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Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes

Troy Dillard · Chris G. Yedinak · Joshi Alumkal · Maria Fleseriu

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Abstract Anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) therapies represent a novel approach to cancer treatment via disruption of immune tolerance to antigens located on tumor cells. Disruption of immune tolerance, however, may occur at a cost. A host of immune related adverse events (IRAEs) are associated with anti-CTLA-4 therapy. Autoimmune hypophysitis has been reported in up to 17% of patients with melanoma and renal cell carcinoma treated with this therapy. Familiarity with the spectrum of IRAEs connected to these therapies is paramount for endocrinologists, oncologists and those involved in the care of these subjects. We review here key aspects of diagnosis and treatment of anti-CTLA-4 antibody therapy resultant IRAEs. We describe the first two cases of hypopituitarism in prostate cancer subjects undergoing experimental therapy with ipilimumab. The clinical evidence strongly suggests that the prostate cancer subjects developed autoimmune

hypophysitis as a consequence of anti-CTLA-4 treatment. High dose glucocorticoid treatment resulted in markedly improved symptoms, and resolution of focal symptoms and diabetes insipidus. One subject recovered pituitary-thyroid axis function after 9 months; however, both continue to require GC replacement. These cases highlight the importance of early screening and treatment for hypopituitarism in all subjects undergoing treatment with anti-CTLA-4 therapy to prevent a potentially fatal outcome from secondary adrenal insufficiency, a readily treatable disease. We recommend mandatory long term follow-up to monitor the development of other hormonal deficits.

Keywords Lymphocytic hypophysitis · Autoimmune hypophysitis · Drug-induced hypophysitis · Hypopituitarism · Cytotoxic T-lymphocyte antigen-4 · Prostate cancer · Immune related adverse events (IRAEs)

T. Dillard · M. Fleseriu
Department of Medicine, Division of Endocrinology, Diabetes and Clinical Nutrition, Oregon Health & Science University, Portland, OR, USA

C. G. Yedinak · M. Fleseriu
Department of Neurological Surgery, Oregon Health & Science University, Oregon Health & Science University, Portland, OR, USA

J. Alumkal
Department of Medicine, Division of Hematology and Oncology, Oregon Health & Science University, Portland, OR, USA

M. Fleseriu (✉)
Departments of Medicine and Neurological Surgery, CH8N, Oregon Health & Science University, 3303 S.W. Bond Avenue, Portland, OR 97239, USA
e-mail: fleseriu@ohsu.edu

Introduction

Interference with host immune-tolerance represents a novel experimental approach to cancer therapy. Cancer cells escape immune activation and surveillance, at least in part, due to the development of immunologic tolerance to their antigens. T-cells play a pivotal role in the development of immune tolerance to self and tumor antigens. Conversely, upon activation, T-cells are central to anti-tumor responses and the development of autoimmunity. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a key surface receptor on T-lymphocytes that modulates immune responses. Inhibitory antibodies directed against CTLA-4 cause disruption of immune tolerance to antigens on cancer cells and are associated with anti-tumor activity in a number of cancers. Disruption of immune tolerance, however, may occur at a

cost. Autoimmunity is the Achilles heel of this approach. Familiarity with the spectrum of immune related adverse events (IRAEs) connected to these therapies is essential for endocrinologists, oncologists and those involved in the care of subjects receiving these experimental medications. Here we review key aspects of anti-CTLA-4 antibody therapy, IRAEs etiology, diagnosis and treatment, and describe the first two cases of autoimmune hypophysitis in subjects with prostate cancer.

