Immune checkpoint inhibitor-induced hypophysitis: lessons learnt from a large cancer cohort

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ABSTRACT

Immune checkpoint inhibitors (ICIs) can cause pituitary dysfunction due to hypophysitis. We aimed to characterize ICI-induced hypophysitis and examine its association with overall survival in this single-center retrospective cohort study of adult patients with cancer who received an ICI from January 1, 2012 through December 31, 2016. A total of 896 patients were identified who received ipilimumab alone (n=120); ipilimumab and nivolumab (n=50); ipilimumab before or after pembrolizumab (n=70); pembrolizumab alone (n=406); and nivolumab alone (n=250). Twenty-six patients (2.9%) developed hypophysitis after a median of 2.3 months. Median age at the start of ICI was 57.9 years and 54% were men. Hypophysitis occurred in 7.9% of patients receiving ipilimumab alone or in combination or sequence with a programmed cell death protein 1 inhibitor; 1.7% after pembrolizumab alone, never after nivolumab alone. Secondary adrenal insufficiency occurred in all hypophysitis cases. Use of ipilimumab alone or in combination was associated with pituitary enlargement on imaging and mass effects more frequently than pembrolizumab alone. Occurrence of hypophysitis was associated with improved overall survival by univariate analysis (median 50.7 vs 16.5 months; p=0.015) but this association was not observed in multivariable landmark survival analysis (HR for mortality 0.75; 95% CI 0.38 to 1.30; p=0.34) after adjusting for age, sex and malignancy type. To conclude, hypophysitis occurred most frequently after ipilimumab and manifested as anterior hypopituitarism affecting the corticotrophs more commonly than thyrotrophs and gonadotrophs. Mass effects and pituitary enlargement occurred more frequently in ipilimumab-induced hypophysitis. The association of hypophysitis with overall survival needs further investigation.

Significance of this study

What is already known about this subject?

- Immune checkpoint inhibitors are emerging as a cause of endocrine dysfunction.
- Pituitary dysfunction is more common with cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors as compared with programmed cell death protein 1 (PD-1) and programmed cell death protein-ligand 1 inhibitors.
- Some studies have suggested a favorable association between immune checkpoint inhibitor-induced pituitary dysfunction and survival.

What are the new findings?

- CTLA-4 inhibitor is more likely to cause pituitary enlargement on imaging and mass effects than PD-1 inhibitor.
- Adrenal insufficiency occurs in all cases of immune checkpoint inhibitor-induced pituitary dysfunction.
- The link between pituitary dysfunction and overall survival in patients with cancer needs further exploration in larger studies.

How might these results change the focus of research or clinical practice?

- A normal-appearing pituitary gland should not rule out hypopituitarism in PD-1 inhibitor-induced pituitary hormone deficiency.
- The non-specific nature of clinical features underlies the importance of screening especially for adrenal insufficiency and central hypothyroidism.
- Larger prospective studies to separately evaluate survival among patients receiving different classes of immune checkpoint inhibitors are required.

INTRODUCTION

Malignancies of various etiologies are able to escape T-cell-mediated destruction through expression of immune checkpoints on T-cells that repress the host's immunologic response.[1] Specifically, cytotoxic T-lymphocyte antigen 4 (CTLA-4) is a surface receptor protein that prevents T-cell proliferation early in the immune response to cancer, while programmed cell death protein 1 (PD-1) and programmed cell death protein-ligand 1 (PD-L1) actions occur downstream in the pathway where they inhibit activation and function of T-cells in peripheral tissue.[1 2] Immune checkpoint inhibitors (ICIs)

are monoclonal antibodies designed to block these checkpoints, thus resulting in a de-repression of T-cell-mediated destruction of cancer cells,[2 3] which is the basis of their efficacy in cancer therapy. The Food and Drug Administration-approved ICIs include CTLA-4 inhibitor ipilimumab; PD-1 inhibitors pembrolizumab, nivolumab and recently approved cemiplimab; and PD-L1 inhibitors atezolizumab, avelumab and durvalumab.

Endocrinopathies including hypophysitis,[4 5] thyroiditis,[6–10] diabetes mellitus,[11 12] adrenalitis[13] and autoimmune hypoparathyroidism[14 15] have now emerged as unintended sequelae of these novel therapies. As the indications for ICIs are continuously expanding, the population burden of these endocrinopathies is expected to increase, hence it is essential for clinicians to identify and initiate their treatment. While a recent meta-analysis[16] has summarized the occurrence of endocrinopathies in clinical trials, trial data are not optimal to fully characterize endocrinopathies because important information such as biochemical dysfunction and possible reversibility of such events has not been reported in detail.

