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Fall in thyroid stimulating hormone (TSH) may be an early marker of ipilimumab-induced hypophysitis

Sunita M. C. De Sousa[1,2,3] · Nisa Sheriff[4,5] · Chau H. Tran[4,6] · Alexander M. Menzies[7,8,9,10] · Venessa H. M. Tsang[8,10,11] · Georgina V. Long[7,8,9,10] · Katherine T. T. Tonks[4,5,6,10]

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Abstract

Purpose Hypophysitis develops in up to 19% of melanoma patients treated with ipilimumab, a cytotoxic T-lymphocyte antigen-4 antibody. Early detection may avert life-threatening hypopituitarism. We aimed to assess the incidence of ipilimumab-induced hypophysitis (IH) at a quaternary melanoma referral centre, and to determine whether cortisol or thyroid stimulating hormone (TSH) monitoring could predict IH onset.

Methods We performed a retrospective cohort study of ipilimumab-treated patients at a quaternary melanoma referral centre in Australia. The inclusion criteria were patients with metastatic or unresectable melanoma treated with ipilimumab monotherapy, and cortisol and TSH measurements prior to ≥ 2 infusions. The main outcomes were IH incidence and TSH and cortisol patterns in patients who did and did not develop IH.

Results Of 78 ipilimumab-treated patients, 46 met the study criteria and 9/46 (20%) developed IH at a median duration of 13.0 weeks (range 7.7–18.1) following ipilimumab initiation. All patients whose TSH fell ≥ 80% compared to baseline developed IH, and, in 5/9 patients with IH, TSH fell prior to cortisol fall and IH diagnosis. Pre-cycle-4 TSH was significantly lower in those who developed IH (0.31 vs. 1.73 mIU/L, $P = 0.006$). TSH fall was detected at a median time of 9.2 (range 7.7–16.4) weeks after commencing ipilimumab, and a median of 3.6 (range of − 1.4 to 9.7) weeks before IH diagnosis. There was no difference in TSH between the groups before cycles 1–3 or in cortisol before cycles 1–4.

Conclusions TSH fall ≥ 80% may be an early marker of IH. Serial TSH measurement during ipilimumab therapy may be an inexpensive tool to expedite IH diagnosis.

Keywords Thyroid stimulating hormone · TSH · Ipilimumab · Hypophysitis · Hypopituitarism

Introduction

Ipilimumab (Ipi), a fully human IgG_1 monoclonal antibody directed against the inhibitory molecule, cytotoxic T-lymphocyte antigen-4 (CTLA-4), enhances T cell activation

Sunita M. C. De Sousa and Nisa Sheriff have contributed equally.

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✉ Katherine T. T. Tonks
k.tonks@garvan.org.au

1 Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, Australia

2 Department of Genetics and Molecular Pathology, Centre for Cancer Biology, an SA Pathology and University of South Australia Alliance, Adelaide, Australia

3 School of Medicine, University of Adelaide, Adelaide, Australia

4 Department of Endocrinology, St Vincent's Hospital, Darlinghurst, Australia

5 Diabetes and Metabolism Program, Garvan Institute of Medical Research, Darlinghurst, Australia

6 St Vincent's Clinical School, University of New South Wales, Sydney, Australia

7 Melanoma Institute Australia, Wollstonecraft, Australia

8 Royal North Shore Hospital, St Leonards, Australia

9 University of Sydney, Camperdown, Australia

10 Mater Hospital, North Sydney, Australia

11 Kolling Institute of Medical Research, St Leonards, Australia

against tumour cells. It was the first therapy in metastatic melanoma to improve survival in a randomised controlled trial [1]. Ipi is associated with immune-related adverse effects (irAEs) as it interrupts self-tolerance. Dermatological, gastrointestinal and endocrine toxicities are reported in up to 72% of patients [2]. Most irAEs remit following glucocorticoid therapy [2]; however, endocrine function rarely returns, including following Ipi-induced hypophysitis (IH) [3]. IH was initially observed in 0–2% of patients in the landmark phase 3 Ipi trials [1, 4]. It has since been reported in up to 19% of Ipi-treated melanoma patients in subsequent phase 3 and cohort studies (Table 1) [3, 5–13], which may reflect increased vigilance for this life-threatening complication over time and/or selection bias.

IH appears to be a common Ipi-related irAE [6, 7, 10], and yet hypophysitis occurs in < 1% of patients treated with other melanoma immunotherapies, such as anti-PD-1 antibodies [4, 11, 14]. This suggests that IH may be mechanistically distinct from other irAEs, possibly involving direct binding of Ipi to CTLA4 ectopically expressed in the pituitary [15].