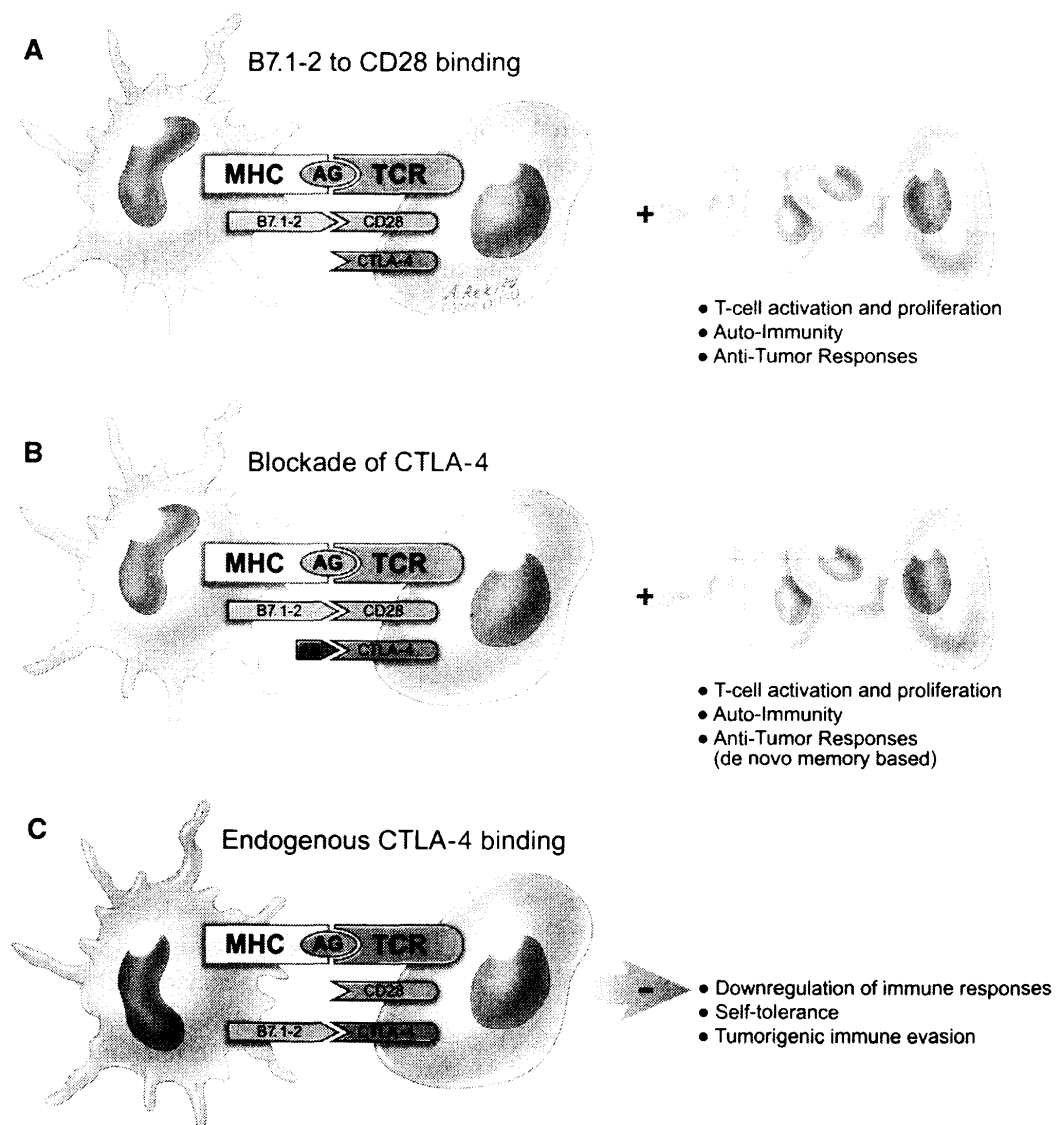
Background

Adaptive immune responses and the development of immune tolerance involve interaction between T-Lymphocytes and antigen presenting cells (APCs), such as dendritic cells and macrophages. APCs bind processed antigens within their major histocompatibility complex (MHC) and present these to the T-lymphocyte through a

ligand-receptor complex involving the T-cell receptor (TCR). Co-stimulatory signals are required for optimal T-cell activation. This is achieved through the binding of non-MHC ligands on APCs to specialized receptors on the T-cell. Ligands B7.1 (CD80) and B7.2 (CD86) on APCs bind to CD28 on T-cells to accomplish co-stimulation. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) competes with CD28 to down-regulate T-cell activation, resulting in immunotolerance and prevention of pathologic immune responses to self-antigens. B7-CTLA4 interactions provide negative feedback to immune activation overall (Fig. 1).

