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Association of Ipilimumab Therapy for Advanced Melanoma With Secondary Adrenal Insufficiency: A Case Series

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Abstract

Objective—To present a case series of ipilimumab-related secondary adrenal insufficiency.

Methods—In this cases series, we review the presentation, evaluation, diagnosis, and management of patients with advanced melanoma who received ipilimumab and were referred to our endocrinology clinic for evaluation of hormonal abnormalities.

Results—Seven patients presented with symptoms, signs, or biochemical evidence of adrenal insufficiency 6 to 12 weeks after starting ipilimumab therapy. Ipilimumab is a CTLA-4 monoclonal antibody that is approved for the treatment of metastatic melanoma and has widespread use for this disease. All 7 patients had biochemical evidence of profound secondary adrenal insufficiency. Thyroid function abnormalities, central hypogonadism, and low insulinlike growth factor 1 levels were seen in a subset of patients. Only 2 patients had abnormal findings on pituitary magnetic resonance imaging. Posterior pituitary function remained normal.

Conclusions—Our findings suggest that the enhanced immune response associated with ipilimumab therapy may have a predilection for corticotroph and possibly thyrotroph cells. We recommend periodic hypothalamic-pituitary-adrenal axis monitoring for patients on this therapy.

Keywords

ipilimumab; monoclonal antibodies; melanoma; hypophysitis; autoimmunity; adrenal insufficiency; corticosteroids; pituitary gland

Introduction

Ipilimumab is a fully human monoclonal antibody against cytotoxic T-lymphocyte antigen **4** (CTLA-4) that was recently approved by the US Food and Drug Administration for the treatment of metastatic melanoma (1). CTLA-4 is an immunoregulatory protein expressed on the cell surface of helper T lymphocytes. It counterbalances the T-cell activation mediated by CD28, a positive immune response regulator. As a result, the proliferation of T

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Abbreviations: cytotoxic T-lymphocyte antigen 4; TSH = thyrotropin

lymphocytes and secretion of interleukin 2 are attenuated by CTLA-4 (2). The potent anticancer efficacy of ipilimumab therapy has been demonstrated in randomized controlled trials in which investigators observed improved overall survival in patients with previously treated or untreated metastatic melanoma (3,4). In conjunction with the beneficial effects of ipilimumab, a variety of immune-related adverse events have been associated with this therapy, including hypophysitis and thyroiditis (3,5). The incidence of autoimmune hypophysitis in anti-CTLA-4 clinical trials ranges from 0% to 17% (6). Herein, we describe 7 patients with advanced melanoma treated with ipilimumab who were referred to our endocrine practice because of secondary adrenal insufficiency.

Methods

The authors evaluated the described patients in the Brigham and Women's Hospital outpatient endocrine clinic after referral from the oncology service; the authors continue to care for these patients longitudinally. This individual case series was created by extracting and summarizing relevant data from chart review with removal of individual identifiers. Because this was not a systematic research investigation of all patients treated with ipilimumab, rather an observational report of a series of clinic patients seen by the authors, institutional review board approval was not required. The authors have no involvement in the clinical trials with ipilimumab for metastatic melanoma.

Case Series

All 7 patients included in this cases series had stage IV metastatic melanoma and were enrolled in a clinical trial involving ipilimumab therapy. The dosage of ipilimumab in all patients was 10 mg/kg administered every 3 weeks. The average age was 58.4 years, and 6 of the 7 patients were men. Patients were screened for adrenal insufficiency after presenting with symptoms that included fatigue, malaise, lethargy, fever, or hypotension. Five of 7 men reported headaches as well. The onset of symptoms occurred after an average of 9.4 weeks on ipilimumab therapy (range, 6-12 weeks).