The objectives of this study were to determine IH incidence in a quaternary melanoma referral centre in Australia, which has the highest prevalence of melanoma internationally, and to assess whether IH onset could be predicted by serial cortisol or thyroid stimulating hormone (TSH) measurements prior to each Ipi cycle. We hypothesised that declines in cortisol and TSH precede symptomatic IH.

Methods

The study was conducted at Melanoma Institute Australia (MIA), Sydney, after institutional Human Ethics Review Committee approval. Seventy-eight consecutive adult patients treated with Ipi for stage IIIc unresectable or stage IV melanoma between August 2013 and December 2014 were identified via the MIA pharmacy database and MIA patient database. Ipi was administered intravenously at 3 mg/kg at a minimum of 3-weekly intervals for a maximum of four doses. Medical records, biochemistry and radiology were reviewed.

Table 1 Previous cohort studies of IH in melanoma patients

Study	Total[a]	IH (%)	Axes deficient (n)	Steroid treatment (n)	Axes recovered at latest f/u (n)
Blansfield et al. [5]	113	6 (5)	TSH (6) ACTH (6) Gn (5) PRL (1)	Supraphysiological (5) Physiological (3)	TSH (4) Gn (4)
Maker et al. [6]	46	8 (17)	–	Supraphysiological (8)	–
Downey et al. [7]	139	13 (9)	–	Mixed	TSH ('many') ACTH (1) Gn ('many')
Sarnaik et al. [8]	75	11 (15)	ACTH (11) Rest uncertain	–	ACTH (3) Rest uncertain
Voskens et al. [9]	752	12 (2)	–	–	Some recovery (5)
Faje et al. [3], updated [10]	154	17 (11)	TSH (17) ACTH (7) Gn (15) PRL (12) GH (1)	Supraphysiological (15) Physiological (2)	TSH (4) ACTH (1) Gn (2)
Albarel et al. [11]	87–131[b]	15 (11–17)	TSH (13) ACTH (11) Gn (12) PRL (3) GH (2)	Supraphysiological (11) Physiological (4)	TSH (11) ACTH (0) Gn (10) PRL (2) GH (1)
Min et al. [12]	187	25 (13)	TSH (22) ACTH (22) Gn (15) PRL (4) GH (3)	Supraphysiological (15) Physiological (10)	TSH (14) ACTH (0) Gn (7)

ACTH adrenocorticotrophin hormone, *f/u* follow-up, *GH* growth hormone, *Gn* gonadotropins (FSH/LH), *n* number of patients if known, *PRL* prolactin, *TSH* thyroid stimulating hormone

[a]Total number of melanoma patients treated with ipilimumab

[b]Some patients remain blinded (ipilimumab vs. placebo)

"–" data not available or uncertain

Since late 2013, cortisol and TSH were routinely measured prior to each Ipi cycle and following completion of Ipi. Individuals with ≥ 2 cortisol measurements before sequential doses of Ipi were included. Exclusion criteria were: insufficient number of cortisol measurements (n = 23), < 2 cycles of Ipi received due to death (n = 5) or other reasons (n = 3), glucocorticoid therapy throughout Ipi treatment (n = 1), and thyroxine therapy for primary hypothyroidism (n = 1). Of the 78 patients treated, 46 met study criteria.

Cortisol values were deemed suitable for analysis if measured before 11 AM and provided the patient was not taking glucocorticoids at the time of measurement. In cases where glucocorticoids were administered intermittently during Ipi therapy, individual cortisol values were included if measured off glucocorticoids. Hypopituitarism was defined as low levels of effector hormones (cortisol, fT4, sex hormone and IGF1), with low or inappropriately normal pituitary hormones (ACTH and TSH); low gonadotrophins for age; or low prolactin for gender. Patients were considered to have IH if the treating physician (oncologist and/or endocrinologist) identified the diagnosis, which was made on the basis of biochemical hypopituitarism, clinical features and/or radiologic findings.

Hormone assays were performed on the following instruments with intra-assay and inter-assay coefficients of variability (CV) as follows: cortisol, ACTH and GH (Seimens Immulite 2000 Xpi. Siemens Healthcare Diagnostics, Bayswater, Victoria, Australia) 5.7–6.8% and 6.1–8.8%, 2.1–3.5% and 4.7–5.5%, 2.4–2.6% and 2.1–4.5%, respectively; TSH, fT3, fT4, FSH, LH and oestradiol (Abbott Architect i2000, Abbott Diagnostics, North Ryde, NSW, Australia) 2.0–2.9% and 3.5–3.7%, 4.3–6.7% and 3.1–10.5%, 2.1–5.4% and 3.7–5.5%, 3.3–4.5% and 3.8–4.2%, 4.5–6.2% and 4.4–5.1%, 1.5–17.3% and 2.5–4.6%, respectively; testosterone and prolactin (Roche E170, Roche Diagnostics, North Ryde, NSW, Australia) 1.3–6.8% and 3.6–3.8%, 1.8–2.1% and 1.7–1.8%, respectively; and IGF1 (DiaSorin Liaison, DiaSorin Australia, Macquarie Park, NSW) 1.04–1.65% and 6.0–7.8%.