Understanding the physiology of CTLA-4 led to the hypothesis that blockade of CTLA-4 might lead to effective cancer therapy by reversing immune tolerance of tumor antigens. CTLA-4 knockout mice develop a lethal lymphoproliferative disorder, further supporting this hypothesis by demonstrating profound effects on the immune system as a whole [1, 2]. Anti-tumor activity of

Fig. 1 Antigen presenting cell (APC) interactions with T-lymphocytes. **a** APCs bind processed antigens within their major histocompatibility complex (MHC) and present these to the T-lymphocyte through a ligand-receptor complex involving the T-cell receptor (TCR). Co-stimulatory signals are required for optimal T-cell activation. Ligands B7.1 (CD80) and B7.2 (CD86) on APCs bind to the CD28 receptor on T-cells to accomplish co-stimulation. This results in T-cell activation, anti-tumor responses and autoimmunity. **b** Antibody-mediated blockade of the Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) receptor results in T-cell activation, anti-tumor responses (both de novo and activation of memory responses) and autoimmunity. **c** Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) competes with CD28 to down-regulate T-cell activation, resulting in immunotolerance and prevention of pathologic immune responses to self-antigens. B7-CTLA4 interactions provide negative feedback to immune activation



anti-CTLA-4 antibodies has been reported in several animal models. Growth inhibition of immunogenic cancers occurs in animals injected with anti-CTLA-4 antibodies in a number of models, including B16 melanoma [3], SM1 breast carcinoma [4], transgenic adenocarcinoma of mouse prostate (TRAMP) [5], colon cancer [6], and lymphoma [7]. Some animals displayed resistance to re-challenge with tumor implantation 4 months later, suggesting an induction of immunologic memory [3–7]. These successes were the basis of trials in a number of human cancers.

Efficacy of anti-CTLA-4 antibody therapy in human trials

There are two anti-CTLA-4 antibodies available for use in human trials: ipilimumab (MDX-010; Medarex Inc., Princeton, NJ) and tremelimumab (CP-675,206; aka ticilimumab; Pfizer, New York, NY). The proposed mechanism of action in humans is, singly or in combination, the development of anti-tumor responses *de novo*, activation of endogenous memory responses, and/or antibody responses.

The development of anti-MICA (MHC Class I-related chain A) antibodies is believed to be an important component of the anti-tumor activity of anti-CTLA4 therapy. MICA and MICB are predominantly expressed in the gastrointestinal epithelium and tumor cells of epithelial origin and can suppress natural killer and CD8 T-lymphocytes. Evidence supports enhanced natural killer cell and CD8 T-lymphocyte cytotoxicity in anti-CTLA- antibody treated subjects who develop high titers of anti-MICA antibodies and decreases in soluble MICA. Anti-MICA antibodies may also affect tumor-cell lysis via complement fixation [8]. Lastly, some tumors, such as melanomas, may express CTLA-4 and undergo apoptosis with binding of antagonistic ligands [9].

A review of cancer immunotherapy clinical trials registered in the United States indicates ongoing trials examining the potential role of anti-CTLA-4 antibody therapy in: prostate cancer, malignant melanoma, lung cancer (small-cell and non-small-cell), chronic myelogenous leukemia, urothelial cancer, pancreatic cancer, lymphoma, ovarian cancer, myelodysplastic syndrome, myeloproliferative disorders, and other solid tumors.

Variable results have been reported in all trials: metastatic melanoma (often in combination with vaccination and other immunotherapies) have shown an objective response in as high as 22%, complete response rates as high as 8.3% and stable disease in up to 84%. At the other extreme is the relatively poor response seen in cancer of the colon or rectum, with only a single partial response and progressive disease in 46/47 [10–21].

Autoimmunity in anti-CTLA-4 antibody trials

Anti-CTLA-4 therapies show remarkable response rates in some subjects, but at the expense of autoimmunity, including autoimmune hypophysitis [10, 14, 17, 18, 20, 22–29]. Strategies to limit autoimmunity include development of therapies that limit anti-CTLA-4 therapy to the local, peri-tumoral region. This approach may enhance the therapeutic efficacy of cancer immunotherapy while reducing systemic exposure [30].