Currently, several major academic centers have reported on their experience with ICI-induced hypophysitis with retrospective cohort studies.[4 7 17–24] While mortality benefit in patients with ipilimumab-treated melanoma was reported in two retrospective studies[4 5] but not in another,[25] a recent and prospective study in this field did support mortality benefit with hypophysitis in melanoma and small cell lung carcinoma.[26] However, this study did not adjust for potential confounding factors. The increased trend in oncology to expand the use of ICIs concomitantly or sequentially for various malignancies underlies the importance of examining outcomes of hypophysitis in such scenarios. Additionally, the impact of high-dose glucocorticoids for treatment of hypophysitis on survival has been unclear, as one study reported no difference[22] while another recently reported worse survival.[5] Hence, to further address these important questions, we aimed to characterize the frequency and course of hypophysitis from various ICIs including combination and sequential therapy, and to investigate its potential impact on survival in one of the largest cohorts of patients with various malignancies.

MATERIALS AND METHODS

Patient selection

We performed a retrospective cohort study of adult patients with cancer treated with CTLA-4 inhibitor ipilimumab or PD-1 inhibitors pembrolizumab and nivolumab at Mayo Clinic, Rochester, Minnesota, USA over a period of 5 years from January 1, 2012 through December 31, 2016. Only participants who had consented to have their medical records used for research were included in this study. Patients were followed to identify the occurrence of hypophysitis through December 31, 2017 (at least 1 year after initiation of an ICI). Hypophysitis was diagnosed if the patient met one or both of the following criteria:

1. MRI evidence of pituitary gland and/or stalk enlargement or contrast enhancement during evaluation.
2. Biochemical evidence of hypopituitarism even in the absence of imaging abnormalities if it was not explained by another etiology like head trauma, radiation, postpartum status, etc.

For patients receiving high-dose glucocorticoids for other immune-related adverse events (irAEs), secondary adrenal insufficiency due to hypopituitarism was diagnosed if the patient required replacement dose of glucocorticoid despite adequate tapering off the higher initial glucocorticoid dose, recognizing this does not definitively exclude inaccurate diagnosis due to the possibility of prolonged corticotroph suppression by exogenous glucocorticoid. However, of the 4 patients with this presentation, 3 had MRI evidence of pituitary enlargement, and the fourth patient had central hypogonadism requiring testosterone replacement, which strongly suggest the underlying etiology as hypopituitarism.

Study measures

The evaluations were performed based on clinical suspicion of the treating physician when a patient presented with features of pituitary hormone deficiency or mass effect. All laboratory testing was performed at the Mayo Medical Laboratory, Rochester, Minnesota. Adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), free thyroxine (T4), total triiodothyronine, follicle-stimulating hormone, luteinizing hormone, prolactin, and oestradiol were tested by Roche Cobas immunoassays (Roche, Indianapolis, Indiana, USA) ; serum cortisol by Beckman Coulter competitive binding immunoassay (Brea, California, USA); and testosterone (total and bioavailable) and insulin-like growth factor 1 (IGF-1) by liquid chromatography-mass spectrometry (Mayo Medical Laboratory). Thyroid irAEs were diagnosed by protocol-based thyroid function testing before each infusion of ICI or if clinical presentation warranted investigation. Central hypothyroidism was diagnosed by low free T4 with low or inappropriately normal TSH tested twice after excluding non-thyroidal illness. The main a priori outcome was to identify difference in overall survival between patients who developed hypophysitis versus those who did not following initiation of a CTLA-4 and/or PD-1 inhibitor; and secondarily to characterize the frequency and natural history of hypophysitis.

Statistics

Categorical variables were described as number and percentage, and continuous variables as median and range. Non-parametric statistical tests were used due to the non-normal distribution and small sample size; these were Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. Kaplan-Meier curves were used to describe overall survival (using log rank p value), and Cox proportional hazards regression model was used to adjust for potential confounding variables. Since hypophysitis occurs after the ICI initiation, we additionally performed landmark survival analysis where age (by decade), sex, cancer type (melanoma, lymphoma, others) and hypophysitis (treated as a time-varying covariate rather than only the presence or absence of it) were used as covariates. The survival analysis was also performed separately for patients with melanoma since other malignancies were present very infrequently in those who developed hypophysitis. Statistical significance was described as p value of <0.05. Statistical testing was performed using SAS software (V.9.04.01).

