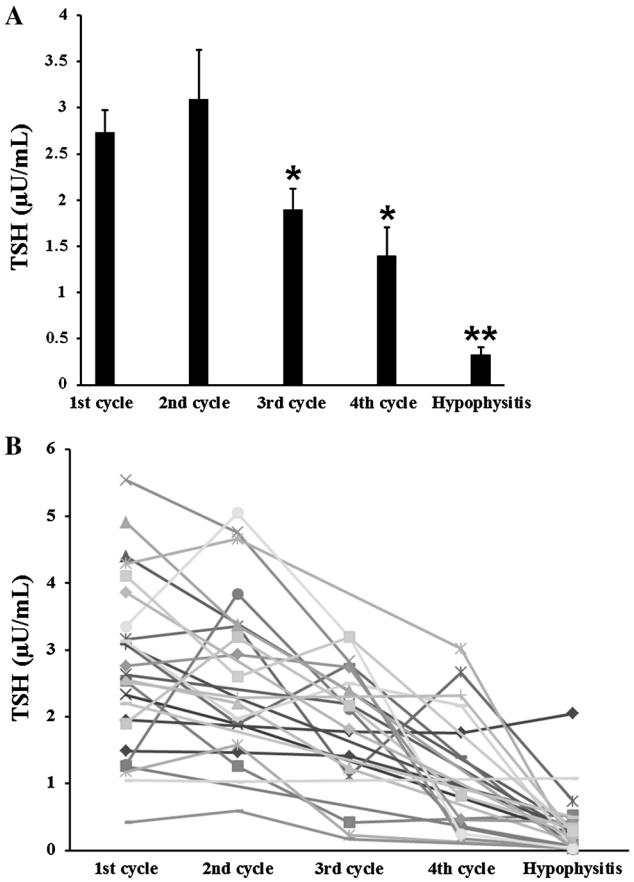

Fig. 3 A progressive decline in TSH values may occur prior to the diagnosis of IH and onset of clinical symptoms. **a** Depicts TSH values (mean ± SEM) in patients diagnosed with IH at our hospital prior to each cycle of Ipi and at the time of hypophysitis. *$p < 0.05$ versus 1st cycle (baseline) TSH value. **$p < 0.05$ versus cycle 4. Group comparisons were performed using the Student unpaired two-tailed *t* test (Wilcoxon rank sum test was used when the Wilk-Shapiro test indicated that data were not normally distributed). **b** Plots TSH values in each IH patient during treatment with Ipi and at the time of hypophysitis diagnosis

Treatment of IH and longitudinal outcomes

Glucocorticoid and thyroid hormone hormone replacement should be instituted early after the diagnosis of IH, and serum sodium concentration should be assessed. Androgen replacement can be deferred initially and potentially instituted at a later time point if hypogonadism persists. Treatment with growth hormone in patients with IH is contraindicated for obvious reasons. A portion of patients with IH may recover some anterior pituitary function. Thyroidal and gonadal axis recovery occurs more often than adrenal recovery, which has rarely been reported (Table 1) [17, 46, 52]. The time course for pituitary function recovery is not well-defined, largely due to variability in patient follow up, laboratory testing, and attempts to wean hormone replacement. Glucocorticoid treatment for other IRAEs and potential radiation therapy for intracranial metastases may also impact hormonal axis recovery. Hypopituitarism may persist in some patients indefinitely.

The development of hypophysitis may predict a more effective antitumor response in melanoma patients treated with Ipi. Overall survival appears to be improved in melanoma patients treated with Ipi who are diagnosed with IH [17]. This survival advantage persisted in an updated review of 228 melanoma patients treated with Ipi at our institution (median survival 21.4 vs. 9.7 months, $p = 0.008$ by log-rank test) (unpublished data). Improved survival was also reported in 32 melanoma patients with hypophysitis from a cohort of 269 treated with Ipi [53]. It is unknown whether patients with IH have an increased risk of other IRAEs.

Initial treatment strategies for IH generally included treatment with high dose glucocorticoids (approximately 1 mg/kg prednisone or equivalent) and permanent cessation of further therapy with Ipi [29]. Subsequent clinical experience has demonstrated that continuation and completion of Ipi therapy with or without temporary interruption may be safely tolerated in some patients with less severe cases of hypophysitis [16, 17, 54]. Physiologic or moderately supraphysiologic glucocorticoid dosages have also been used successfully in the treatment of IH [17, 18]. In a recent study, treatment with higher dosages of glucocorticoids did not appear to improve the frequency of pituitary function recovery or affect overall survival [18]. In the absence of significant hyponatremia, severe headache, or pituitary enlargement that compresses or approaches the optic apparatus (or other IRAEs which may require treatment), physiologic cortisol replacement may

be a reasonable alternative to the routine use of high-dose glucocorticoid regimens.