Of additional concern to endocrinologists is the development of primary adrenal insufficiency (AI) and autoimmune thyroid disease in subjects treated with anti-CTLA-4 antibodies. As might be expected, the development of autoimmune disease has been shown to correlate with favorable responses to therapy and tumor regression [10, 17]. Autoimmunity (including autoimmune-like enterocolitis, hypophysitis, and hepatitis) is common across clinical trials, with up to 62% of subjects experiencing some IRAEs and more severe Grade III/IV IRAEs occurring in up to 43%, ultimately leading to early termination in one trial [17]. Interestingly, IRAE time course development is variable and unpredictable. IRAEs can occur rapidly, a case in point being one subject with a normal colonoscopy on day 3 after the first dose of ipilimumab, and diffuse colitis with crypt abscess formation observed 4 days later [31]. A list of some major clinical trial IRAEs is detailed in Table 1.

Autoimmune hypophysitis in subjects treated with ipilimumab

Clinical, histopathological, and morphological findings in lymphocytic hypophysitis (LYH) and its association with other autoimmune disorders identify it as a pituitary autoimmune disease [32]. Autoimmune LYH can cause headache, changes in visual fields, and pituitary dysfunction. At disease onset, patients present with symptoms and signs of extrasellar pituitary enlargement, and only later do features of hypopituitarism become apparent. Thus, headache is sometimes a sentinel symptom, followed by visual field

Table 1 Immune related adverse events due to anti-CTLA-4 therapy

Lymphocyte hypophysitis	Iritis	Arthritis
Thyroiditis	Uveitis	Aseptic meningitis
Primary adrenal insufficiency	Episcleritis	Tubulointerstitial nephritis
Enteritis	Dermatitis	Alopecia areata
Colitis (fatal)	Alveolitis	Red cell aplasia
Gastritis	Pruritus	
Hepatitis	Vitiligo	

impairment. Among the ‘isolated’ pituitary hormone deficiencies, adrenocorticotropin (ACTH) deficiency is the earliest and most frequent alteration, present in about 65% of cases [33, 34]. Hypopituitarism involving almost all hormones usually occurs when the inflammatory process induces pituitary tissue destruction [35]. Lymphocytic infundibuloneurohypophysitis (LINH) typically presents as acute onset diabetes insipidus (DI) with intracranial mass-effect symptoms. A combination of extensive anterior pituitary involvement and DI is characteristic of lymphocytic infundibulopanhypophysitis (LIPH) [36–38]. Cases of presumed autoimmune hypophysitis associated with anti-CTLA-4 therapy have been described in both melanoma and renal cell carcinoma with an incidence of 0–17% (see Table 2).

In a trial of 46 subjects with Stage IV metastatic melanoma [26] treated with various doses of ipilimumab, 16 subjects (35%) experienced Grade III/IV IRAEs requiring GC therapy. An additional 16 subjects (35%) experienced Grade I/II IRAEs, five of whom experienced concurrent III/IV IRAEs. Autoimmunity was predictive of tumor response in this trial, but the difference between responders and non responders was not statistically significant. Eight patients (17%) experienced autoimmune hypophysitis, the majority occurring at a higher dose level (9 mg/kg). Autoimmune hypophysitis was diagnosed by “decreased levels of pituitary and secondary hormone levels”. The authors note a difference in the rate of occurrence in comparison to their previous study (lower doses: 1–3 mg/kg), where this complication was observed in only 1 of 56 subjects (1.8%). In these particular cases, autoimmune hypophysitis, unlike other IRAEs, did not respond well to treatment with high dose GCs. Importantly, the authors admit that with increasing experience, they have come to

recognize autoimmune hypophysitis more readily and this complication may have been missed in the earlier trial, thus the lower prevalence in that particular trial.

In a large study of 139 subjects [23] with metastatic melanoma, treatment with ipilimumab (1–3 mg/kg every 3 weeks) with and without peptide vaccine, the study included screening for endocrine IRAEs with each cycle of therapy, including measurements of adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), cortisol, and free T4. Enterocolitis and hypophysitis were the most common Grade III/IV IRAEs in this trial occurring with a frequency of 17 and 9%, respectively. These IRAEs were treated with “high dose systemic steroids”, in varying undisclosed doses. Subjects with hypophysitis were noted to have swelling of the pituitary gland on MR imaging and clinical symptoms of headache and fatigue. Despite early treatment with high dose IV GCs, most subjects with autoimmune hypophysitis continued to require hormone replacement therapy. The HP-gonadal and HP-thyroidal axes frequently recovered, but only one subject was able to discontinue GC replacement therapy.