Statistical analyses were completed using GraphPad Prism version 6 for Mac OS X (GraphPad Software, La Jolla California USA). Values are shown as medians with ranges, unless stated otherwise. Where data were missing, values were imputed using time-point group means. Two-way repeated measures ANOVA and Tukey post-hoc analyses were used to detect group differences for cortisol, and TSH. Laboratory values below the level of detection were imputed with the maximum possible value—for example, cortisol < 28 nmol/L (1.01 mcg/dL) on the Seimens platform was imputed as 27 nmol/L (0.97 mcg/dL). P values < 0.05 were considered statistically significant. Wilcoxon signed rank test was used to test statistical significance.

Results

Patient characteristics

Of 46 included patients, 32 (70%) were male. Patients received a median of four Ipi doses. 9 (20%) were diagnosed with IH. Age and sex were not associated with the development of IH (Table 2). There was a trend towards earlier stage disease in patients who developed IH (stage IIIc disease in 44% IH vs. 3% non-IH, $P = 0.13$). Four of the non-IH and none of the IH patients underwent re-treatment with Ipi following the initial four cycles.

All patients with pre-existing cerebral metastases (IH n = 3, non-IH n = 11) had undergone radiotherapy. This was in the form of stereotactic radiosurgery in the three IH patients and the sudden decline in cortisol/TSH in these patients (Online Resource) favoured Ipi as the cause of hypopituitarism, whereas radiotherapy-induced hypopituitarism would have been expected to cause a gradual decline in pituitary function [3], and preferential loss of somatotrophs and gonadotrophs [12]. The timing of radiotherapy was known in 2/3 patients and occurred 13 and 16.5 weeks prior to IH diagnosis. No IH patients had a history of whole brain or sellar irradiation, sellar metastases or bilateral adrenal metastases that might provide alternate diagnoses for their hormone abnormalities.

Clinical presentation of IH

Of the nine patients who developed IH, median time from first Ipi dose to diagnosis of IH was 13.0 weeks (range 7.7–18.1) (Table 3). Where symptoms possibly related to IH preceded the formal diagnosis they were non-specific (e.g. fatigue), and may not have been directly or solely a consequence of IH. Presenting symptoms included headache (6/9), fatigue (7/9), anorexia (4/9), postural lightheadedness (2/9), weight loss (2/9), nausea (2/9), visual flashing (1/9) and low mood (1/9). One patient presented with hyponatremia (Na 127 mmol/L) in the setting of hypocortisolism and hypothyroidism. No patients experienced visual loss or diabetes insipidus.

On the basis of these symptoms, the nine patients underwent complete biochemical testing of pituitary function, which confirmed IH diagnosis. All patients had biochemical evidence of central hypocortisolism and hypothyroidism at time of diagnosis, with sporadic involvement of other axes (Table 3). Median hormone levels at time of IH diagnosis were: cortisol 27 (range 6–110) nmol/L (0.97, 0.22–3.96 mcg/dL), ACTH 1.5 (range 0.2–9.9) pmol/L (7, 1–45 ng/L), TSH 0.18 (range 0.004–0.89) mIU/L, fT4 9.7 (range 8.2–13.2) pmol/L (0.8, 0.6–1.0 ng/dL),

Table 2 Characteristics of melanoma patients with and without hypophysitis

	No hypophysitis n (%)	Hypophysitis n (%)	*P* value
Total	37 (80)	9 (20)	
Male	26 (70)	6 (67)	0.84
Age at first dose Ipi (years ± SEM)	65 ± 2.3	63 ± 4.2	0.69
Weight at first dose Ipi (kg ± SEM)	86 ± 3.2	89 ± 8.7	0.68
Number of Ipi cycles (median)	4	4	N/A
Stage IV	36 (97)	5 (56)	0.13
Stage IIIc unresectable	1 (3)	4 (44)	0.13
Pre-existing autoimmune comorbidities	1 (3)	1 (11)	> 0.99
CNS metastases[a]			
Diagnosed prior to Ipi initiation	11 (30)	3 (33)	0.63
Diagnosed after Ipi initiation	3 (8)	0	> 0.99
Adrenal metastases	10 (27)	2 (22)	> 0.99
Prior systemic therapy (PD1, MEK/BRAF, BRAF inhibitors)	8[b] (22)	0	0.50
irAEs (non-hypophysitis)	20 (54)	7 (78)[d]	> 0.99
Rash	9 (24)[c]	5 (56)	0.13
Colitis	12 (32)[c]	1 (11)	0.0078
Thyroiditis	1 (3)[c]	0	> 0.99

irAE immune-related adverse effect, *MEK* mitogen activated protein kinase, *N/A* not applicable, *PD1* programmed-cell death 1

