Ipilimumab-Induced Hypophysitis: A Detailed Longitudinal Analysis in a Large Cohort of Patients With Metastatic Melanoma

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Context: Ipilimumab (Ipi) is approved by the Food and Drug Administration for the treatment of unresectable or metastatic melanoma. Little is known about Ipi-induced hypophysitis (IH), an important treatment complication.

Objective: The objectives of the study were as follows: 1) to examine the prevalence of IH, 2) to characterize the clinical course and treatment outcomes in IH, 3) to identify the risk factors for the development of IH, and 4) to determine optimal strategies for the management of IH.

Design: This was a retrospective review.

Setting: The study was conducted at a tertiary referral center.

Subjects: One hundred fifty-four adult patients with metastatic melanoma were evaluated at Massachusetts General Hospital and were treated with Ipi between March 2008 and December 2013.

Intervention(s): The intervention included treatment with Ipi.

Main Outcome Measure(s): Pituitary magnetic resonance imaging, pituitary hormone assessment, and patient survival were measured.

Results: IH was diagnosed in 17 patients (11%). Male gender ($P = .02$) and older age ($P = .005$), but not the cumulative dose of Ipi, were risk factors for IH. All patients with IH had anterior hypopituitarism (none had diabetes insipidus). Hypopituitarism was persistent in most individuals (76%). Diffuse pituitary enlargement was observed exclusively in all cases of IH and, upon retrospective review of magnetic resonance imaging scans, this finding preceded the clinical diagnosis of hypophysitis in eight patients. Pituitary enlargement resolved rapidly (within 40 d in seven of seven patients). Median survival in patients with IH was 19.4 vs 8.8 months ($P = .05$) in the remainder of the cohort.

Conclusions: Male gender and older age are risk factors for IH. Pituitary enlargement is sensitive and specific for IH in the appropriate setting, can precede the clinical diagnosis, and resolves rapidly. Anterior pituitary function recovery is uncommon. The incidence of hypophysitis may positively predict survival in melanoma patients treated with Ipi. **(*J Clin Endocrinol Metab* 99: 4078–4085, 2014)**

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Abbreviations: CNS, central nervous system; CTLA-4, cytotoxic T-lymphocyte antigen-4; FT4, free T_4; IH, Ipi-induced hypophysitis; Ipi, ipilimumab; IRAE, immune-related adverse event; MGH, Massachusetts General Hospital; MRI, magnetic resonance imaging.

Ipilimumab (Ipi) was approved in 2011 by the US Food and Drug Administration for the treatment of unresectable or metastatic melanoma, and ongoing studies are evaluating Ipi to treat other solid tumors including prostate cancer, small-cell lung cancer, ovarian cancer, gastric cancer, and bladder cancer (1–5). Ipi is a fully humanized monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4), an inhibitory molecule expressed on antigen-stimulated T cells, and thereby enhances T-cell activation. Immune-related adverse events (IRAEs) may occur in some patients as a consequence of increased T-cell activation (6). Multiple endocrine abnormalities, including hypophysitis, primary hyper- and hypothyroidism, and primary adrenal insufficiency have been reported in patients treated with Ipi (7, 8).

A limited number of ipilimumab-induced hypophysitis (IH) cases have previously been reported, and relatively little is known about this important treatment complication. The antigenic target(s) in IH has not been identified. The precise incidence of IH and risk factors for its development remain largely undefined. Long-term clinical and radiological follow-up has been reported in very few cases of IH. It is unknown whether the incidence of IH predicts the length of survival. Whether pituitary enlargement is specific for hypophysitis in patients treated with Ipi has not been well established. Although many patients with IH receive high doses of glucocorticoids, it is not clear whether this practice is necessary or represents an optimal management strategy in this population (7).

The use of Ipi and other immunotherapeutic agents in the treatment of various malignancies is expanding; it is important to define the incidence and clinical characteristics of hypophysitis and other IRAEs. We reviewed the clinical, laboratory, and radiological records of all patients with metastatic melanoma who were evaluated at the Massachusetts General Hospital (MGH) and treated with Ipi to identify potential risk factors for IH and devise strategies for the management of this complication. This series of patients with IH represents a large collection of cases and includes detailed longitudinal follow-up.

