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Ipilimumab-induced hypophysitis in melanoma patients: an Australian case series

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Key words
melanoma, ipilimumab, hypophysitis, immune-related adverse event, hypopituitarism, immunotherapy.

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Abstract

Background: Ipilimumab (Yervoy; Bristol-Myers Squibb) is a novel fully humanised monoclonal antibody that blocks cytotoxic T-lymphocyte antigen 4, an immune checkpoint molecule, to augment anti-tumour T-cell responses. It is associated with significant immune-related side-effects including hypophysitis.

Aim: We reviewed the clinical and biochemical characteristics of 10 patients with ipilimumab-induced hypophysitis (IH), and developed guidelines for the early detection and management of IH based on our experiences at three major teaching hospitals in Sydney.

Methods: All patients were evaluated at the Crown Princess Mary Cancer Centre and Department of Endocrinology, Westmead Hospital, Department of Endocrinology, Royal Prince Alfred Hospital, the Melanoma Institute Australia and Macarthur Cancer Therapy Centre, Campbelltown Hospital from 2010 to 2014. Relevant data were extracted by review of medical records. Main outcome measures included clinical features, hormone profile and radiological findings associated with IH, and presence of pituitary recovery.

Results: Ten patients were identified with IH. In four patients who underwent monitoring of plasma cortisol, there was a fall in levels in the weeks prior to presentation. The pituitary–adrenal and pituitary–thyroid axes were affected in the majority of patients, with the need for physiological hormone replacement. Imaging abnormalities were identified in five of 10 patients, and resolved without high-dose glucocorticoid therapy. To date, all patients remain on levothyroxine and hydrocortisone replacement, where appropriate.

Conclusions: There is significant morbidity associated with development of IH. We suggest guidelines to assist with early recognition and therapeutic intervention.

Introduction

Ipilimumab (Yervoy: Bristol-Myers Squibb, New York, NY, USA) is a fully humanised monoclonal antibody that blocks cytotoxic T-lymphocyte antigen 4 (CTLA-4), an immune checkpoint molecule, to augment anti-tumour T-cell responses. In metastatic melanoma, ipilimumab was the first drug shown to improve overall survival in a phase 3 trial.[1] In 2013, ipilimumab was listed on the Pharmaceutical Benefits Scheme (PBS) in Australia for use as monotherapy in patients with unresectable stage III and IV metastatic melanoma. Despite its clinical efficacy, ipilimumab can cause potentially life-threatening immune-related adverse events (irAE) due to unrestrained T-cell activation. In clinical trials, irAE occurred in 61–77% of patients, with 10–23% experiencing a grade 3 adverse event or higher.[2] The most commonly reported irAE were enterocolitis, rash and hepatitis, while the most common endocrinopathy was hypophysitis with hypopituitarism.[3,4] There is some evidence that autoimmune toxicity may correlate with more favourable tumour control.[3]

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Abbreviations: iH, ipilimumab-induced hypophysitis; irAE, immune-related adverse events.

Ipilimumab-induced hypophysitis (IH) is classified as an autoimmune hypophysitis, and is defined by decreased levels of pituitary and secondary target hormones.[5] Its incidence varies between 0% and 17%, with differences depending on dosage, frequency of hormonal monitoring and detection rates, as presenting symptoms are often similar to cancer-related constitutional symptoms.[4,6] In Australia, an incidence of 8% has been reported, with the local prevalence likely to increase with greater use of ipilimumab, following its listing on the PBS.[7] Given the significant morbidity associated with this condition, it is important that this condition is recognised promptly by the medical community outside of the highly supervised clinical trial environment. Here, we describe a case series of 10 patients with metastatic melanoma who developed IH.