[a]All patients received radiotherapy for brain metastases

[b]2 PD1, 4 MEK/BRAF, 1 BRAF, 1 PD1 and MEK/BRAF; BRAF, B-Raf proto-oncogene

[c]One person with colitis also had thyroiditis, and one person with colitis also had rash

[d]One person had vitiligo

Table 3 Cases of Ipilimumab-induced hypophysitis

Patient	1	2	3	4	5	6	7	8	9
Age	75	43	67	71	62	72	46	66	74
Gender	F	F	M	M	M	M	M	M	F
Disease stage	4	4	3c	3c	4	3c	3c	4	4
Time of IH diagnosis (weeks after Ipi cycle 1)	14.7	10.6	18.1	7.7	13.4	8.9	13.0	9.2	15.4
Prior RT	y	y	n	n	n	y	n	n	n
Deficient axes at presentation/most recent follow up									
Thyrotroph	y/y	y/y	y/y	y/y	y/y	y/y	y/y	y/n	y/y
Corticotroph	u/y	y/y	y/y	u/y	y/y	n/y	y/y	y/y	y/y
Gonadotroph	y/y	y/y	y/y	n/n	n/n	n/n	n/n	y/y	y/y
Somatotroph	n/n	n/y	y/y	n/y	n/n	n/n	n/n	n/n	y/y
Lactotroph	n/n	n/n	y/y	n/n	n/n	n/y	n/n	n/n	n/n
Axes recovered	None	None	None	None	None	None	None	Thyroid	None
Initial glucocorticoid	P 30 mg	P 5 mg	P 10 mg	P 75 mg (colitis)	P 50 mg	P 50 mg	P 60 mg	HC 30 mg	P 10 mg
Maintenance glucocorticoid	HC 24 mg	P 5 mg	P 15 mg	P 2.5 mg	HC 30 mg	P 5 mg	P 7.5 mg	HC 30 mg	P 5 mg

HC hydrocortisone, *IH* ipilimumab-induced hypophysitis, *n* no, *P* prednisolone, *RT* radiotherapy, *u* unable to be assessed as taking glucocorticoids at time of IH diagnosis, *y* yes

fT3 3.5 (range 2.1–4.6) pmol/L (0.2, 0.1–0.3 ng/dL), testosterone (males) 2.1 (range 0.2–28.3) nmol/L (60.5, 17.3–815.0 ng/dL), LH 1.4 (range 0.3–7.9) IU/L, FSH 8.2 (range 1.6–14.0) IU/L, GH 0.8 (range 0.3–9.6) mIU/L (0.3, 0.1–3.2 mg/mL), IGF1 26.3 (range 6.0–44.0) nmol/L (201, 46–337 ng/mL) and prolactin 219 (range 16–470)

mIU/L (10.3, 0.8–22.1 ng/mL). In the women with IH, serum oestradiol was < 50 pmol/L (14 pg/mL) in the patient who was premenopausal, and gonadotrophin levels were inappropriately low in the other two women who were postmenopausal, and thus all three were considered to have hypogonadism. Two patients were taking glucocorticoids for management of other irAEs (rash and colitis) at time of IH presentation and thus serum cortisol could not be interpreted. IH was diagnosed in these patients by pituitary hormone deficiencies other than ACTH and abnormal radiographic appearances, and confirmed by endogenous hypocortisolism after cessation of the supraphysiologic glucocorticoid therapy. Investigations were performed in the absence of glucocorticoid therapy in the other seven IH patients.

Serial biochemistry

Among the 46 patients, adequate cortisol values were available for 36, 21, 25, 14 and 16 patients prior to Ipi cycles 1–4 and after all four cycles, respectively. A total of 47 cortisol measurements were excluded due to collection time after 11 AM (n = 37) or concurrent glucocorticoid therapy (n = 10). No significant difference in cortisol levels was observed between non-IH and IH groups until *after* Ipi cycle 4 [405 vs. 217 nmol/L (14.58 vs. 7.81 mcg/dL), respectively, Wilcoxon Rank Sum test $P = 0.001$] (Fig. 1a). Cortisol levels taken 4–8 weeks prior to IH diagnosis were normal in all patients: 240–698 nmol/L (8.64–25.13 mcg/dL), mean 454 nmol/L (16.34 mcg/dL), median 417 nmol/L (15.01 mcg/dL) (Fig. 2).