Subjects and Methods

The study was performed at MGH (Boston, Massachusetts) and was approved by the Institutional Review Board of Partners HealthCare (Boston, Massachusetts). Adult patients with metastatic melanoma treated with Ipi at MGH between March 2008 and December 2013 were included in the study. The study group included 154 individuals who received Ipi as part of prior research protocols (at doses of 3 mg/kg or 10 mg/kg) and those who were treated with Ipi after Food and Drug Administration approval of the medication (3 mg/kg). Patient medical records, including provider encounters, laboratory results, medication records, and radiological images were reviewed in detail. The vital status of the study group and dates of death were confirmed by hospital medical records and the Social Security Death Index. All patients with IH continued their clinical care at MGH through the end of the study period or until death. The median length of follow-up after the initiation of Ipi was 11.5 months (range 2.9–35.7 months) in patients with IH. One female patient was diagnosed with IH at an outside facility and placed on glucocorticoid and thyroid replacement. Laboratory values, radiological imaging, and initial treatment details at the time of her diagnosis were unavailable.

Serum hormone measurements were performed by chemiluminescence immune assays as follows: cortisol (Architect; Abbot Laboratories), ACTH and IGF-1 (Immulite 2000; Siemens Medical Solutions Diagnostics), TSH, free T_4 (FT4), total T_4, T, LH, and prolactin (ADVIA Centaur; Siemens Healthcare Diagnostics), and FSH (Elecsys; Roche Diagnostics). The frequency of hormonal measurements and attempts to wean hormone replacement following the diagnosis of IH varied among patients, according to physician practice.

Statistical analysis was completed using JMP (version 11; SAS Institute). All values are shown as means ± SEM, unless otherwise noted. Values of $P < .05$ were considered statistically significant. Group comparisons for continuous outcomes 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) and those for binary outcomes using the Fisher's exact test, where effect size was estimated by odds ratios. Survival was evaluated by the log-rank test.

Results

Group characteristics

IH was diagnosed in 17 of 154 patients (11.0%) in our cohort. Fifteen patients with IH were male, and two were female (Table 1). The prevalence of IH in males was 15.6%, compared with 3.6% in females [$P = .02$, odds ratio 4.73 (95% confidence interval 1.27–30.79)]. Patients with IH were also significantly older compared with the remainder of the cohort (68.2 ± 2.4 vs 59.9 ± 1.0 y, $P = .005$) (Table 2). The prevalence of hypophysitis appeared to be greater in patients treated with Ipi more recently (14.9% of patients treated after Food and Drug Administration approval of the medication in March 2011) compared with earlier patients (6.0%), but this difference was not statistically significant ($P = .11$).

The mean number of Ipi treatment cycles did not differ in patients diagnosed with IH compared with those without IH (3.06 ± 0.18 vs 3.72 ± 0.23, respectively; $P = .27$). IH was diagnosed after a median of 8.4 weeks (interquartile range 6.9 to 10.3 wk) after the initiation of Ipi (Table 2). One patient was diagnosed with IH approximately 4 months after completing four cycles of treatment with Ipi. [This patient was receiving treatment with nivolumab at

Table 1. Cases of Ipilimumab-induced Hypophysitis

Case Number	Age, y	Gender	Disease Stage	Ipi Dosage, mg/kg	Number of Cycles Prior to Diagnosis	Hormone Axis Recovery	Survival After Ipi, mo	Additional IRAEs	Symptoms at Diagnosis
1	73	M	4c	3	3		5.3		HA, fatigue, LOA, hypoNa
2	59	M	4c	3	3	Gonadal	11.5+		HA, fatigue, hypoNa
3	65	M	3b	10	2		35.7+	Colitis	HA, confusion
4	60	M	3b	10	2		23.3		HA
5	73	M	4c	3	4		9.7		HA, fatigue, LOA, dizziness, blurry vision, hypoNa
6	75	M	4c	10	3	Gonadal	7.1		Fatigue, LOA, weight loss, hypoNa
7	66	F	4c	3	4		24.6+		Unknown
8	80	M	4c	10	4		31.3+		HA, fatigue, nausea, hypoNa
9	82	M	4b	3	4	Adrenal	11.8+		HA, fatigue, cold intolerance
10	40	M	3c	10	2		19.4		HA, nausea
11	71	M	4c	3	3		10.0	Panc enzyme incr	HA, hypoNa
12	78	M	4c	3	3	Thyroidal	8.7+	Colitis	Fatigue
13	75	F	4c	3	3		18.4	Ileitis	HA, hypoNa
14	70	M	4c	3	3		6.4+	Colitis, dermatitis	HA, fatigue, LOA, nausea, hot flashes
15	70	M	4c	3	4		2.9+		HA, fatigue
16	59	M	4c	3	2		13.6+		HA, nausea
17	65	M	4c	3	3		6.3+		HA, fatigue, hypoNa