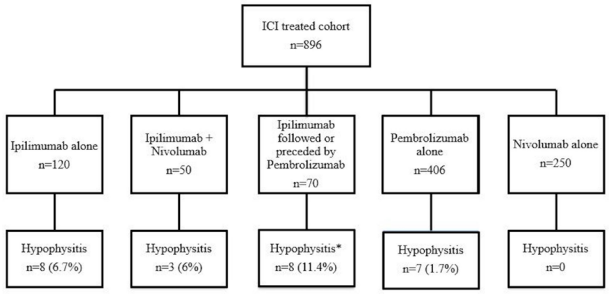

Figure 1 Flow chart demonstrating occurrence of hypophysitis from various immune checkpoint inhibitors (ICIs) in our study.

RESULTS

Study population

During the study period, a total of 896 patients were treated with CTLA-4 inhibitor or 1 of the 2 PD-1 inhibitors in use at that time, divided as ipilimumab alone (n=120); ipilimumab combined with nivolumab (n=50); ipilimumab before or after pembrolizumab (n=70), pembrolizumab alone (n=406), and nivolumab alone (n=250) (figure 1). The median age at the initiation of ICI was 61.7 (range: 19.9–93.4) years, 544 (60.7%) were men, and the most common malignancy was melanoma in 361 (40.3%) (table 1). This cohort was followed for a median of 14.8 months (range: 0.1–93.4; IQR 5–32.3). Individual characteristics of patients with ICI-induced hypophysitis are detailed in online supplemental table 1.

Frequency and presentation of hypophysitis

Overall, hypophysitis occurred in 26 (2.9%) of the 896 patients treated with an ICI, detailed in figure 1. Among the total of 240 patients who were treated with ipilimumab, 19 (7.9%) developed hypophysitis. Hypophysitis occurred more frequently in patients treated with ipilimumab alone as compared with pembrolizumab alone analyzing the entire cohort (6.7% vs 1.7%; p=0.009); and in patients with melanoma as compared with lung cancer and other malignancies (5.8% vs 0.6% vs 1.1%; p=0.001). However,

Table 1 Baseline characteristics of patients prior to initiation of ICI, comparing patients who developed hypophysitis and those who did not

Characteristics	Hypophysitis (n=26)	Lack of hypophysitis (n=870)	All ICI-treated patients (n=896)	p value
Male, n (%)	14 (53.8)	530 (60.9)	544 (60.7)	0.467
Age at ICI initiation (y), median (range)	57.9 (42.4–78.5)	61.7 (19.9–93.4)	61.7 (19.9–93.4)	0.402
Primary malignancy, n (%)				0.001*
Melanoma	21 (80.7)	340 (39.1)	361 (40.3)	
Lung	1 (3.8)	154 (17.7)	155 (17.3)	
Head and neck	2 (7.7)	21 (2.4)	23 (2.6)	
Breast	1 (3.8)	10 (1.2)	11 (1.2)	
Esophagus	1 (3.8)	12 (1.4)	13 (1.5)	
Lymphoma/leukemia		164 (18.9)	164 (18.3)	
Kidney		27 (3.1)	27 (3.1)	
Gastrointestinal		36 (4.1)	36 (4.0)	
Uterus/cervix		18 (2.1)	18 (2.0)	
Multiple myeloma		13 (1.5)	13 (1.5)	
Uroepithelium		12 (1.4)	12 (1.3)	
Ovary		10 (1.2)	10 (1.1)	
Skin		9 (1.0)	9 (1.0)	
Sarcoma		7 (0.8)	7 (0.8)	
Prostate		6 (0.7)	6 (0.7)	
Thyroid		5 (0.6)	5 (0.6)	
Hepatobiliary		5 (0.6)	5 (0.6)	
Bone		4 (0.5)	4 (0.4)	
Unknown		4 (0.5)	4 (0.4)	
Merkel cell		3 (0.3)	3 (0.3)	
Brain		3 (0.3)	3 (0.3)	
Pancreas		3 (0.3)	3 (0.3)	
Adrenal		3 (0.3)	3 (0.3)	
ICI therapy, n (%)				0.001†
Ipilimumab alone	8 (30.7)	112 (12.9)	120 (13.4)	
Ipilimumab f/b pembrolizumab	7 (26.9)	58 (6.7)	65 (7.2)	
Pembrolizumab alone	7 (26.9)	399 (45.9)	406 (45.3)	
Ipilimumab and nivolumab	3 (11.5)	47 (5.4)	50 (5.6)	
Pembrolizumab f/b ipilimumab	1 (3.8)	4 (0.5)	5 (0.5)	
Nivolumab alone	0 (0)	250 (28.7)	250 (27.9)	
Time from ICI start to last follow-up visit or death (mo), median (range)	30.6 (4.2–76.8)	14.3 (0.1–93.4)	14.8 (0.1–93.4)	0.007