Methods

Ten cases of IH were retrospectively identified in patients with advanced and/or metastatic melanoma across four centres between 2010 and 2014. Patients were evaluated at the Crown Princess Mary Cancer Centre and Department of Endocrinology, Westmead Hospital, the Department of Endocrinology, Royal Prince Alfred Hospital, the Melanoma Institute Australia and Macarthur Cancer Therapy Centre, Campbelltown Hospital. Patients were identified to have IH if they satisfied one or more of the following:[6] (i) secondary adrenal insufficiency with acute onset of symptoms, associated with low serum cortisol levels and inappropriately low adrenocorticotrophin (ACTH) levels on biochemistry, (ii) secondary hypothyroidism with persistently low free thyroxine (fT4) level and an inappropriately normal or suppressed thyrotrophin (TSH) level, (iii) magnetic resonance imaging (MRI) changes in the pituitary gland consistent with hypophysitis. The authors were directly involved in their clinical care, and data were extracted by chart review. Two patients have been described previously.[8]

Results

All 10 patients had advanced melanoma, and nine patients received standard therapy with ipilimumab 3 mg/kg every 3 weeks. Patient 5 received four doses of induction ipilimumab at 10 mg/kg followed by maintenance therapy every 3 months. Three patients received dacarbazine before ipilimumab, and one patient, patient 4, received pembrolizumab, an anti-programmed death 1 (PD-1) antibody, 8 months before treatment with ipilimumab. Patient 7 received the NY-ESO-1 vaccine prior to commencement of ipilimumab.

Baseline characteristics are described in Table 1. The mean patient age was 59 , and nine were male. The most

Table 1 Characteristics of patients with ipilimumab-induced hypophysitis (n = 10)

	Age (years)	Sex	Disease stage	Presenting symptoms	Headache	Cerebral metastases	Prior treatment	Number of ipilimumab cycles	Time of presentation (weeks after initiating ipilimumab)	MRI brain
Patient 1	60	Female	IV	Shortness of breath, lethargy, nausea	No	No	Dacarbazine	4	11	Normal
Patient 2	53	Male	IV	Headache, fatigue, loss of appetite, weight loss	Yes	No	Dacarbazine	4	12	Enlarged pituitary with increased uptake on PET scan
Patient 3	69	Male	IV	Lethargy, nausea, dizziness	No	No	Nil	2	10	Normal
Patient 4	61	Male	IV	Lethargy, cold intolerance, nausea	No	Yes	Pembrolizumab (Anti-PD1)	4	6	Normal
Patient 5	50	Male	IIIc	Lethargy and fatigue	No	No	Nil	Four cycles with 12 weekly maintenance therapy	24	Normal
Patient 6	70	Male	IV	Headache, fatigue, unsteady gait	Yes	No	Nil	2	7	Enlarged pituitary
Patient 7	46	Male	IIIc	Headache, lethargy, nausea, anorexia	Yes	No	NY-ESO-1 vaccine	4	13	Normal CT but increased pituitary uptake on PET scan
Patient 8	53	Male	IV	Headache, shortness of breath, fatigue, nausea, decreased exercise tolerance, abdominal discomfort	Yes	No	Nil	4	12	Normal
Patient 9[8]	65	Male	IV	Fatigue, lethargy, headache, postural dizziness, body ache, anorexia	Yes	No	Nil	4	7	Enlarged pituitary
Patient 10[8]	63	Male	IV	Headache, emesis	Yes	No	Radiotherapy to T7–T9	4	7	Enlarged pituitary

CT, computed tomography; MRI, magnetic resonance Imaging; PD-1, programmed death receptor 1; PET, positron emission tomography.

common presenting symptoms were profound fatigue and nausea, with mean onset of symptoms 9 weeks (range: 7–13 weeks) ($n = 9$) from the first dose, except patient 5, who was receiving maintenance ipilimumab and presented at 24 weeks. Headache was present in six patients (2, 6, 7, 8, 9 and 10). Patients 1, 4, 7 and 8 required hospitalisation due to nausea and significant weakness. Patient 3 had significant hyponatraemia on admission (serum sodium 123 mmol/L; ref 135–145 mmol/L).