Abbreviations: F, female; HA, headache; hypoNa, hyponatremia, incr, increase; LOA, loss of appetite; M, male. + indicates that the patient was alive at the date of the most recent follow-up.

the time of his diagnosis. Records indicated, however, that symptomatic new onset central hypothyroidism developed approximately 2 months after the completion of ipilimumab (prior to the initiation of nivolumab), and magnetic resonance imaging (MRI) scans demonstrated relative pituitary enlargement at this time.]

Most patients diagnosed with IH (13 of 17) were treated with a dose of 3 mg/kg of Ipi (four patients received treatment with 10 mg/kg). Additional IRAEs were diagnosed in five patients with IH (Table 1).

Clinical, laboratory, and radiological findings in patients with IH

The most common presenting symptom of IH was headache (14 of 17), and it was the sole symptom in two patients. Fatigue was also a common symptom (10 of 17). Additional reported symptoms included nausea (4 of 17), decreased appetite (4 of 17), cold intolerance (1 of 17), hot flashes (1 of 17), weight loss (1 of 17), dizziness (1 of 17), blurry vision (1 of 17), and confusion (1 of 17). Hyponatremia occurred in eight patients; serum sodium nadirs

Table 2. Clinical Characteristics of Patients With and Without Hypophysitis

	+ Hypophysitis (n = 17)	No Hypophysitis (n = 137)	*P* Value
Age, y	68.2 ± 2.4	59.9 ± 1.0	.005
Male, %	88.2	61.3	.02
Number of Ipi cycles	3.06 ± 0.18	3.72 ± 0.23	NS
Median time until IH diagnosis, wk, IR	8.4 (6.9–10.3)		
Median Survival after Ipi, mo	19.4	8.8	.05
Disease stage, n			
3a	0	1	
3b	2	0	
3c	1	3	
4a	1	7	
4b	1	8	
4c	12	118	

Abbreviations: IR, interquartile range; NS, not significant.

ranged from 113 to 134 in these patients. Nine patients with IH had central nervous system (CNS) metastases, and six of these patients developed hyponatremia. Three of the four cases with significant hyponatremia (nadir < 130) occurred in patients who were diagnosed with IH in 2011 or earlier.

All patients with IH developed anterior hypopituitarism. No patient had evidence of diabetes insipidus. Multiple anterior pituitary hormone deficiencies were documented in 14 patients. Central hypothyroidism, defined as a low serum FT4 and low or inappropriately normal TSH, occurred in all cases of IH. Adrenal insufficiency, defined as a morning serum cortisol below 3 μg/dL or peak iv cortrosyn-stimulated (250 μg) value below 18 μg/dL, was observed in 7 of 14 patients. Plasma ACTH was measured in six of these seven patients, and all values were below 10 pg/mL (laboratory assessment of adrenal function was indeterminate in eight patients, and two patients among this group had undetectable levels of ACTH but did not have cortisol levels assessed prior to exogenous glucocorticoid administration.) Prolactin levels were measured in 13 patients; the levels were below 3.3 ng/mL in 12 of these patients. T levels were assessed in 14 patients and were low in all cases. Serum T was undetectable in seven individuals, less than 129 ng/dL in six additional patients, and was 201 ng/dL in one individual. Concurrent levels of FSH or LH were measured in 11 patients. Levels of LH did not exceed 2.2 IU/L, and FSH levels were below 6.5 mIU/mL. Serum estradiol or progesterone was not measured in either female patient with IH, both of whom were postmenopausal. IGF-1 levels were measured in six patients at the time of the diagnosis of IH, and it was low in one patient. Serum levels of GH were not assessed in any patient.