*Comparison between melanoma, lung cancer and others.
†P=0.009 for ipilimumab alone versus pembrolizumab alone.
ICI, immune checkpoint inhibitor.

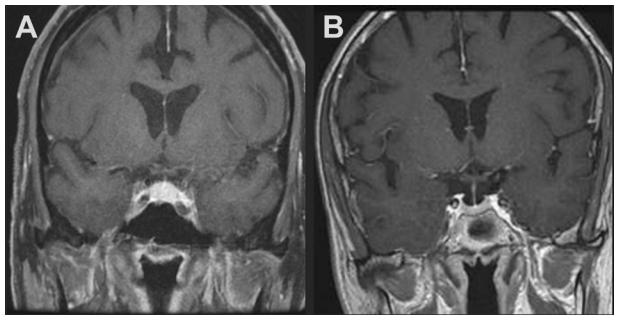

Figure 2 (A) T1-weighted MRI of the brain demonstrating enlarged and enhancing pituitary body and stalk after gadolinium administration in a patient who developed hypophysitis after ipilimumab alone. (B) T1-weighted MRI of the brain demonstrating normal-appearing pituitary gland in a patient who developed hypophysitis after pembrolizumab alone.

ipilimumab alone use was also more frequent in melanoma as compared with lung cancer (65% vs 28.8%; p<0.001). The most common malignancy in this cohort was melanoma (n=316), out of which 21 patients (5.8%) developed hypophysitis.

Hypophysitis developed after a median of 2.3 months following ICI initiation. The median age at initiation of ICI in patients with hypophysitis was 57.9 years, and 14 (53.8%) were men. ICIs were used for various malignancies, predominantly for melanoma in 21 patients (80.7%). Sixteen (64%) of 25 patients who underwent MRI within 3 months of clinical or biochemical features of pituitary dysfunction demonstrated classic pituitary enlargement and contrast enhancement on imaging (figure 2A) which usually preceded the hormone deficiency and resolved on follow-up imaging in all. Hypophysitis developed earlier in those with classic pituitary enlargement on imaging (median 2.6 vs 5.1 months; p=0.032). The most common presenting symptom was fatigue (n=16, 61.5%). Mass effect symptoms occurred in 13 patients (50%), all of which had classic MRI features, and presented as headache alone (n=11), headache with diplopia (n=1), and diplopia with visual field defect (n=1) (table 1).

Natural history and management of hypophysitis

Secondary adrenal insufficiency occurred in all 26, central hypothyroidism in 10 (38.5%) and secondary male hypogonadism in 3 (21.4%) of 14 men. AM cortisol was <1 µg/dL (reference range: 7–25 µg/dL) (<27.6 nmol/L) in 13 patients and <5 µg/dL (<138 nmol/L) in the rest; ACTH was <5 pg/mL (reference range: 7.2–63) (<1.1 pmol/L) in 11 patients and low/inappropriately normal in the rest. Eight out of 12 women were post-menopausal at the time of ICI initiation; 1 premenopausal woman developed hypogonadotropic hypogonadism, 2 maintained normal menstruation, and 1 had unknown status. IGF-1 was below normal in 1 of 4 tested. MRI evidence of pituitary enlargement occurred in 13 of 19 (68.4%) with ipilimumab either alone (figure 2A) or in combination or sequence with a PD-1 inhibitor as compared with 2 of 5 (40%) with pembrolizumab alone (p=0.029). Figure 2B demonstrates a normal-appearing pituitary gland in a patient with pembrolizumab-induced hypophysitis. Mass effects that occurred in 13 patients were managed by initial high-dose glucocorticoids, most frequently prednisone in 9 (median 90 mg (range: 30–130)), dexamethasone in 3 (2, 6 and 8 mg each) and 2 mg methylprednisolone in 1 patient. Mass effects were more common with ipilimumab either alone or in combination or sequence with a PD-1 inhibitor as compared with pembrolizumab alone (63.1% vs 14.3%; p=0.048). Thyroiditis occurred in 5 patients (19.2%) with hypophysitis (table 2). During follow-up, all patients continued hormone replacement for hypopituitarism.