Table 2 lists the available laboratory values at baseline and at the onset of hypophysitis, following treatment with ipilimumab. Five patients underwent plasma cortisol monitoring during ipilimumab treatment, with a variable decrease prior to presentation (Fig. 1). Nine patients had low early morning cortisol levels (range <28–125 nmol/L; ref 130–650 nmol/L) at presentation, associated with inappropriately low levels of ACTH (range <1.1–4.3 pmol/L; ref 1.8–11.4 pmol/L), consistent with secondary adrenal insufficiency. Patient 10 was provisionally treated for cerebral metastases with dexamethasone, then changed to prednisone (initially 25 mg/day, then 10 mg/day) when hypophysitis was diagnosed following pituitary MRI with other evidence of hypopituitarism. Insulin tolerance tests were performed in patients 2 and 5, prior to exposure to exogenous glucocorticoids, and patient 10, 2 months after treatment with prednisone 10 mg/day (dose withheld on day of test). Their peak cortisol levels were <28 nmol/L, 301 nmol/L, and 17 nmol/L, respectively, in response to nadir plasma glucose levels of <1.9 mmol/L. While it was difficult to interpret the results of patient 10, given his prior treatment with prednisone, the lack of cortisol response was thought to be consistent with ACTH deficiency resulting from hypophysitis, given the changes observed on MRI scan, together with other hormonal evidence supportive of this diagnosis.

Patients 9 and 10 were treated with an intermediate immunosuppressive regimen of prednisone 30 mg/day, tapered over 3 weeks, followed by replacement hydrocortisone and prednisone respectively. Patients 1, 4, 7 and 8 required hospitalisation and received hydrocortisone (50 mg IV thrice daily) for 2 days, due to severity of their presenting symptoms, and inability to tolerate oral medications. They were later discharged on replacement hydrocortisone. Patients 2, 3, 5 and 6 were treated acutely with physiological doses alone. All patients received appropriate maintenance hormonal replacement with 15–30 mg/day of hydrocortisone (or equivalent doses of prednisone).

Of the other anterior pituitary hormones, five patients (3, 6, 7, 9 and 10) had low fT4 and inappropriately low TSH levels at diagnosis which was consistent with secondary hypothyroidism. All were commenced on

Table 2 Laboratory values of patients at baseline before starting ipilimumab and at onset of hypophysitis ($n = 10$)

	Morning ACTH (1.8–11.4 pmol/L)		Morning cortisol (138–650 nmol/L)		TSH (0.4–3.5 mIU/L)		Free T4 (10–22 pmol/L)		Total testosterone (9.5–28 nmol/L)		LH (2–10 U/L)		FSH (1.5–3.0 U/L)		Growth Hormone (0–15 mIU/L)		IGF-1 (5–24 nmol/L)		Prolactin (95–500 mIU/L)	
	Initial	At Dx	Initial	At Dx	Initial	At Dx	Initial	At Dx	Initial	At Dx	Initial	At Dx	Initial	At Dx	Initial	At Dx	Initial	At Dx	Initial	At Dx
Patient 1	–	–	314	48	0.78	0.01	–	10.4	–	–	–	–	–	–	–	–	–	–	–	–
Patient 2	–	3.4	220†	53	0.96	1.68	16	11	–	16.6	–	5.4	–	3.7	–	–	–	–	–	163
Patient 3	–	<1.1	–	<28	2.47	3.01	–	4	–	1.3	–	1.6	–	4.7	–	0.2	–	4	–	–
Patient 4	–	2.9	151†	50	1.12	0.48	15.1	13.5	–	15.7	–	11.9	–	23.8	–	–	–	22	–	135
Patient 5	4.0	3.5	295	125	1.62	2.69	16	14	10.4	10.5	–	–	–	–	–	–	–	–	–	332
Patient 6	–	3.8	281†	<28	1.19	0.07	10.5	7.6	–	0.2	–	–	–	–	–	–	–	–	–	138
Patient 7	–	<1.1	–	50	–	2.76	–	6.6	–	<0.1	–	3.7	–	6.1	–	2.2	–	3.3	–	258
Patient 8	3.3	<1.1	290	<28	0.76	1.56	19.1	14.2	–	10.9	–	5.7	–	9.9	–	<0.2	–	27.5	–	100
Patient 9	–	1.2	323	<28	2.47	0.20	–	8.9	–	2.8	–	3.7	–	14.0	–	0.8	–	24	–	219
Patient 10	–	4.3	–	619	–	0.24	–	11.4‡	–	0.9	–	2.2	–	9.4	–	0.3	–	21.9	–	217