TSH values were available for 40, 42, 39, 35 and 28 patients prior to Ipi cycles 1–4 and after all four cycles, respectively. In contrast to cortisol differences between the non-IH and IH group, a significant difference in TSH between non-IH and IH groups was observed prior to Ipi cycle 4 (1.07 vs. 0.17 mIU/L, Wilcoxon Rank Sum test $P = 0.006$) (Fig. 1b). If TSH fell, fT4 and fT3 were measured, and found to be low or inappropriately low-normal: fT4 median 11.5 (range 8.9–13.6) pmol/L (0.9, 0.7–1.1 ng/dL), fT3 median 3.2 (range 2.1–4.7) pmol/L (0.2, 0.1–0.3 ng/dL), consistent with central hypothyroidism. TSH fall (Fig. 2) was detected at a median time of 9.2 weeks after commencing Ipi (range 7.7–16.4 weeks), and 3.6 weeks prior to IH diagnosis (range 9.7 weeks before to 1.4 weeks after). In 5/9 IH patients (56%; patients 1, 2, 6, 8 and 9), TSH fell below the reference range prior to cortisol fall and IH diagnosis. One patient was on pharmacological glucocorticoid therapy which might have contributed to this decline; however, central hypothyroidism was confirmed when glucocorticoid therapy was ceased. All patients who had a TSH fall ≥ 80% prior to Ipi cycle 4 compared to baseline developed IH.

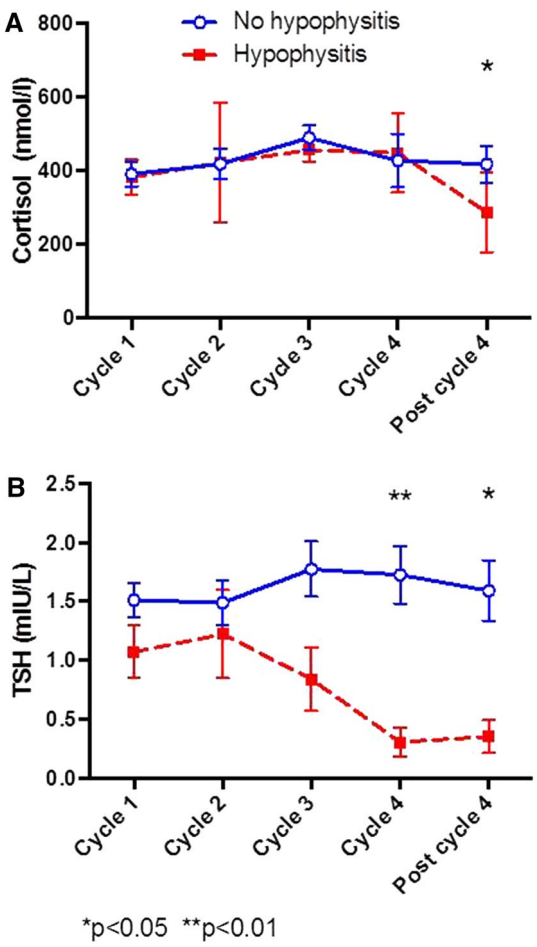

Fig. 1 **a** Cortisol and **b** TSH levels prior to Ipi cycles in patients with and without IH

Radiographic studies

All nine IH patients underwent CNS imaging at 0–60 days after IH diagnosis, primarily to exclude other pathologies such as sellar metastases, but also to identify radiological features of hypophysitis. Three MRI studies—performed 12, 21 and 60 days after IH diagnosis—demonstrated a normal pituitary. Independent review by a neuroradiologist confirmed that hypophysitis features were absent in these cases. Another patient showed pituitary fossa FDG avidity, without structural abnormality, 3 weeks prior to IH diagnosis, followed by a partially empty sella 3 weeks after IH diagnosis. The remaining five IH patients demonstrated various pituitary abnormalities on MRI, including superior convexity (3), symmetrical enlargement with homogeneous enhancement (3), slight heterogeneity of pituitary enhancement (2) and loss of the posterior pituitary bright spot (2). Three patients underwent repeat imaging, which showed resolution of their pituitary abnormalities.