No patient with IH had a known metastasis to the sellar or suprasellar region. Eight patients received cranial radiotherapy for CNS metastases prior to the diagnosis of IH. Six of these patients received radiation treatment less than 3 months before the diagnosis of IH. All eight of these patients had normal TSH levels at baseline when treatment with Ipi was initiated, and levels decreased significantly at the time of IH diagnosis.

MRI demonstrated mild to moderate diffuse pituitary enlargement in all patients with IH. Pituitary enlargement did not cause compression of the optic apparatus in any patient. Stalk thickening was observed in 10 cases. Homogeneous or heterogeneous patterns of enhancement were visible in the pituitaries of IH patients after contrast administration. Upon retrospective review of MRIs, relative pituitary enlargement preceded the clinical diagnosis of hypophysitis in eight patients, often by several weeks. Two of these patients were asymptomatic at the time of imaging. Twenty-seven patients treated with Ipi who were not diagnosed with hypophysitis had brain MRIs performed less than 3 months prior to the initiation of Ipi, during treatment with Ipi, and less than 3 months after the completion of Ipi. Pituitary enlargement did not occur in 26 of these patients. Mild pituitary enlargement occurred in one patient during Ipi treatment and was resolved on a subsequent MRI. This finding may have represented an undiagnosed case of IH. (This patient developed headaches after treatment with Ipi was initiated. The headaches were treated with dexamethasone and resolved. The patient had previously undergone a total thyroidectomy and had chronically suppressed TSH values secondary to supraphysiological dosages of levothyroxine. No additional hormone measurements were performed in this patient; Figures 1 and 2).

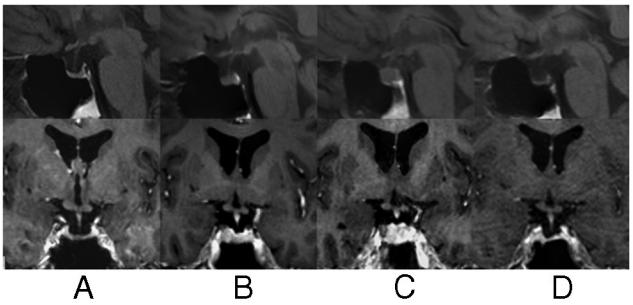

Figure 1. Pituitary enlargement and resolution in a 59-year-old male with IH. Panel A depicts the pituitary gland is shown 1 month prior to the initiation of Ipi (panel A). Mild interval enlargement of the pituitary is evident after two cycles of Ipi (the patient was asymptomatic; panel B). Further enlargement is visible approximately 1 week after receiving a third cycle of Ipi (the patient had symptoms of headache and fatigue, and laboratory analysis demonstrated anterior hypopituitarism; panel C). Panel D demonstrates complete resolution of pituitary enlargement approximately 1 month later.

Management of IH and longitudinal outcomes

Fifteen patients were treated with high-dose glucocorticoids after the diagnosis of IH. One patient transiently received mildly supraphysiological dosages of prednisone

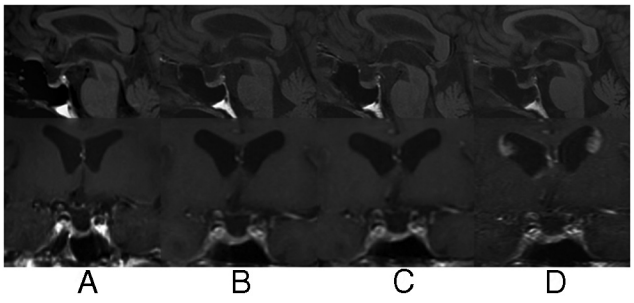

Figure 2. Pituitary enlargement does not occur in individuals receiving Ipi who do not develop hypophysitis. A 70-year-old male received 16 cycles of Ipi (10 mg/kg). Panels A and D depict the pituitary gland 5 days before the initiation of Ipi and 2 weeks after completion of treatment, respectively. Panels B and C shows the pituitary gland during treatment with Ipi, after approximately 1.5 years and 2.5 years of therapy, respectively.