Overall survival and mortality risk

Kaplan-Meier survival analysis revealed that the median overall survival duration in the patients who developed hypophysitis was 50.7 months (95% CI 23.78 to not reached) as compared with patients without hypophysitis where it was 16.5 months (95% CI 14.19 to 19.84; p=0.015) (figure 3). In the subgroup of patients with melanoma (for all ICIs), Kaplan-Meier survival analysis revealed that those with hypophysitis did not reach median overall survival as compared with patients without hypophysitis where it was 25.7 months (95% CI 17.4 to 37.4; p=0.06). Among 26 patients with hypophysitis, there was no difference in overall survival between those who received high-dose glucocorticoids and those who did not (median not reached vs 50.7 months; p=0.78), but our study was not adequately powered to answer this question. The multivariable landmark survival regression analysis using age (as decade), sex, cancer type (melanoma, lymphoma, others), and hypophysitis (as a time-varying covariate rather than only the presence or absence of it) as covariates revealed HR for mortality with hypophysitis of 0.75 (95% CI 0.38 to 1.30; p=0.34). Increase in age by each decade had HR for mortality of 1.11 (95% CI 1.04 to 1.18; p=0.002). Upon restricting the analysis to melanoma-only cohort, the HR for mortality with hypophysitis was 0.71 (95% CI 0.32 to 1.35; p=0.35) (online supplemental table 2).

DISCUSSION

In this comprehensive clinical study of a large oncological patient cohort treated with an ICI, we have demonstrated that hypophysitis occurs most frequently after CTLA-4 inhibitor, secondary adrenal insufficiency is the most common hormone deficiency and PD-1 inhibitors may cause hypopituitarism without classic pituitary enlargement or mass effects. Hypophysitis occurred in 2.9% of the 896 patients; those treated with ipilimumab alone or in combination or sequence with a PD-1 inhibitor developed this in 7.9%, but less frequently with pembrolizumab alone (1.7%) and never with nivolumab alone. PD-L1 inhibitors were not in use at the time of study initiation, however, our group has separately analyzed a cohort of 91 PD-L1 inhibitor-treated patients where hypophysitis did not occur during a median follow-up of 1 year.[10] Our findings are consistent with CTLA-4 inhibitor ipilimumab causing hypophysitis with the highest frequency among all ICIs in observational studies[4 7 21 23] and trials.[16] This is supported by the observation that CTLA-4 is expressed on pituitary cells, and when blocked by the administration of a specific monoclonal antibody, leads to site-specific deposition of complement components, pituitary infiltration, and antibody

Table 2 Clinical, laboratory and imaging characteristics of ICI hypophysitis cases

Disease characteristics	ICI-induced hypophysitis (n=26)	Ipilimumab (alone or in combination or sequence with PD-1 inhibitor) (n=19)	Pembrolizumab alone (n=7)	p value
Male, n (%)	14 (53.8)	9 (47.4)	5 (71.4)	0.27
Pituitary hormone dysfunction, n (%)				
Secondary adrenal insufficiency	26/26 (100)	19/19 (100)	7/7 (100)	–
Central hypothyroidism	10/26 (38.5)	8/19 (42.1)	2/7 (28.6)	0.52
Central male hypogonadism	3/14 (21.4)	2/9 (22.2)	1/5 (20)	0.92
Central female hypogonadism	1/4* (25)	1/3* (33.3)	0/1* (0)	–
Low insulin-like growth factor-1	1/4* (25)	1/3* (33.3)	0/1* (0)	–
Prolactin elevated	1/5* (25)	1/4* (25)	0/1* (0)	–
Prolactin low	3/5* (60)	3/4* (75)	0/1* (0)	–
Other endocrine irAE, n (%)				0.26
Thyroiditis	5 (19.2)	3 (16.7)	2 (28.5)	
Mass effects, n (%)	13 (50)	12 (63.1)	1 (14.3)	0.048
Headache	12 (46.2)	11 (57.9)	1 (14.3)	
Diplopia	2 (7.7)	1 (5.3)	1 (14.3)	
Visual deficits	1 (3.8)	0 (0)	1 (14.3)	
MRI done at time of symptoms, n (%)	24 (92.3)	19 (100)	5 (71.4)	0.017
MRI evidence of pituitary gland and/or stalk enlargement or contrast enhancement, n (%)	15/24 (62.5)	13/19 (68.4)	2/5 (40)	0.029
Duration from ICI initiation to laboratory evidence of hypopituitarism (mo), median (range)	2.9 (1.05–17.7)	2.9 (1.05–17.7)	4.6 (1.2–8.9)	0.84
Duration from ICI initiation to MRI evidence of hypophysitis (mo), median (range)	2.3 (0.8–11.7)	2.4 (0.8–11.7)	1.3 (1.2–1.3)	0.07
High-dose glucocorticoids for hypophysitis mass effects, n (%)	13 (50)	10 (52.6)	2 (28.6)	0.27