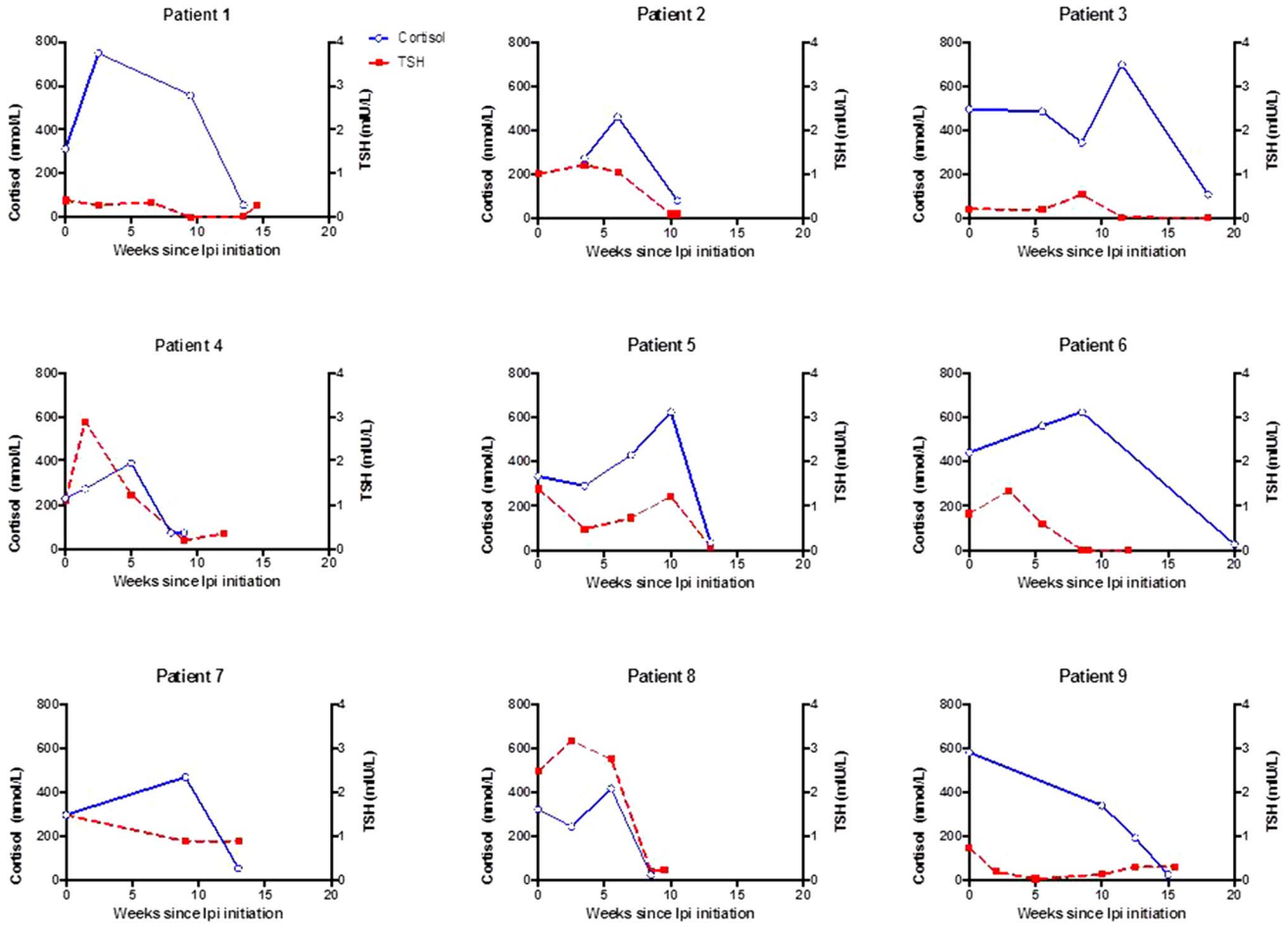

Fig. 2 Changes in cortisol and TSH values vs. time since Ipi initiation in individual patients who developed IH. IH diagnosis coincided with the last cortisol measurement for each patient

Follow-up

Patients were followed up for a median duration of 8.9 months (2.0–28.2) after starting Ipi. Supraphysiological glucocorticoid therapy (prednisolone > 7.5 mg or hydrocortisone > 30 mg) was initiated in 7/9 IH patients, and replacement doses were used in the remaining two. Doses were lowered to replacement levels in the maintenance phase of all but one patient (Table 3). Only one patient experienced any hormone recovery, and this was only in TSH. New deficiencies were seen in GH in two patients and in prolactin in one (Table 3). More people were deceased at follow-up in the non-IH group (18/36, 50%) compared to the IH group (2/9, 22%; $P = 0.2$). There was no significant difference in survival between the two groups (Fig. 3).