The cases are summarized in Table 1. All patients had very low serum morning cortisol levels, ranging from 0.45 to 1.1 μg/dL (morning reference range, 6.2-19.4 μg/dL) with concomitant undetectable corticotropin levels (Table 2). None had received exogenous glucocorticoids within 6 months of presentation. The data were consistent with secondary adrenal insufficiency from hypothalamic/pituitary disease. Cosyntropin stimulation testing was not performed. Only 1 of 7 patients presented with transient and mild hyponatremia. No other electrolytes or glucose abnormalities were present. Ipilimumab was not discontinued in most of the patients; it was discontinued in Patient 7 because of hypophysitis and in Patient 1 because of temporal arteritis. Results of evaluation for other anterior pituitary hormonal deficiencies are shown in Table 2. Four of the 7 patients (Patients 1, 2, 5, and 6) were on stable dosages of levothyroxine and had normal thyroid function at baseline. During the course of ipilimumab therapy, Patient 1 and Patient 5 developed marked decrements in thyrotropin (TSH), Patient 6 had a mild reduction in TSH, and Patient 2 had a frankly low free thyroxine concentration with an inappropriately normal TSH level. Two of the remaining 3 patients without preexisting thyroid disease (Patients 3 and 4) also developed

low free thyroxine with inappropriately low TSH levels, consistent with central hypothyroidism.

Total testosterone levels were low in 5 of the 6 men in the series. In these 5 hypogonadal men, luteinizing hormone was low or inappropriately normal. Age-corrected insulinlike growth factor 1, an integrated measure of growth hormone secretion and action, was low in 3 of the 5 hypogonadal men. None of the patients had hyperprolactinemia or evidence of diabetes insipidus.

Brain imaging occurred on a regular basis in all patients as part of melanoma surveillance. During the course of ipilimumab therapy, Patient 4 and Patient 5 developed diffuse pituitary enlargement with gadolinium enhancement. In contrast, pituitary imaging remained normal during our observation period in the other 5 patients (Patients 1, 2, 3, 6, and 7). The magnetic resonance imaging results for Patient 4 are shown in Figure 1. Before beginning ipilimumab, magnetic resonance imaging of the pituitary region was completely normal (Fig. 1, Panel A). Eight weeks after starting therapy, this patient developed headaches, fatigue, and lightheadedness, and findings from laboratory studies were consistent with panhypopituitarism (Table 2). Repeated magnetic resonance imaging revealed homogeneous enlargement of the pituitary with suprasellar extension (Fig. 1, Panel B). One month after initiation of hydrocortisone therapy, the pituitary appeared normal on magnetic resonance imaging (Fig. Panel C) and the patient's headaches improved. This rapid resolution was thought to be most consistent with a reversible hypophysitis and not metastatic disease. It is unclear whether the reduction in pituitary size was a spontaneous process or a response to exogenous glucocorticoids; the patient received only 15 mg of hydrocortisone daily. However, previous studies have suggested that replacement-dosage exogenous glucocorticoids may reduce pituitary size on serial neuroimaging (7). All patients received appropriate hormonal replacement therapy with hydrocortisone, as well as levothyroxine and testosterone when appropriate. Replacement hydrocortisone dosages ranged from 15 mg to 30 mg daily, usually divided into 2 doses. In general, patients had resolution of symptoms and felt greatly improved with hormonal replacement. Patient 5 died of widely metastatic melanoma, but the other 6 patients remain alive 2 to 28 months after presentation.

Discussion

We have presented a series of 7 patients who developed secondary adrenal insufficiency while taking ipilimumab therapy for stage IV metastatic melanoma. The symptoms and abnormal laboratory studies usually occurred after 3 to 4 doses of ipilimumab, which is administered every 3 weeks. Presenting symptoms were nonspecific, although fatigue, lethargy, and headache were the most common complaints. In all cases, serum cortisol levels were very low with undetectable corticotropin, consistent with a hypothalamic/pituitary disorder. If not recognized, adrenal insufficiency can be life threatening, and the symptoms may be misinterpreted as progression of disease or adverse effects of cancer therapy. In the patients we describe, the adrenal insufficiency appeared permanent and did not reverse, even when pituitary imaging reverted to normal (Patient 4). To extend previous observations of ipilimumab-related hypophysitis, we hypothesize that ipilimumab may cause a preferential

autoimmune destruction of corticotropin cells of the anterior pituitary, leading to irreversible secondary adrenal insufficiency.