†Random afternoon cortisol level. ‡Normal range 12–22 pmol/L. ACTH, adrenocorticotropic hormone; At Dx, at diagnosis; FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor 1; LH, luteinising hormone; TSH, thyroid-stimulating hormone.

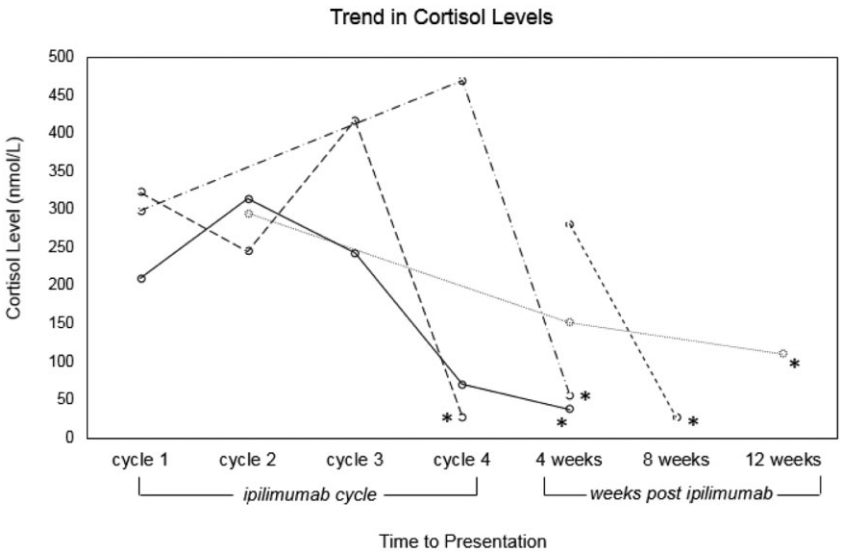

Figure 1 Fall in cortisol levels following initiation of ipilimumab. 'Weeks post-ipilimumab' denotes time frame following completion of ipilimumab cycles. Patients 1 and 9 received four cycles of ipilimumab; patient 6 received two cycles, and patient 5 received four cycles followed by maintenance therapy. *Denotes time of presentation. (-•-), Patient 1; (-◦-), patient 5; (-→-), patient 6; (-•-), patient 7; (-•-), patient 9.

levothyroxine, except for patient 7, who had spontaneous recovery of thyroid function after 2 weeks. Patients 1 and 4 developed marked decreases in TSH, and levothyroxine was commenced despite normal levels of fT4, given other evidence of hypophysitis, in anticipation of a future decline in fT4, and has not yet been withdrawn.

Total testosterone levels were low in five of nine men (patients 3, 6, 7, 9 and 10). These patients were also more likely to have secondary hypothyroidism, perhaps reflecting the severity of the hypophysitis. In three out of five men (patients 3, 6 and 7) who were initially hypogonadal, testosterone replacement was not commenced and serum testosterone levels subsequently normalised in parallel with their clinical recovery. Patients 9 and 10 commenced testosterone replacement as gonadal function did not recover, but this was self-ceased due to lack of subjective improvement. Luteinising hormone was low in patient 3 and inappropriately low in three of seven patients for the level of testosterone, consistent with secondary hypogonadism. Age-corrected insulin-like growth factor 1 (IGF-1), an integrated measure of growth hormone secretion and action, was low in two of six patients. Prolactin levels were normal (low to mid-range) in the six patients in whom they were measured.