for a few days but otherwise was treated with physiological glucocorticoid replacement dosages of prednisone. Patients treated with high-dose glucocorticoids typically received prednisone 60 mg daily, followed by a taper to a physiological replacement dose over a variable period of time (often 6–8 wk). Thyroid hormone replacement was also begun at the time of IH diagnosis. T replacement was typically started at a later date if hypogonadism was persistent. Additional cycles of Ipi were administered in three patients after the diagnosis of IH (including the one patient who received treatment with low doses of prednisone).

Hypopituitarism was persistent in most patients (13 of 17) at the time of the last follow-up (median length of follow-up 11.5 mo; range 2.9–35.7 mo). Adrenal recovery occurred in one patient, thyroidal recovery was observed in one patient, and gonadal function normalized in two patients. Pituitary hormone deficiencies have not recovered in one patient 3 years after the diagnosis of IH.

Radiographic resolution of pituitary enlargement was observed in 15 patients with IH (two patients have not yet had a repeat MRI). Reversal occurred rapidly and was observed in all patients (seven of seven) who underwent repeat imaging within 40 days of the diagnosis of IH. Pituitary enlargement resolved in one patient after only 12 days. This patient received moderate supraphysiological dosages of glucocorticoids (one dose of hydrocortisone 50 mg iv, followed by one dose of prednisone 15 mg, and then prednisone 10 mg daily thereafter until the patient died 4 mo later).

Median survival after the initiation of treatment with Ipi was 9.8 months in the entire cohort. The median survival in patients diagnosed with IH was 19.4 months, compared with 8.8 months in those without IH. The difference between the groups was borderline significant ($P = .05$). Most patients in both groups had stage 4 disease (Table 2 and Figure 3).

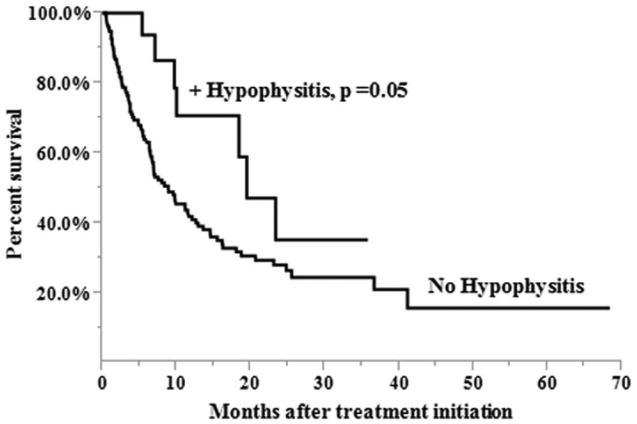

Figure 3. Kaplan-Meier plots for survival in metastatic melanoma patients, with and without hypophysitis, after the initiation of Ipi.

Nonhypophysitis endocrine IRAEs

Eight patients potentially developed primary hypothyroidism as a consequence of treatment with Ipi. All of these patients had normal TSH levels at baseline prior to treatment with Ipi. Two patients developed transient thyrotoxicosis during treatment with Ipi, followed by primary hypothyroidism. Six patients had newly elevated TSH levels during Ipi treatment or immediately after the conclusion of therapy, but they did not have preceding laboratory results demonstrating thyrotoxicosis (or results suggesting recovery from nonthyroidal illness). Four of these six patients had elevated TSH levels and concurrent low levels of FT4. Two patients had mild TSH elevations (6.6 and 6.8), but FT4 levels were not measured.

Primary adrenal insufficiency was not diagnosed in any individual in the cohort.

Discussion

IH is a recognized complication of treatment with Ipi, but relatively little information exists regarding its clinical course, associated radiological findings, and optimal management. Our cohort represents a large collection of cases, it is the first series to identify clinical risk factors for the development of IH and assess survival in patients with IH, and provides detailed biochemical and radiological information at the time of IH diagnosis, during follow-up, and in comparison with patients without IH.