Patients with metastatic melanoma treated with ipilimumab (3 mg/kg every 3 weeks) in conjunction with vaccination with two modified HLA-A*0201-restricted peptides from the gp100 melanoma-associated antigen [17] exhibited further Grade III/IV IRAEs (43% of subjects). Brain MR imaging was obtained at baseline and after every two cycles and endocrine hormonal screening included only TSH and free T4. One subject (1/14; 7.1%) developed autoimmune hypophysitis that manifested clinically by personality changes and memory problems soon after receiving fourth and fifth cycles. After the fifth treatment, the subject had undetectable levels of TSH, free T4, ACTH, cortisol, growth hormone, prolactin, and testosterone indicating hypopituitarism. The authors note that these tests had been in the normal range when cryopreserved pre-therapy samples were analyzed. High dose GC therapy was withheld out of concern that anti-tumor responses might be compromised. The subject was prescribed replacement doses of levothyroxine, testosterone, and hydrocortisone with clinical improvement. MR imaging performed 6 weeks later showed a slight decrease in pituitary size, but no follow-up on pituitary hormonal recovery is reported.

Patients with metastatic renal cell carcinoma have also been treated with [29] ipilimumab (1–3 mg/kg every 3 weeks). Though specific screening protocols are not mentioned, 2 of 61 subjects (3.3%) developed hypophysitis. They had pituitary “swelling” on MR images and abnormalities of ACTH, TSH, testosterone, cortisol, and T4. Subjects who developed hypophysitis in this trial received hormonal replacement at unspecified doses. One subject had pituitary swelling on MR images, but a laboratory evaluation was consistent with primary AI. Subjects

Table 2 Incidence of autoimmune hypophysitis in clinical trials of anti-CTLA-4 therapy

Percentage	Disease	References
17.0	Metastatic melanoma	Maker et al. [26]
9.0	Metastatic melanoma	Downey et al. [24]
7.1	Metastatic melanoma	Phan et al. [17]
4.9	Metastatic melanoma, renal cell carcinoma	Blansfield et al. [22]
4.0	Metastatic melanoma	Weber et al. [20]
3.3	Renal cell carcinoma	Yang et al. [29]
2.5	Metastatic melanoma	Ribas et al. [18]
1.8	Metastatic melanoma	Attia et al. [10]
0	Metastatic melanoma	Weber et al. [28]
0	Prostate cancer	Small et al. [27]
0	Prostate cancer	Fong et al. [14]
0	Metastatic melanoma	Maker et al. [25]

who developed hypopituitarism in this trial continued to require physiologic replacement doses of GCs at the time of publication, but experienced resolution of thyroid and testosterone deficiencies.

In the largest study to date of 163 subjects (The National Cancer Institute) treated with ipilimumab singly (3–9 mg/kg every 3 weeks) or in combination with other immunotherapies for both advanced melanoma or renal cell carcinoma [22], eight subjects (4.9%) developed presumed autoimmune hypophysitis. Subjects presented with non-specific symptoms that included fatigue, headache, memory loss, and loss of libido. The majority (7/8) had evidence of pituitary swelling on MR images with evidence of suprasellar extension; one patient was noted to have an empty sella before enrollment. All had low cortisol, with a majority (7/8) showing inappropriately low levels of ACTH. Likewise TSH and free T4 were low in all subjects. The majority (7/8) also had low serum testosterone and two subjects had elevated prolactin levels. Treatment of autoimmune hypophysitis in this group varied throughout the study. The first three patients were treated with physiologic replacement doses of GCs, thyroxine and testosterone. One patient still requires therapy with all these hormones at 2-year follow-up. Subsequent subjects were treated with high dose intravenous dexamethasone (4 mg IV every 6 h) for 1 week rapidly tapered down after it has been shown that high dose GCs would not impair anti-tumor responses. Regardless of management, all patients with autoimmune hypophysitis continued to require replacement GC at the time of publication with 4–26 months follow up and some continued to require thyroxine and testosterone replacement [22].

Autoimmune hypophysitis in patients with prostate cancer

In a Phase I, pilot study of the anti-CTLA-4 antibody, ipilimumab (MDX-010; Medarex[®] Inc., Princeton, NJ), autoimmune hypophysitis was not observed, although no screening for hypophysitis was undertaken [27].