Imaging abnormalities were present in the five of the six patients who presented with headache. Patients 2, 6, 9 and 10 had MRI evidence of pituitary enlargement, while patients 2 and 7 had abnormal pituitary uptake on positron emission tomography scan. Patient 7 had normal pituitary imaging on computerised tomography scan, 4 days after commencement of hydrocortisone. Following commencement of replacement hydrocortisone (patients 2 and 7), and prednisone (patients 9 and 10), repeat imaging after 6 months showed a reduction in size of the pituitary gland. Repeat imaging was not performed in patient 6 nor in the five patients whose initial pituitary imaging was normal.

All patients had almost immediate resolution of symptoms following hormonal replacement. Of the five patients in whom hypophysitis was diagnosed before completion of treatment, three continued on ipilimumab. According to current practice guidelines, the next dose of ipilimumab was delayed until symptoms had resolved, and the dose of glucocorticoids was ≤7.5 mg/day prednisone (or equivalent).[9] Ipilimumab was discontinued in two patients due to progression of disease. To date, all remain on the same hormonal replacement with no evidence of recovery of affected pituitary hormone function.

Discussion

CTLA-4 is an immune molecule that dampens T-cell activation and proliferation in response to antigen presentation. Ipilimumab inhibits CTLA-4, resulting in improved anti-tumour immunity. A spectrum of irAE including IH has been reported when ipilimumab was used to treat both solid and haematological malignancies.[4] IH tends to occur later compared with other irAE involving the skin and gastrointestinal tract, which typically develop between 3 and 7 weeks. The average onset of IH occurs at a median time of 11 weeks after initiation of ipilimumab, with a higher incidence reported in patients treated with ipilimumab 9 mg/kg versus 3 mg/kg (15% vs 2%).[5,10] It is also associated with a survival benefit, possibly reflecting successful immune augmentation.[4]

IH shares similar clinical and radiological features to classic autoimmune (lymphocytic) hypophysitis (LyH). However, it is associated with older age, and has a male predominance, which may reflect the population undergoing treatment with ipilimumab.[4] It also results in preferential hypofunction of corticotrophic and thyrotrophic cells.[10] The majority of male patients have hypogonadotrophic hypogonadism.[11] Low levels of IGF-1, and elevated, as well as low levels of prolactin, have been reported.[10,12] The extent of recovery of pituitary function following IH is unclear. There are published reports of recovery of pituitary–thyroid function in 37–50% of patients,[10] pituitary–gonadal function in 57% of men[13] but recovery of pituitary–adrenal function (or discontinuation of glucocorticoid replacement therapy) occurs rarely.[10,11,14]

The pathogenesis is considered autoimmune. As apart from the similarities it shares with LyH, there is infiltration of other tissues affected by irAE with cytotoxic T cells.[15] CTLA-4 gene polymorphisms are associated with the development of autoimmune diseases such as Grave's disease and Hashimoto's thyroiditis.[16] A higher rate of hypophysitis has also been reported with dual blockade of both CTLA-4 and PD-1,[6] another immune checkpoint regulator, while treatment with cytotoxic chemotherapy, which depletes immune cells, has a protective effect.[6,10] Mouse studies also suggest a direct toxic effect of ipilimumab on the pituitary through complement activation,[17] and pituitary antibodies have been demonstrated in patients with IH.[17]

Half of our patients received other therapies for melanoma prior to ipilimumab treatment. Patient 7 was treated with the NY-ESO-1 peptide vaccine, another form of immunotherapy against tumour-specific antigens expressed by cancer cells, which has been associated with the development of thyroiditis,[18] but not pituitary dysfunction. Patient 4 received pembrolizumab 8 months prior to ipilimumab. Pembrolizumab is a monoclonal antibody against PD-1, another key immune checkpoint molecule and has also been associated with irAE including hypophysitis. However, given the normal baseline pituitary function prior to initiation of ipilimumab, as well as the time interval between pembrolizumab therapy and the onset of symptoms, it is unlikely to be the cause of hypophysitis, although this cannot be completely excluded given the combination of anti-PD-1 therapy and ipilimumab may increase the risk of developing IH.[6]