Glucocorticoid administration, when utilized to treat IRAEs, does not appear to inhibit the antitumor effects of Ipi or negatively impact survival. As noted above melanoma patients receiving glucocorticoids for the treatment of IH actually appear to have improved overall survival (vs. non-IH patients), and IH patients receiving high dosages of glucocorticoids (compared to physiologic replacement or moderately supraphysiologic dosages) did not have reduced survival. Results from additional studies have also been reassuring. High dosages of dexamethasone did not impact tumor growth inhibition by previously administered CTLA-4 antibody on implanted fibrosarcoma cells [55]. In a study of melanoma patients receiving Ipi, the development of an IRAE was associated with a greater probability of antitumor response and greater duration of treatment response. All patients in that study with a complete treatment response received high dosages of glucocorticoids. Additionally, glucocorticoid administration among responders did not have a significant effect on the duration of response [52]. Patients with Ipi-related enterocolitis who were treated with systemic glucocorticoids appeared to have a greater tumor response versus those patients without enterocolitis [56]. Other studies have also reported an association between severe IRAEs (which were presumably treated with systemic glucocorticoids) and treatment response rate or disease control rate [57, 58]. In melanoma patients with long-term follow up, prolonged glucocorticoid treatment for IRAEs did not appear to affect survival [59]. Although the sum of available evidence to date appears to suggest that glucocorticoid administration for the treatment of IRAEs does not negatively impact survival in patients receiving Ipi, selection bias may influence some of these results. Patients with longer survival by definition have a greater period for observation and may also potentially receive a higher number of Ipi doses, factors which could increase the likelihood of IRAEs. Physiologic glucocorticoid replacement may be prudent in mild cases of IH if there is no clear benefit from high-dose regimens.

Mechanism of IH

The precise mechanism(s) for IH remains unclear, but recent studies have provided evidence that multiple pathways might contribute to the development of hypophysitis. Treatment with Ipi putatively releases an autoimmune process targeting unidentified pituitary antigens. Consistent with this hypothesis, pituitary autoantibodies recognizing thyrotrophs, corticotrophs, and gonadotrophs were identified in the serum of patients with IH (pituitary autoantibodies were not detectable in these patients before treatment with Ipi), but these antibodies were absent in a group of patients receiving Ipi who did not develop hypophysitis [45]. In a mouse model, administration of anti-CTLA-4 was also able to induce the production of pituitary autoantibodies [45]. Interestingly, Iwama et al. also demonstrated ectopic CTLA-4 expression in mouse and human anterior pituitary cells. Deposition of C3, C3d, and C4d onto mouse pituitary cells occurred following treatment with CTLA-4 antibody, suggesting activation of the classical complement pathway [45]. Direct binding of Ipi to anterior pituitary cells may also activate antibody-dependent cell-mediated cytotoxicity (ADCC) [60, 61]. Ipilimumab is an IgG1-based monoclonal antibody, and tremelimumab is an IgG2 antibody. Both of these IgG subclasses can activate the classical complement pathway and ADCC. IgG4-based antibodies, such as nivolumab, pembrolizumab, and the PD-1L agent BMS-936559/MDX1105, can not activate the classical complement pathway and are less effective for ADCC [62–65]. Another PD-1 antibody, pidilizumab, and the PD-1L agents MEDI4736, MPDL3280A, and MSB0010718C are IgG1-based therapies. It is unknown whether PD-1 or PD-L1 is expressed by pituitary cells, and clinical data from many of these agents is limited.

Two recent studies identified individuals with germline CTLA-4 mutations. The majority of these patients had severe autoimmune diseases, many which resembled IRAEs that can occur after treatment with Ipi (including colitis and autoimmune thyroiditis). Notably, no case of hypophysitis or hypopituitarism was reported among the 25 individuals with CTLA-4 mutations [66, 67]. The absence of pituitary abnormalities in these individuals supports the hypothesis that pituitary CTLA-4 expression is a significant factor which mediates IH.

Our group recently assessed CTLA-4 gene expression in normal pituitary glands and a large number of pituitary adenomas. CTLA-4 expression varied widely in both groups; this variability may influence the risk of developing hypophysitis after treatment with Ipi. CTLA-4 expression did not differ between normal pituitary glands and pituitary tumors and did not appear to predict tumor behavior [68]. The physiologic role of CTLA-4 in the pituitary is unknown.