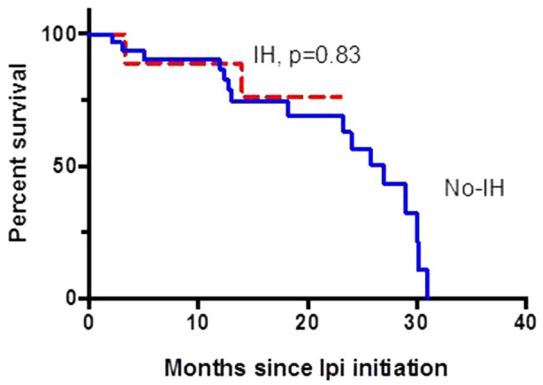

Fig. 3 Kaplan–Meier plots for percent survival in patients with and without IH after initiation of Ipi

Non-hypophysitis irAEs

irAEs beyond the pituitary were common with no significant difference in incidence between IH (7/9, 77.8%) and non-IH (20/37, 54%) patients (Table 2). Other than thyroiditis in one non-IH patient, these irAEs were limited to rash and colitis, the most common irAEs related to treatment with Ipi [2].

Discussion

Early recognition and treatment of IH are paramount to ensure appropriate glucocorticoid and other hormonal replacement, and stress dosing where required [3]. To our knowledge, this is the first study comparing the utility of serial cortisol and TSH monitoring in patients treated with Ipi. We diagnosed IH in nine patients (20%), and while no patients had a fall in cortisol prior to IH diagnosis, 5 (56%) patients had a preceding fall in TSH and all patients whose TSH fell ≥ 80% compared to baseline developed IH, suggesting that TSH fall may be an early marker of IH. It remains to be seen if the natural history of IH can be altered by early diagnosis and subsequent management strategies. At the very least, early IH diagnosis should allow closer patient monitoring and provision of a contingency glucocorticoid prescription to facilitate the rapid institution of hormone replacement, thereby reducing IH symptom duration and risk of complication.

Our study represents one of the highest IH prevalences amongst melanoma studies. This may reflect our small sample size and/or improved detection due to growing awareness and routine surveillance at MIA. This trend is seen in the literature, with earlier studies reporting IH in 0–2% of patients [1, 4] compared to more recent prevalence rates of 11–19% [3, 11–13]. One group showed a rise in IH incidence from 6.1% in 2011 to 15.3% following FDA approval ($P = 0.07$) [10]. Hypothesised IH risk factors such as male gender [3, 5, 6], older age [3], autoimmune comorbidity [1, 6–8, 16], Ipi dose [6, 10, 11] and exposure to CNS radiotherapy or systemic therapy [10, 16] did not differ between our IH or non-IH groups.

The gold standard test for confirmation of HPA axis hypofunction is the insulin tolerance test (ITT). We previously reported a flat cortisol response on ITT in a patient with IH [17] and the ITT has been used in the diagnosis and follow-up of other IH patients [11]. However, no patient in the present study underwent diagnostic ITT and this investigation has not been validated in the metastatic melanoma population which may be at increased risk of complications such as syncope, seizures and cardiac events [18]. Morning serum cortisol measurement is a practical alternative, but it may be confounded by diurnal variation, sleep-wake cycle, physiological stress, and suppression by exogenous corticosteroids or opioids [19, 20]. Amongst oncology patients, the measurement of cortisol along with other oncological investigations at various times of the day and during pharmacological steroid therapy is particularly problematic. Moreover, cortisol may fall precipitously rather than gradually during the development of IH. Inter-assay variability may complicate the interpretation of cortisol values [20]. The lack of difference in cortisol values between IH and non-IH patients in our study may partly reflect the small numbers of values available for analysis, but this too demonstrates the practical barriers to serial cortisol measurement. TSH measurement, on the other hand, is less susceptible to confounding and has a narrower intra-assay CV than cortisol. Finding a low TSH level should prompt fT4 measurement to exclude key differential diagnoses such as immunotherapy-related thyroiditis, sick euthyroid syndrome and exogenous glucocorticoid use. fT4 was not routinely measured with TSH in our study, but all patients with a low TSH level were subsequently found to have a low fT4 level, consistent with central hypothyroidism.

We found TSH decline preceded IH diagnosis by 3.6 weeks (range of − 1.4 to 9.7) prior to IH diagnosis. Our findings support recent preliminary data by Faje in 25 patients with IH [10], which showed TSH falls of approximately 30% before cycle 3 ($P < 0.05$) and 52% before cycle 4 ($P < 0.05$) compared to baseline. These declines were less sharp than our decline before cycle 4, and how long this occurred before IH diagnosis was unclear. Intriguingly, there was a trend towards *increased* TSH before cycle 2 in both our data and the study by Faje [10]. This could represent thyrotroph death and release of intracellular TSH, analogous to thyroid hormone release in the established model of thyroiditis. Previous studies serially measured TSH and fT4 [5, 6, 16], but measurements were performed after the Ipi dose [6], performed after IH onset [5], or haphazard in timing with too few patients who developed IH to determine the predictive value of serial measurements [16]. Other studies measured TSH and fT4 in addition to ACTH and cortisol with each Ipi cycle [7, 11, 21], but data were either not reported [7, 11] or only available for a subset of IH patients with no control data [21]. The superiority of TSH as an early marker of IH is consistent with the predilection of Ipi for thyrotroph damage. Iwama et al. [15] found ectopic CTLA4 expression in the mouse pituitary in only the thyrotrophs and lactotrophs, and the only circulating antibody shared amongst the seven IH patients in this study was directed against the thyrotroph. We speculate that antibody-mediated destruction of thyrotrophs with intracellular TSH release followed by TSH depletion might underlie the initial rise then fall of TSH in IH.