The majority of patients in our series were treated with ipilimumab at the PBS listed dose of 3 mg/kg every 3 weeks, with a mean onset of symptoms after 9 weeks, consistent with published reports,[10] with headache being a common presenting symptom.[11,13,19] None of our patients experienced visual dysfunction, which although infrequent, has been reported in IH.[20] Pituitary imaging was normal in half of our patients, similar to the findings by Min *et al*.,[19] but in contrast to other case series in which abnormal imaging has been reported in up to 100% of patients.[4] Variability in the reported MRI findings may reflect the timing of the scan within the natural history of this disorder, prior glucocorticoid therapy or under-reporting of subtle changes in pituitary size in an older patient population.[4,6] The characteristic MRI changes of IH are usually of lesser magnitude when compared with LyH, and include diffuse pituitary enlargement with typically homogenous enhancement, and enlargement of the pituitary stalk (without diabetes insipidus) in up to 60%. Pituitary enlargement may precede the clinical diagnosis of IH by several weeks[4,21,22] and subsequent scans often reveal reduction in size of the pituitary.[4,6,8]

The benefit of immunosuppressive glucocorticoid therapy in IH is unknown, in contrast to other irAE, such as colitis, where rapid permanent reversal occurs following treatment,[10–12] without compromising the anti-tumour effectiveness of ipilimumab.[3] Current recommendations for management of IH include withholding ipilimumab, treatment with immunosuppressive glucocorticoids (1–2 mg/kg/day of prednisone or equivalent, tapered over 4 weeks) and resumption of ipilimumab when symptoms have resolved, and the patient is receiving ≤7.5 mg prednisone (or equivalent) per day.[9] However, recovery of pituitary function, unlike the other irAE does not usually occur,[10] and the rationale of high-dose (immunosuppressive) glucocorticoid therapy has therefore been questioned. None of our patients received the glucocorticoid doses recommended in the guidelines. The majority received a maximum dose of hydrocortisone 150 mg/day for 2 days followed by physiological doses (15–20 mg/day), and all demonstrated rapid clinical and radiological improvement.[19] Immunosuppressive glucocorticoids may be indicated, however, if vision is compromised.[12] Failure to appreciate the lack of benefit of high-dose glucocorticoid therapy in reversing hypophysitis may also result in an adrenal crisis when glucocorticoid therapy is (inappropriately) withdrawn.[23] Thus, our cases suggest that immunosuppressive glucocorticoid therapy may not be necessary, and may only be required for patients with visual disturbance due to pituitary enlargement. Similarly, continuation of ipilimumab therapy does not appear to have any further detrimental effect on pituitary function, and may be continued if otherwise clinically appropriate.

To date, all of our patients continue to be treated with glucocorticoid replacement, without evidence of recovery of their pituitary–adrenal axis. One patient had spon-