IH was diagnosed in approximately 11% of our cohort, which is within the range reported by prior studies (9–14). Variations in the observed incidence rate of IH have been attributed to differences in Ipi dosage, associated medication use, the intensity and frequency of hormonal monitoring, and, perhaps most significantly, clinical awareness and suspicion for IH (7, 15). The prevalence of IH in our cohort appeared to be higher in patients treated more recently, likely reflecting a greater clinical awareness of this treatment complication. Our data did not suggest that the cumulative dose of Ipi affects the incidence of IH. A large majority of patients with IH received the standard dose of Ipi, 3 mg/kg, and the number of treatment cycles did not differ in patients with IH compared with those without IH. No case of IH occurred in patients receiving greater than four cycles of treatment with Ipi.

Pituitary enlargement was a highly sensitive and specific indicator of hypophysitis in patients treated with Ipi. On retrospective review, relative radiographic enlargement of the pituitary preceded the diagnosis of IH in eight patients. Two of these patients were asymptomatic, but most also reported the presence of headaches. We recommend that pituitary function be fully evaluated in any pa-

tient treated with Ipi who exhibits gross pituitary enlargement or relative enlargement compared with prior imaging studies. Radiology reports of brain MRIs in patients receiving Ipi should routinely include comparisons of pituitary size with prior studies. Although pituitary enlargement seems to be a sensitive indicator for IH, we do not recommend that clinicians obtain routine MRIs in asymptomatic patients treated with Ipi because most patients do not develop IH. In agreement with manufacturer recommendations (16), we routinely measure thyroid function tests before each Ipi treatment cycle. Declining thyroid function test values and/or the presence of severe headache and fatigue should prompt further investigation with an MRI, pituitary function tests, and serum sodium evaluation. The consistent development of central hypothyroidism in all patients with IH in our cohort complements recent observations that CTLA-4 is expressed preferentially by thyrotropin-secreting cells in the anterior pituitary (17).

Homogeneous or heterogeneous patterns of enhancement were visible in the pituitaries of IH patients after contrast administration. Metastatic disease is a consideration in the differential diagnosis of patients with pituitary enlargement who are receiving Ipi. Pituitary enlargement rapidly resolved in our patients with IH. Our data suggests that persistence of gland enlargement 2 months after the diagnosis of IH may indicate the presence of an alternative process, such as metastatic disease. Radiographic enlargement could potentially persist for longer periods of time in patients who receive additional cycles of Ipi after the diagnosis of IH. (Three of our patients received additional treatment with Ipi after the diagnosis of IH, and two of these individuals have not yet had subsequent MRIs.)

The degree of pituitary enlargement in patients with IH was mild. Chiasm compression did not occur in any case of IH. Patient morbidity from IH was primarily related to the presence of pituitary hormone deficiencies, headache, and hyponatremia. Because almost all patients in our series and others were treated with high-dose glucocorticoids, it is not clear whether higher dosages of glucocorticoids are superior to physiological replacement regimens in the initial management of IH, based on our data. There are some concerns that treatment with high dosages of glucocorticoids may even affect the antitumor efficacy of Ipi, although studies suggest that survival is not decreased in these patients and that the function of activated T cells is not inhibited by glucocorticoids (12, 18). Hormonal deficits persisted in most our patients despite the usage of high-dose glucocorticoids and pituitary enlargement resolved most rapidly (12 d) in the patient transiently treated with mildly supraphysiological dosages of prednisone.

In the absence of comparative data that demonstrates an advantage with higher dosages of glucocorticoids, based on our experience, we presently recommend that high-dose glucocorticoid therapy be reserved for IH patients with significant hyponatremia, severe headache, or substantial pituitary enlargement (that abuts or approaches the optic chiasm). Although treatment with additional cycles of Ipi is not contraindicated in patients with IH (and can be beneficial to many patients), we speculate that further therapy could potentially lengthen the duration of some symptoms of IH, such as headache.