The most frequent IH symptoms in our study were fatigue and headache, consistent with previous data [3, 7, 11, 12, 22]. As in other studies [3, 11, 12], visual field defects and posterior pituitary dysfunction did not develop in our cohort. Although suprasellar extension is common in IH [17], there may be insufficient time for visual field disturbance to develop given the transient nature of pituitary enlargement.

TSH and ACTH were the most frequent deficiencies in the present study. However, a minority of IH patients never develop TSH deficiency, necessitating a high index of suspicion for hypophysitis in Ipi-treated patients even if TSH

does not fall. A recent combined analysis of 472 Ipi-treated patients found central hypothyroidism in 93% of IH patients, hypogonadism in 86%, hypocortisolism in 71%, hypoprolactinemia in 61% and GH deficiency in 29% [10]. Given that antibodies against lactotrophs were not found in any of the IH patients studied by Iwama et al. [15], the observed predominance of hypoprolactinemia may instead arise due to direct Ipi binding to CTLA4-bearing lactotrophs, or it may reflect rapid lactotroph destruction as occurs in pituitary apoplexy [23]. The hyperprolactinemia found in other IH studies [9, 11, 12] is probably related to the more typical effect of infundibular compression [5].

Though CNS imaging was primarily performed to exclude metastases and other mass lesions, pituitary enlargement appeared to be a sensitive and early sign of IH in our study and others [3, 5, 7, 11, 12]. The 'normal' radiological appearance of three patients may be explained by delays in MRI following IH diagnosis, or failure to capture dedicated pituitary views. In addition, pituitary appearance should be interpreted in light of age and gender [24]. As in our study, the majority of melanoma patients are older men, who have the smallest pituitary glands [24], and so the relative enlargement associated with IH may otherwise be missed [5]. Loss of the posterior pituitary bright spot and empty sella were noted in some of our patients and in other studies, but these abnormalities may be considered normal variants [5, 25, 26]. Pituitary fossa FDG avidity was found weeks prior to IH diagnosis in one patient, suggesting that pituitary inflammation may occur early in IH.

Regarding IH management, our findings support physiological glucocorticoid replacement as no endocrine recovery was achieved in the seven patients treated with supraphysiological doses (prednisolone 10–75 mg daily) and physiological doses were sufficient for normalizing pituitary size in our patients and in other studies [11, 12, 22]. None of the IH patients in our study were re-treated with Ipi, but cessation of Ipi does not appear to influence IH outcome [12].

In conclusion, an 80% fall in TSH had 100% specificity, albeit with 55% sensitivity, as an early marker for IH. Although periodic hormone levels may be performed in at-risk patients, especially in highly specialised quaternary oncology centres, our evidence now argues for serial TSH monitoring in all patients treated with Ipi. Larger, prospective studies of TSH monitoring in Ipi-treated patients are required to determine whether fT4 measurement is additive given that a normal TSH but low fT4 may occur in early central hypothyroidism. It is also possible that the sensitivity of TSH as an early detection tool for IH may be increased by more frequent sampling of TSH, particularly around the time of the third Ipi dose when IH incidence peaks. It remains to be seen whether other pituitary hormone measurements may be better early markers, although this is unlikely given that the thyroid and adrenal axes are the most frequently affected. Anti-pituitary antibodies, MRI and positron emission topography have been proposed as potential predictive tools [10–12]. However, these alternatives are more costly, less accessible and arguably more uncomfortable. In the absence of other reliable early markers of IH, and because of the life-threatening nature of undiagnosed IH and the relatively low cost of TSH measurement, we support serial TSH measurements in patients being treated with Ipi. We do not recommend routine cortisol monitoring to screen for IH.

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Compliance with ethical standards

Conflict of interest AMM: Advisory board MSD, Novartis, Chugai, Pierre Fabre, honoraria BMS, Roche. GVL: Consultant advisor to Amgen, BMS, Merck, Array, Novartis, Pierre-Fabre and Roche.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Formal consent was not required for this type of study.

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