*Number of patients in whom this was tested.
ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PD-1, programmed cell death protein 1.

formation.[27] The activation of T-cells has been postulated to result in inflammatory destruction of pituitary cells thus leading to the effects of hypophysitis-like mass effect and/or hormone deficiencies. Thus, close pituitary monitoring is required for patients receiving CTLA-4 inhibitor and combination ICIs.[28]

Clinical presentation with fatigue and headache in our study was similar to that reported by others.[7 21 22] Mass effects occurred in 50% of the cohort, more frequently with ipilimumab alone or in combination or sequence with a PD-1 inhibitor as compared with pembrolizumab alone. The time from ICI initiation to onset of hypophysitis was a median of 3 months, like that reported by others,[4 7 17] but our cohort exhibited a wider range, which can be attributed to our longer duration of follow-up. Age and sex were not associated with occurrence of hypophysitis, findings in contrast to another study that described male sex and older age to be associated with it.[4] This difference could be attributed to variations in cohort size and diversity of malignancies between the two studies. In our study, the higher rate of hypophysitis in patients with melanoma is possibly due to more frequent use of ipilimumab in these patients, since ipilimumab itself was associated with higher frequency of hypophysitis.

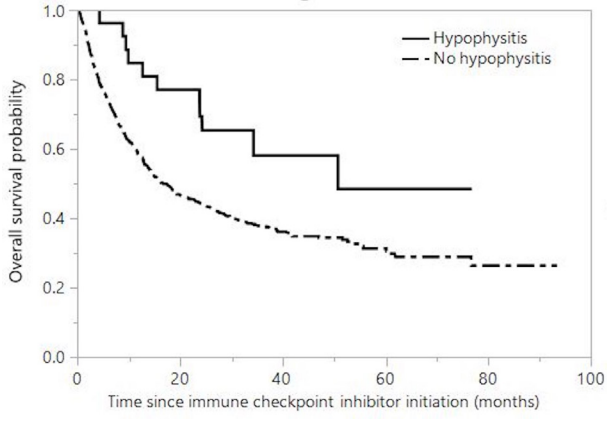

Figure 3 Kaplan-Meier plots for survival in patients with cancer with and without hypophysitis (p=0.015), after treatment with immune checkpoint inhibitors ipilimumab, pembrolizumab or nivolumab.

In contrast to the meta-analysis of clinical trials by Barroso-Sousa *et al* which reported central hypothyroidism as the most common endocrine disturbance followed by central hypogonadism and central adrenal insufficiency,[16] all patients with hypophysitis in our cohort developed central/secondary adrenal insufficiency, followed in frequency by central hypothyroidism and hypogonadotropic hypogonadism. This suggests that clinical trial data under-represent the frequency of secondary adrenal insufficiency due to the non-specific nature of symptoms in most cases. Recently, Nguyen *et al*[24] reported higher frequency of central hypothyroidism than secondary adrenal insufficiency in ICI-induced hypophysitis, however they excluded patients who had only one pituitary hormone deficiency