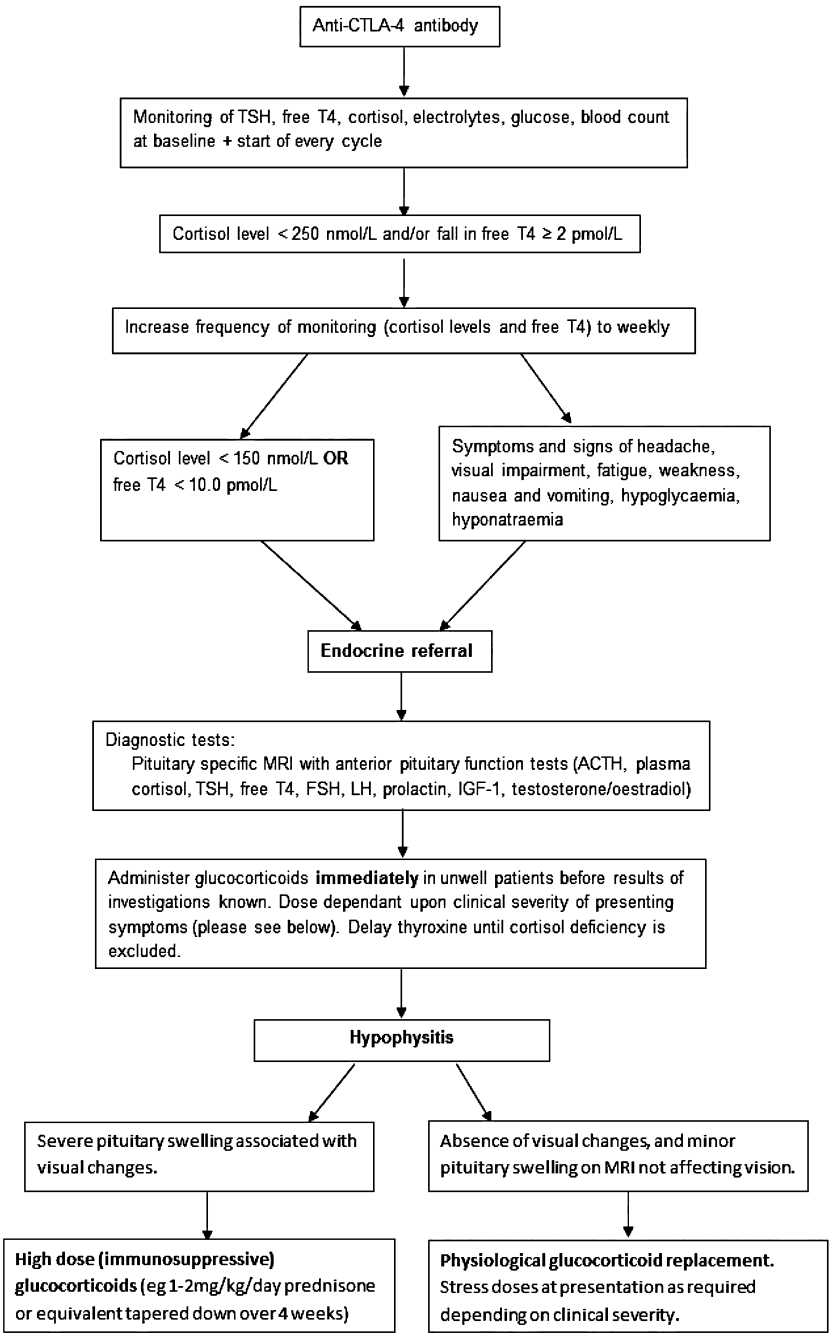

Figure 2 Flowchart for diagnosis and treatment of hypophysitis induced ipilimumab. ACTH, adrenocorticotropic hormone; CTLA-4, cytotoxic T-lymphocyte antigen 4; free T4, thyroxine; FSH, follicle-stimulating hormone; IGF-1, insulin growth factor receptor 1; LH, luteinising hormone; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone.

taneous recovery of his pituitary–thyroid axis, while three men who were initially hypogonadal demonstrated recovery of their pituitary–gonadal axis.

In our case series, half of the patients had a random serum cortisol measured intermittently prior to the onset of clinical hypophysitis. In the two patients whose hypophysitis developed relatively late, there was a gradual decline in their random serum cortisol concentrations, whereas in the three patients whose hypophysitis developed relatively early, the drop in their serum cortisol levels was both rapid and dramatic (Fig. 1). It is also interesting to note that fT4 levels in patients 3 and 6 in our series fell 2–3 weeks prior to their presentation with hypocortisolism. While interpretation of dynamic changes in pituitary or target hormone levels is difficult, the use of simple guidelines for monitoring of hormone levels in patients receiving ipilimumab may facilitate earlier diagnosis and prevent significant