We also found evidence of other anterior pituitary abnormalities. Six of 7 patients had abnormal thyroid function while on ipilimumab, which was consistent with TSH suppression and overt central hypothyroidism in some cases. However, we cannot exclude sick euthyroid syndrome or effects that other medications may have had on thyroid function. Note that all patients were seen as outpatients when laboratory tests were performed, and, thus, this would not fit the typical “sick euthyroid” clinical scenario. Similarly, the hypogonadotropic hypogonadism found in 5 of the 6 men suggests decrements of luteinizing hormone from ipilimumab, but we cannot confidently exclude effects of other drugs or acute illness on the hypothalamic-pituitary-gonadal axis. The low insulinlike growth factor 1 levels in some patients were consistent with, but not diagnostic of, ipilimumab-related hypophysitis.

Care of patients with secondary adrenal insufficiency while on ipilimumab can be challenging because high dosages of glucocorticoid can suppress the ipilimumab-induced immune attack and block the clinical effect of the drug. Because the goal of anti-CTLA-4 therapy is to stimulate an immune response against cancer cells, treating patients with glucocorticoid could theoretically reverse the antitumor benefit of CTLA-4 blockade. Interestingly, our own experience and the accumulated evidence in the literature suggest that systemic glucocorticoid administration does not alter the antitumor activity of CTLA-4 blockade (5,7-9). Clearly, more data are required to clarify this issue. In the 7 patients we describe, we initiated therapy with physiological dosages of glucocorticoid, and we also replaced levothyroxine and/or testosterone if hypothyroidism and hypogonadism persisted. We did not initiate growth hormone therapy in any patients. Unlike corticotropin deficiency, some of the other pituitary deficiencies appear to be reversible; in Patients 1, 3, and 4, TSH levels normalized in 2 to 8 weeks. This could suggest reversal from ipilimumab-related suppression or that the abnormality was secondary to other mechanisms, such as medications or the sick euthyroid syndrome.

It is unclear why the anterior pituitary is particularly susceptible to ipilimumab therapy. Although polymorphisms in the *CTLA4* gene have been suggested to be related to certain autoimmune endocrinopathies such as Graves disease and Hashimoto thyroiditis (10,11), there have been no reports describing the association of *CTLA4* polymorphisms with ipilimumab-related hypophysitis. In a phase I trial of ipilimumab therapy, Sanderson et al (12) noted that the GG genotype in JO33 that encodes 3 alleles correlating with the level of *CTLA4* expression on T cells was associated with a higher risk of developing autoimmunity with CTLA-4 blockade. Epigenetic studies may help us understand the mechanism of secondary adrenal insufficiency associated with ipilimumab therapy.

Of note, 4 patients in our series were treated simultaneously with bevacizumab along with ipilimumab. To our knowledge, there have been no reports suggesting an association of autoimmune hypophysitis or secondary adrenal insufficiency with bevacizumab therapy.

Limitations of our report include the small number of patients and the observational nature of our findings.

Conclusion

In 7 patients, ipilimumab therapy was associated with symptomatic corticotropin deficiency and severe hypoadrenalism, with the potential for life-threatening adrenal crises. Other anterior pituitary abnormalities including TSH, luteinizing hormone, and insulinlike growth factor 1 deficiencies were found in many of the patients. None developed posterior pituitary hormone deficiency. These findings suggest that the enhanced immune response associated with ipilimumab therapy may have a predilection for corticotroph and possibly thyrotroph cells. Periodically screening these patients for adrenal insufficiency and other pituitary hormone deficiencies is therefore important. The incidence of ipilimumab-related endocrinopathies may become more common as use of this drug increases. Our descriptions may provide novel insights for future clinical care decisions and research studies.