without characteristic MRI features. As has been shown in our study and others,[23] PD-1 inhibitors may cause isolated secondary adrenal insufficiency without characteristic pituitary enlargement on MRI, hence these cases would be missed by the criteria for Nguyen *et al*,[24] thus leading to lower rate of secondary adrenal insufficiency in their study. The frequency of growth hormone (GH) deficiency is likely under-represented in our study because we did not screen for biochemical GH deficiency, as GH replacement would not be indicated in the setting of active malignancy in these patients. Characteristic MRI evidence of hypophysitis (figure 2A) occurred in 62.5% of patients who had MRI performed within 3 months of presentation, occurring more frequently with ipilimumab either alone or in combination or sequence with a PD-1 inhibitor as compared with pembrolizumab alone, suggesting that a normal-appearing pituitary gland on MRI (figure 2B) should not rule out pituitary dysfunction, especially in those treated with a PD-1 inhibitor, as has also been reported by some other studies.[23 29] At the same time, it is important to perform MRI to evaluate pituitary gland in any patient with concern for hypophysitis because we observed shorter time to onset of hypophysitis in those with classic pituitary enlargement on MRI, and is supported by Nguyen *et al*[24] demonstrating that some cases of hypophysitis may be missed if MRI is not performed in the setting of clinical suspicion.

For management of hypophysitis, high-dose glucocorticoids (usually prednisone ranging from 0.5 to 1 mg/kg/day based on managing team) were administered initially in 50% of patients, comprising of those who presented with mass effect symptoms (severe headache, diplopia or visual field defect). Our study, along with others.[7 21 22] supports the use of high-dose glucocorticoids only for significant mass effect to reduce the inflammation and improve acute symptoms. Even though our study was not powered to answer this question, the use of high-dose glucocorticoids did not affect overall survival, which is in accordance with the notion that short-term use of high-dose glucocorticoids does not negatively influence ICI efficacy. These findings are similar to those by Min *et al*[22] who reported neither improvement nor worsening of survival, but in contrast to recently reported reduced survival with use of high-dose glucocorticoids even after adjusting for age, sex and tumor status by Faje *et al*.[5] Both these studies included patients with ipilimumab-treated melanoma. In literature, hormone deficiencies from anterior hypopituitarism usually persist in >70% of cases, with adrenal insufficiency being permanent in almost all cases.[4 7 24] In our study as well, while the acute course of hypophysitis was mitigated, no patient was successfully tapered off their hormone replacement during follow-up, regardless of the pituitary axis affected or use of high-dose glucocorticoids.

We explored the potential association of ICI-induced hypophysitis with overall survival by various methods. We observed a signal for improved overall survival (median 50.7 vs 16.5 months), however, this association was not observed in landmark survival analysis after adjusting for age, sex and cancer type when hypophysitis was used as a time-varying covariate. Restricting the analysis to only patients with melanoma also did not demonstrate a significant survival difference by both analytical methods but our sample size is a limitation. Faje *et al* were the first to report a possible survival advantage with ipilimumab-induced hypophysitis (median overall survival 19.4 vs 8.8 months, p=0.05).[4] They further expanded on this cohort, reporting improved overall survival in total of 64 analyzed patients with hypophysitis (median 28.2 vs 9.5 months, p=0.003).[5] However, in contrast to our study, theirs were purely patients with ipilimumab-treated melanoma and the survival difference based on hypophysitis occurrence was not adjusted for potential confounding variables such as age and sex. A recently published study by Snyders *et al* demonstrated no significant mortality benefit in 15 patients with ipilimumab-induced hypophysitis.[25] In the latter study, the authors did not adjust for other potential factors that could affect survival, and the total sample size was 117. A study published in abbreviated abstract form reported 51% lower mortality risk in the setting of hypophysitis in patients with ipilimumab-treated melanoma.[30] Recently, Kobayashi *et al* prospectively evaluated patients with non-small cell lung carcinoma and malignant melanoma treated with various ICIs, demonstrating survival benefit with hypophysitis, but also did not adjust for other factors that could affect survival.[26] It should be noted that none of these studies performed landmark survival analysis to incorporate the time variable for occurrence of hypophysitis. Since hypophysitis occurs after the initiation of ICIs, we performed this analysis and adjusted for age, sex and cancer type, in addition to also analyzing the melanoma-only cohort, which did not show the association of hypophysitis with overall survival. In lieu of the above available results in literature (table 3), our study, analyzing one of the largest cohorts of patients with cancer with various types of malignancies treated with CTLA-4 or PD-1 inhibitor or their combination, is the first to use landmark survival analysis adjusting for potential confounding factors in the field of ICI-induced hypophysitis. While this analysis is noteworthy, we cannot precisely document at which point the immune processes within pituitary gland leading to eventual diagnosis of hypophysitis exactly occur following ICI exposure. Therefore, we believe it is important to present the data by both analyses.