morbidity and mortality due to hypopituitarism. Apart from educating patients regarding the prompt reporting of symptoms related to possible irAE, it is currently recommended that laboratory testing (cortisol, ACTH, TSH, fT4) and clinical evaluation should be done at baseline and at the start of every cycle 3–4 weeks apart.[12,20] However, such recommendations do not provide advice about the interpretation of dynamic changes in pituitary function. There may be an observable decline in hormone levels (both trophic and target) during development of hypophysitis prior to the onset of symptoms in some patients, which should alert clinicians to the possibility of hypophysitis, prompting early referral to an endocrinologist.

We therefore propose the guidelines outlined in Figure 2, based on our clinical experience. Serum levels of morning cortisol, TSH and fT4 should be measured at baseline and at the start of every cycle. If early morning cortisol is ≤250 nmol/L, or if there is a fall in fT4 ≥ 2 pmol/L, frequency of monitoring should be increased to weekly. Urgent referral to an endocrinologist is indicated if early morning cortisol is ≤ 150 nmol/L, fT4 ≤ 10 pmol/L or if there is headache, visual impairment and/or symptoms of hypoadrenalism. Anterior pituitary function tests including ACTH, cortisol, TSH, fT4, prolactin, IGF-1, growth hormone, FSH, LH, testosterone (men), oestradiol (women) levels should be taken before administration of glucocorticoids, which should be given immediately in the unwell patient before results of investigations are known. High-dose glucocorticoids at immunosuppressive doses (1–2 mg/kg/day of prednisone or equivalent) are advisable if there is visual compromise. However, in the absence of visual disturbances, physiological doses can be given, with stress doses given at presentation, depending on the severity of the presenting symptoms. Treatment with levothyroxine should be delayed until cortisol deficiency is excluded (and treated) given the risk of precipitating an adrenal crisis. An insulin tolerance test may be required if there is doubt about the presence of ACTH (and therefore cortisol) deficiency, but this should be at the discretion of the endocrinologist. Monitoring should be continued for at least 4 months after commencing ipilimumab, although the latency period for developing IH may be up to 19 months.[6] The increased risk of developing IH in patients previously treated with inhibitors of other immune checkpoint regulators such as PD-1 may also warrant more frequent monitoring.

Conclusion

As the use of ipilimumab becomes more widespread, hypophysitis, a previously uncommon condition, will be increasingly encountered by clinicians. Thus, guidelines for surveillance and management of IH are worthwhile to ensure early recognition and timely intervention to prevent the significant morbidity and potential mortality associated with this irAE.[7]

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BRIEF COMMUNICATIONS

Disseminated *Mycobacterium haemophilum* skeletal disease in a patient with interferon-gamma deficiency

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Abstract

Disseminated non-tuberculous mycobacterial (NTM) infection is rare in immunocompetent adults. Anti-interferon-gamma (IFN-γ) autoantibodies have recently been associated with NTM infections, particularly in patients of Asian ethnicity. We describe a case of disseminated *Mycobacterium haemophilum* skeletal infection due to anti IFN-γ autoantibodies in a 71-year-old Cambodian man. He responded to a combination of anti-mycobacterial antibiotics without requirement for immunomodulator therapy. Testing for acquired IFN-γ deficiency due to IFN-γ autoantibodies should be considered when standard tests for immunodeficiency are negative in patients with unusual or severe opportunistic infections, including NTM.

A 71-year-old Cambodian-born man, permanent resident of Australia with a history of frequent travels to South East Asia, presented with 2 days of cough, fever and left-sided pleuritic chest pain on a background of atrial fibrillation on warfarin. Chest X-ray demonstrated left lower lobe consolidation. He was treated for presumptive community-acquired pneumonia to which he had a complete clinical response. One month later, he travelled to Cambodia for 2 weeks. Two months post-return, he presented with 3 weeks of fever, night sweats,

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