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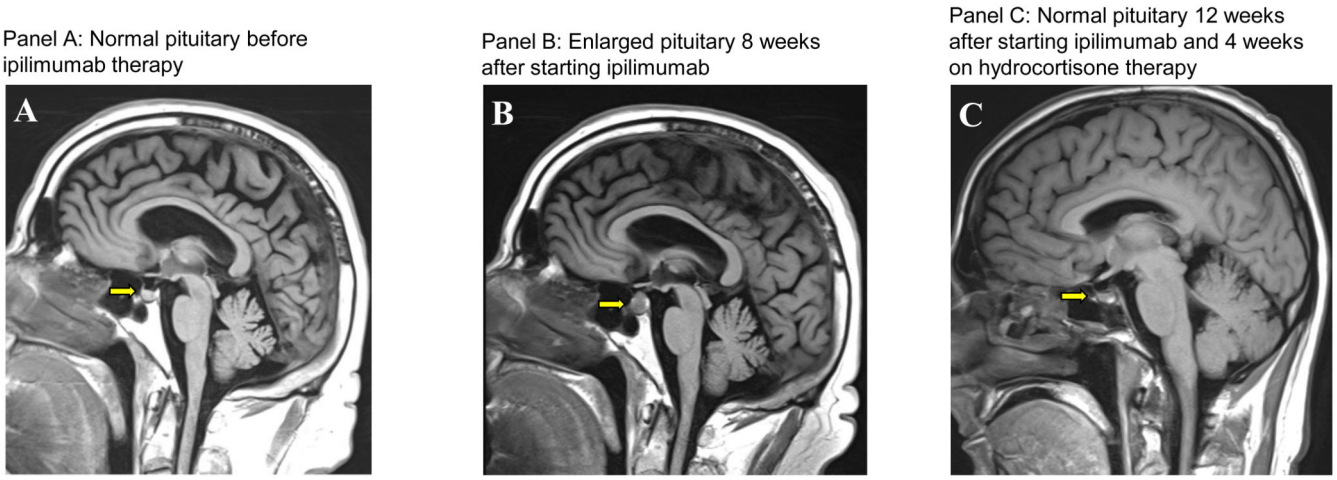

Figure 1.

Sequential MRI scans of pituitary in a 55 year old man with headaches and panhypopituitarism on ipilimumab (Case 4).

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Table 1

Demographic data and MRI results

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Sex	male	male	male	male	female	male	male
Age (years)	64	44	57	55	70	55	64
Time of Presentation (weeks after initiating ipilimumab)	6	12	9	8	12	12	10
Reason for referral	Fatigue and headache	Fatigue, and headache	Headache, and high fever	Low energy, headache and lightheadedness	Fatigue, and headache	Hypotension	Malaise, anorexia, and lethargy
On levothyroxine prior to ipilimumab	Yes	Yes	No	No	Yes	Yes	No
MRI brain	Normal	Normal	Normal	Enlarged pituitary	Enlarged pituitary	Normal	Normal

Table 2

Laboratory values before and after ipilimumab therapy

	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7		Reference Range
	B	P	B	P	B	P	B	P	B	P	B	P	B	P	
Morning Corticotropin	-	<10	-	<10	-	<10	-	<10	-	<10	-	<10	-	<10	10-60 pg/ml
Morning Cortisol	-	0.77	-	0.6	-	0.9	-	0.9	-	1.1	-	0.5	-	0.45	6.2-19.4 μg/dL
Thyrotropin	5.2	0.07	1.66	0.086	0.86	0.28	1.6	0.45	-	<0.01	1.3	0.22	1.1	2.4	0.5 -5 mIU/L
Free Thyroxine	1.2	1.5	1.1	0.5	-	0.5	0.8	0.5	-	0.94	-	1.1	-	1.2	0.8-1.8 ng/dL
Total testosterone	-	3034	3010	710	-	undetec table	-	undetec table	-	-	-	1449	-	-	1800-6650 pg/ml
Luteinizing Hormone	-	13.5	-	0.8	-	7.2	-	1.1	-	-	-	3.2	-	-	1.7-8.6 mU/ml
IGF1	-	52	-	355	-	77	-	56	-	173	-	-	-	-	84-233 ng/ml

B: Before ipilimumab therapy; P: labs at initial presentation; -: not measured;

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