Cases of autoimmune hypophysitis in prostate cancer subjects treated with ipilimumab

Here we describe the first two cases of hypopituitarism due to presumed autoimmune hypophysitis in subjects undergoing experimental therapy with ipilimumab for prostate cancer. On the basis of these cases and the occurrence of autoimmune hypophysitis in subjects treated with anti-CTLA-4 antibody in other cancer subtypes, we recommend early screening for all patients undergoing this therapy.

Case 1

A 67-year-old male was diagnosed with castrate-resistant, metastatic prostate cancer 2 years prior to presentation with an initial prostate-specific antigen (PSA) of 270 ng/ml. The subject had previously received palliative external beam radiation (8 Gy) to the right hip and was taking leuprolide and bicalutimide prior to enrollment in a clinical trial with ipilimumab. Four monthly doses of ipilimumab (10 mg/kg) were administered.

Four weeks after the initial infusion, the subject developed progressive frontal headache with eye pain, profound asthenia, anorexia, labile moods, insomnia, and subjective sensations of fever and chills. The subject denied subjective visual changes, nausea, vomiting, abdominal pain, increased urination or thirst, dizziness, palpitations, or constipation. Laboratory evaluation revealed a low TSH. Previous thyroid function studies obtained before drug infusion were normal. The patient received two additional cycles of therapy. Further work-up revealed a persistently low TSH and a low free T4, which was misinterpreted to represent primary hypothyroidism. Hormonal replacement with hydrocortisone, 20 mg in the morning and 10 mg in the evening, and levothyroxine 125 µg/day resulted in rapid symptom improvement. The subject received one further infusion of ipilimumab. He was referred to Ophthalmology for visual symptoms and concern for hemianopsia, and a visual field assessment revealed a small right superotemporal visual field defect. A more complete assessment of pituitary function was undertaken by Endocrinology, which revealed findings consistent with panhypopituitarism (Table 3). Additionally, a contrast-enhanced MR imaging revealed a homogeneous, intensely enhancing pituitary, measuring 9 mm in height with convex margins at the infundibular insertion (Fig. 2). In this context, MR imaging findings and laboratory findings were most consistent with autoimmune hypophysitis and panhypopituitarism secondary to ipilimumab. High dose prednisone therapy was initiated at 60 mg daily, tapered slowly to 10 mg daily over approximately 3 months. Follow-up MR imaging revealed complete resolution of inflammatory syndrome findings. Although a biopsy was not performed to confirm the diagnosis, the patient's clinical presentation was consistent with hypophysitis.

The subject's symptoms continue to ameliorate with slightly supraphysiologic doses of prednisone (10 mg/day) and replacement doses of levothyroxine (125 µg/day). Recent testing indicated persistent secondary adrenal insufficiency (SAI) mandating continued replacement GC. Thyroid hormone replacement was discontinued after normal thyroid function tests. A recent PSA, despite no further anti-cancer therapy since discontinuation of ipilimumab 9 months ago, was 0.2 ng/ml.

Table 3 Subject laboratory characteristics

	Case 1		Case 2	
	67		50	
	Before anti-CTLA4	After anti-CTLA4	Before anti-CTLA4	After anti-CTLA4
TSH (uIU/ml)	2.1	<0.1 (ref: 0.34–5.60)	2.1	0.5 (ref: 0.27–4.20)
Free T4 (ng/dl)	NA	0.4 (ref: 0.6–1.6)	NA	0.62 (ref: 1.09–1.79)
Total T3 (nmol/l)	NA	NA	NA	1.2 (ref: 1.4–2.8)
ACTH (pg/ml)	28	<5	NA	<5
Cortisol (ug/dl) (CST) ^a	NA	<1 (1.3/6.3) ^a	NA	1.0 (0.83/6.45) ^a
Prolactin (ng/ml)	NA	3	NA	3
IGF-1 (ng/ml)	NA	108	NA	188
LH (mIU/ml)	NA	<1 ^b	NA	<1 ^b
FSH (mIU/ml)	NA	1 ^b	NA	3 ^b
Testosterone (ng/dl)	NA	<10 ^b	21	NA
PSA (ng/ml)	15	0.69	21	NA

^a One microgram ACTH stimulation test (baseline and 30 min)