CTLA-4 expression has been demonstrated in human placental trophoblasts and in myocytes of patients with inflammatory myopathies. It has been hypothesized that peripheral CTLA-4 expression may help maintain maternal-fetal tolerance and protect against immune injury [69–72]. CTLA-4 expression has been demonstrated in a variety of solid and hematologic malignancies [73–76]. Although PD-L1 expression may help tumors evade immune surveillance [77–79], it is not clear that CTLA-4 has similar effects [73, 80–83].

Conclusions and future directions

Greater understanding of immune regulation has yielded tremendous advances in the treatment of melanoma, and results from ongoing studies suggest that immune checkpoint inhibitors will likely assume an expanding role in the treatment of various malignancies. The number of patients with IH and other endocrine IRAEs will likely increase in future years. The potential for durable treatment responses and long-term survival in patients receiving immunotherapy highlights the importance of prompt recognition of IH and appropriate treatment. Fortunately, visual defects are extremely rare in patients with IH. DI is also rare. Anterior hypopituitarism, especially thyroidal and gonadal deficiencies, may reverse in some patients or be permanent. Declining TSH values and/or relative pituitary enlargement can precede the development of clinical symptoms or overt biochemical hypopituitarism. Radiographic changes in patients with IH can be mild and overlooked; it is important to routinely compare any head MRI obtained during therapy with Ipi (or soon after treatment completion) with prior imaging studies. FT4 levels (in addition to TSH) should also be checked prior to each treatment cycle in patients receiving Ipi and PD-1 agents, since both primary thyroid dysfunction and hypophysitis can occur (sometimes concurrently). In patients with IH, thyroid hormone and glucocorticoid replacement should be initiated promptly, and serum sodium concentration should be evaluated. No prospective study has compared physiologic replacement versus treatment with high-dose glucocorticoids in patients with IH. Limited retrospective data did not suggest that clinical outcomes were superior in IH patients receiving pharmacologic dosages of glucocorticoids. In the absence of data which demonstrates clinical benefit from high-dose glucocorticoid therapy, it may be reasonable to reserve higher dosages for patients with significant hyponatremia, severe headache, or pituitary enlargement that threatens the optic apparatus. Further treatment with additional cycles of Ipi is not routinely contraindicated in patients who develop IH.

Hypophysitis occurs in a significant minority of patients treated with Ipi and appears to be the most common endocrine IRAE from this medication. Conversely, hypophysitis appears to be an extremely rare event in patients treated with other immunotherapies, such as anti-PD-1/PD-L1 agents. Male gender and older age may be risk factors for the development of IH. Concurrent treatment with chemotherapy or targeted therapies does not appear to increase the risk of IH.

Tumor mutational load and more specifically, the presence of specific shared tumor neoepitopes (which appear to resemble certain viral and bacterial antigens), may predict treatment efficacy and overall survival in patients receiving Ipi [84]. Potential pituitary antigenic targets in patients with IH have not yet been identified. The development of pituitary autoantibodies in patients with IH and the association of IH with improved overall survival in melanoma patients suggest that hypophysitis may be a consequence of global immune activation from Ipi. Although general immune activation may contribute to the pathogenesis of IH, the comparative rarity of hypophysitis after treatment with immunotherapies that do not target CTLA-4, the apparent high variability of pituitary CTLA-4 expression, the ability of Ipi to activate the classical complement pathway and ADCC, and the apparent absence of hypophysitis or hypopituitarism in patients with germline CTLA-4 mutations all support the hypothesis that direct binding of Ipi to anterior pituitary cells may mediate hypophysitis. The high expression levels of CTLA-4 in a subset of pituitary adenomas raises the possibility that CTLA-4 may represent a novel direct therapeutic target for the treatment of aggressive pituitary tumors in selected patients. Additionally, a chelated 64Cu-isotope labeled anti-CTLA-4 monoclonal antibody has recently been developed for use in positron emission tomography [85]. If pituitary CTLA-4 expression levels do correlate with the development of IH, targeted imaging may be able to predict the risk of hypophysitis in patients treated with Ipi or possibly identify candidate patients with aggressive pituitary adenomas for therapeutic treatment with Ipi.

IH may also offer insight into the mechanisms of idiopathic autoimmune hypophysitis. It is unknown whether pituitary CTLA-4 expression is altered in these patients. T cells are the dominant mediators in a mouse model of autoimmune hypophysitis [86], and often comprise the majority of infiltrating lymphocytes in human cases [87, 88]. Two FDA-approved CTLA-4 fusion proteins, abatacept and belatacept, are commercially available and could represent useful tools for further research or perhaps have potential application in the clinical treatment of idiopathic autoimmune hypophysitis. Additional medications that target a number of immune pathways are currently under development. Off-target effects, such as IH, may yield further unexpected opportunities and biologic insights.

Compliance with Ethical Standards

Conflict of interest None.

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