Two smaller studies have reported higher rates of thyroidal and gonadal function recovery compared with our series (19). One patient in our cohort demonstrated the recovery of adrenal function. To our knowledge adrenal recovery has been reported in only one other patient with IH (12). Because GH replacement would be contraindicated in patients receiving Ipi (due to the presence of an active malignancy), few data exist regarding the status of the GH axis in patients with IH. Differences in the reported rates of pituitary hormone recovery likely result from variations in patient follow-up (due to limited patient survival), frequency of hormonal evaluation, and attempts to wean hormone replacement. Our manuscript is limited by the lack of standardized patient follow-up and the retrospective design. Hormone replacement was rarely weaned in our cohort, even in cases when laboratory results suggested possible partial recovery of pituitary function. We recommend that pituitary hormone deficiencies be periodically reevaluated after the resolution of IH. We anticipate that the likelihood of hormone recovery is lower after a substantial period of time has passed since the occurrence of IH.

Diagnoses of IH were based on the combined presence of new hypopituitarism and pituitary enlargement after treatment with Ipi. Histological specimens have not been obtained for any previously reported case of IH. Although eight patients with IH in our cohort had previously received cranial radiotherapy for CNS metastases prior to the diagnosis of IH, it seems unlikely that radiation treatment affected pituitary function in these individuals at the time of IH diagnosis. Six of these patients received radiation treatment less than 3 months before the diagnosis of IH. Furthermore, as previously noted, all eight of these patients had normal TSH levels at baseline when treatment with Ipi was initiated, and levels decreased significantly at the time of IH diagnosis. It is possible, however, that the effects from radiation could influence the probability of long-term pituitary function recovery in some of these patients with IH. Most of these patients received proton beam stereotactic radiosurgery to isolated metastases that were not located near the pituitary or hypothal-

amus. Two patients underwent fractionated whole-brain radiotherapy, and one patient received fractionated proton therapy to a retinal metastasis.

Three patients received additional Ipi treatment cycles after the diagnosis of IH. Earlier studies have advocated that treatment with Ipi ought to be terminated in patients with IH, but this practice has been questioned by some groups (19–21). In the absence of additional IRAEs, such as severe colitis, we do not believe that the presence of IH necessarily precludes further treatment with Ipi.

Prior studies have suggested that the presence of IRAEs in patients treated with Ipi may be associated with greater antitumor efficacy and clinical benefit (21). Selection bias may have affected these results. Patients with increased survival necessarily have greater time periods for observation and may also receive additional doses of Ipi, thereby potentially increasing the likelihood of IRAEs. In our cohort, length of survival was greater in patients with IH compared with those without IH. The number of Ipi treatment cycles administered did not differ in the two groups. With the exception of one patient (who was diagnosed with IH 4 months after completion of treatment with Ipi), IH was diagnosed prior to the completion of planned treatment or shortly thereafter.

Our study demonstrates that male gender and older age are risk factors for the development of IH, which confirms early observations regarding male preponderance (7) and contrasts with observations in lymphocytic hypophysitis (22). The two women with IH in our cohort were 75 and 66 years old. It is tempting to speculate that the presence of higher estrogen levels attenuates the risk of developing IH. Most women in our cohort who received Ipi, however, had ages greater than 50 years. Male gender remained a significant predictor of IH if women below the age of 50 years were excluded from the analysis (data not shown).

In conclusion, hypophysitis was diagnosed in 11% of the patients in our cohort treated with ipilimumab, and male gender and older age were risk factors for the development of IH. The presence of IH appears to be associated with longer survival and relatively low morbidity in patients who receive appropriate hormonal replacement therapies. Based on this series, pituitary imaging is appropriate in Ipi-treated patients who develop significant headache or have declining thyroid function tests. Relative transient pituitary enlargement in patients receiving Ipi appears to be sensitive and specific for IH and may precede the onset of clinical symptoms or development of overt anterior hypopituitarism on laboratory tests. It remains unclear whether higher dosages of glucocorticoids are superior to physiological replacement regimens in the initial management of IH. The consistent development of central hypothyroidism in patients with IH (vs other pituitary hormone axes, which may be spared) and the comparative rarity of reported cases of hypophysitis in patients treated with nivolumab (a monoclonal antibody, which blocks programmed death 1 receptors on T lymphocytes) also support the hypothesis that pituitary (thyrotroph and lactotroph cells) expression of CTLA-4 is a significant factor, which mediates IH (17).

Acknowledgments

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