^b In presence of GnRH agonist

Case 2

A 50-year-old male with castrate-resistant, metastatic prostate cancer developed headache, fatigue, weakness, visual blurriness, and decreased libido after a fourth infusion of ipilimumab. Notably, he developed extreme polydipsia and polyuria, urinating large volumes (up to 25 times/day), consistent with diabetes insipidus (DI). No confounding diseases such as diabetes mellitus were evident to explain the polydipsia and polyuria. Computed tomography (CT), performed overseas, did not reveal any notable pathology. However, CT has low sensitivity for detecting pituitary anomalies, and therefore MR imaging was planned. Laboratory testing revealed: a low TSH in the setting of a low free T4 and total T3, undetectable ACTH, an abnormal ACTH stimulation test indicating SAI. As a result the subject was treated with high dose prednisone (120 mg/day) for presumed autoimmune hypophysitis. Glucocorticoid therapy resulted in dramatic improvement of symptoms and polyuria resolved over 2–3 days. MR imaging after 3 weeks of high GC treatment failed to reveal significant pituitary abnormalities (Fig. 3).

Discussion

Despite the encouraging safety results of Phase I and small pilot studies, the cases we present demonstrate the importance of monitoring for autoimmune hypophysitis and hypopituitarism in subjects with prostate cancer being treated with anti-CTLA-4 antibody therapy. Indeed, given the consistency with which this adverse event is now seen

across populations, it is prudent to undertake screening for autoimmune hypophysitis in all trials of anti-CTLA-4 therapy. Encouragingly, therapeutic doses of GC to treat IRAEs do not seem to abrogate the anti-neoplastic benefits of anti-CTLA-4 treatment [25, 31].

Subjects who develop signs and symptoms of hypophysitis and SAI such as new or severe headache, visual disturbances, polyuria, polydipsia, nausea, vomiting, abdominal pain or orthostasis, should undergo prompt medical evaluation. Likewise, given the potential morbidity and mortality associated with unrecognized hypopituitarism, we recommend early empiric treatment with replacement GC pending biochemical confirmation, followed by high-dose GC and cessation of the study drug upon confirmation. Optimal GC therapy is not defined. Initial daily doses equivalent to 60–250 mg of methylprednisolone, both oral and intravenous, have been used with success in treating IRAEs, with tapering doses over 1–3 months [31]. In one of the cases we present a smaller dose (prednisone 60 mg daily with slow taper) achieved resolution of symptoms and improvement as observed by MR imaging. Treatment with levothyroxine should be delayed pending adequate treatment of GC deficiency so as not to precipitate adrenal crisis. Polydipsia and polyuria should prompt testing for DI. Given the rapidity with which autoimmune hypophysitis may occur in treatment, laboratory testing and clinical evaluation should be considered within the first 1–2 weeks of therapy and intermittently thereafter. Optimal surveillance intervals and protocols remain undefined. Laboratory screening every 3–4 weeks during treatment seems reasonable and should include a.m. cortisol, free thyroxine, TSH and serum sodium. ACTH