As for the underlying mechanism behind a signal of improved survival in patients with ICI-induced hypophysitis, it is hypothesized that hypophysitis may indicate enhanced T-cell function and signaling after CTLA-4 inhibition, leading to immune-mediated inflammation of anterior pituitary cells and increased anti-tumor activity. In the literature, overall survival has also been evaluated in the setting of other irAEs. Haratani *et al*, using landmark survival analysis, reported that all irAEs combined, skin irAEs and endocrine irAEs (did not separate different types) were associated with better overall survival and reduced mortality rate in patients with nivolumab-treated non-small cell lung cancer,[31] while skin irAEs only were associated with improved overall survival in patients with nivolumab-treated melanoma.[32] PD-1 and PD-L1 inhibitor-induced thyroid irAEs have also been reported to be associated with better overall survival,[8 10] but these studies did not perform landmark survival analysis. A recent meta-analysis[33] demonstrated that with landmark survival analysis to address immortal time bias, the association between irAE and survival remained significant but the effect size was smaller. This could have been a reason behind our

Table 3 Cohort studies which have reported the association between hypophysitis occurrence and survival in ICI-treated patients

Study	Faje *et al*[4]	Faje *et al**[5]	Snyders *et al*[25]	Kobayashi *et al*[26]	Eatrides *et al* (abstract)[30]
ICI-treated cohort	Melanoma (n=154)	Melanoma (n=249)	Melanoma (n=117)	All (n=174) Melanoma (n=66) NSCLC (n=108)	Melanoma (n=269)
Hypophysitis, n (%)	17 (11)	98 (64 in survival analysis) (% not available)	15 (12.8)	16 (9.2)	32 (11.9)
Median overall survival with vs without hypophysitis	19.4 vs 8.8 mo (p=0.05)	28.2 vs 9.5 mo (p=0.003)	53.3 vs 29.5 mo (p=0.307)	Melanoma: 885 vs 298 d (p=0.038) NSCLC: not reached vs 441 days (p=0.036)	Not reported
HR for mortality in hypophysitis	Not reported	0.53 (95% CI 0.36 to 0.75; p=0.003)	0.66 (95% CI 0.30 to 1.46; p=0.307)	Not reported	0.49 (95% CI 0.24 to 0.98; p=0.04)†

*Included the first cohort published in 2014.
†Adjusted for potential confounders (age, sex, race, tumor status).
ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung carcinoma.

study demonstrating longer survival in those with hypophysitis, but this association was not significant after landmark survival analysis.

The limitations of our study include its retrospective nature and limited pituitary hormone testing in all patients treated with an ICI, which limits our ability to analyze subtle hormone deficiencies that were not clinically evident. Due to sample size limitation, we could not analyze the effects of radiologic pituitary abnormality, severity of hypophysitis, mass effects, or separate analysis by different ICIs on overall survival, and this is also a limitation for our subgroup analysis in patients with melanoma. Landmark survival analysis has the advantage of using hypophysitis as a time-varying covariate, however, the time to onset of hypophysitis defined by hypopituitarism diagnosis in our study is also a limitation since it is possible that the hypophysitis may have occurred before laboratory diagnosis. The median follow-up of 14.8 months of the entire cohort was adequate to identify the occurrence of most cases of ICI-induced hypophysitis but might be limited to characterize their full course and also precludes us from reporting an accurate overall survival probability in the entire cohort of patients with ICI-treated cancer. Our cohort is more heterogeneous as compared with other studies as it is not limited to a single ICI or malignancy, however, we did perform survival analysis restricted to melanoma cohort as well.

In conclusion, we have demonstrated that hypophysitis, usually but not always accompanied by classic MRI features, occurs within a few weeks in patients with ICI-treated cancer. It occurs most frequently after ipilimumab alone or in combination with a PD-1 inhibitor, manifesting as hypopituitarism in all patients involving the corticotrophs more commonly than thyrotrophs and gonadotrophs. Hypophysitis after pembrolizumab may not present with pituitary enlargement on MRI or mass effects unlike that commonly encountered with ipilimumab. There may be a signal of improved survival with the occurrence of hypophysitis which needs to be further evaluated in larger studies.

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