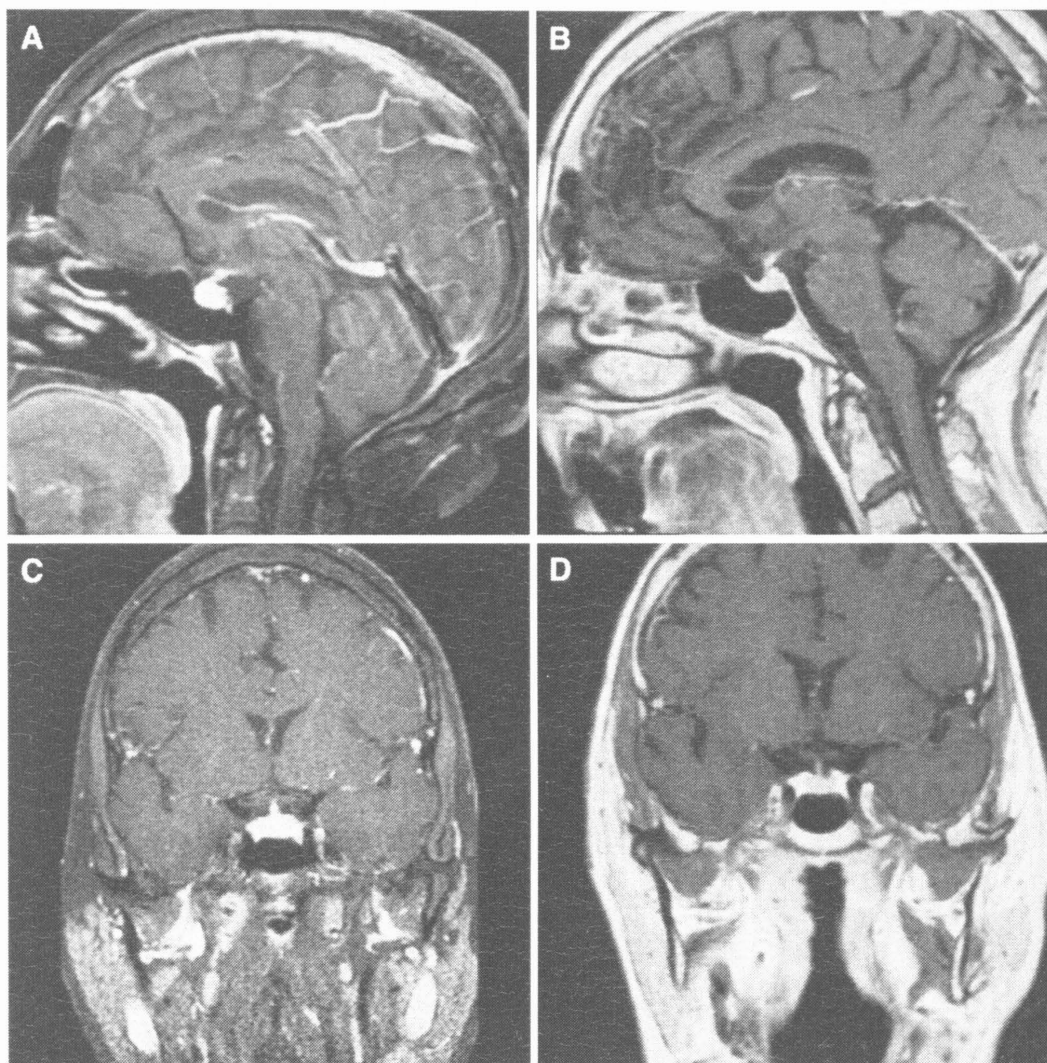


Fig. 2 Case 1 MR images. Pre-treatment sagittal T1-weighted post-contrast image revealing an homogeneous, intensely enhancing pituitary, measuring 9 mm in height with convex margins at the infundibular insertion (**a**); post-treatment sagittal T1-weighted post-contrast image with resolution of radiographic evidence of

hypophysitis (**b**); pre-treatment coronal T1-weighted post-contrast image revealing an homogeneous, intensely enhancing pituitary, measuring 9 mm in height with convex margins at the infundibular insertion (**c**); post-treatment coronal T1-weighted post-contrast image with resolution of radiographic evidence of hypophysitis (**d**)

determination in the setting of low cortisol values can help distinguish primary from secondary adrenal insufficiency. MR imaging can be supportive of the diagnosis and is recommended in case of clinical suspicion.

When LYH is suspected, basal and dynamic hormonal pituitary function must be studied to disclose subclinical or overt alterations. It is not clear if addition of other therapies such as methotrexate [39], cyclophosphamide [36, 40] or cyclosporin-A [41] will also play a role in these cases of hypophysitis.

The literature indicates that SAI related to anti-CTLA-4 therapy is rarely transient. It is unclear at this time what percentage of subjects will respond to early treatment with therapeutic doses of GC and what percentage will require long-term treatment for persistent hypopituitarism. Our subjects were treated with high dose GC and continue to require maintenance GC therapy at the time of this report.

However, one subject recovered thyroid axis function after 9 months of GC treatment and thyroid replacement was discontinued. While little is known at this time of the natural history of autoimmune hypophysitis related to anti-CTLA-4 therapy, we caution the need for increased awareness of this severe disease.

Conclusions

The cases we present demonstrate the clinical course of autoimmune hypophysitis and consequent hypopituitarism after treatment with ipilimumab and highlight the possible role of CTLA-4 blockade in its pathogenesis. Our subjects were treated with a relatively short course of high-dose GC followed by physiologic hormone replacement and have demonstrated partial recovery of pituitary function and

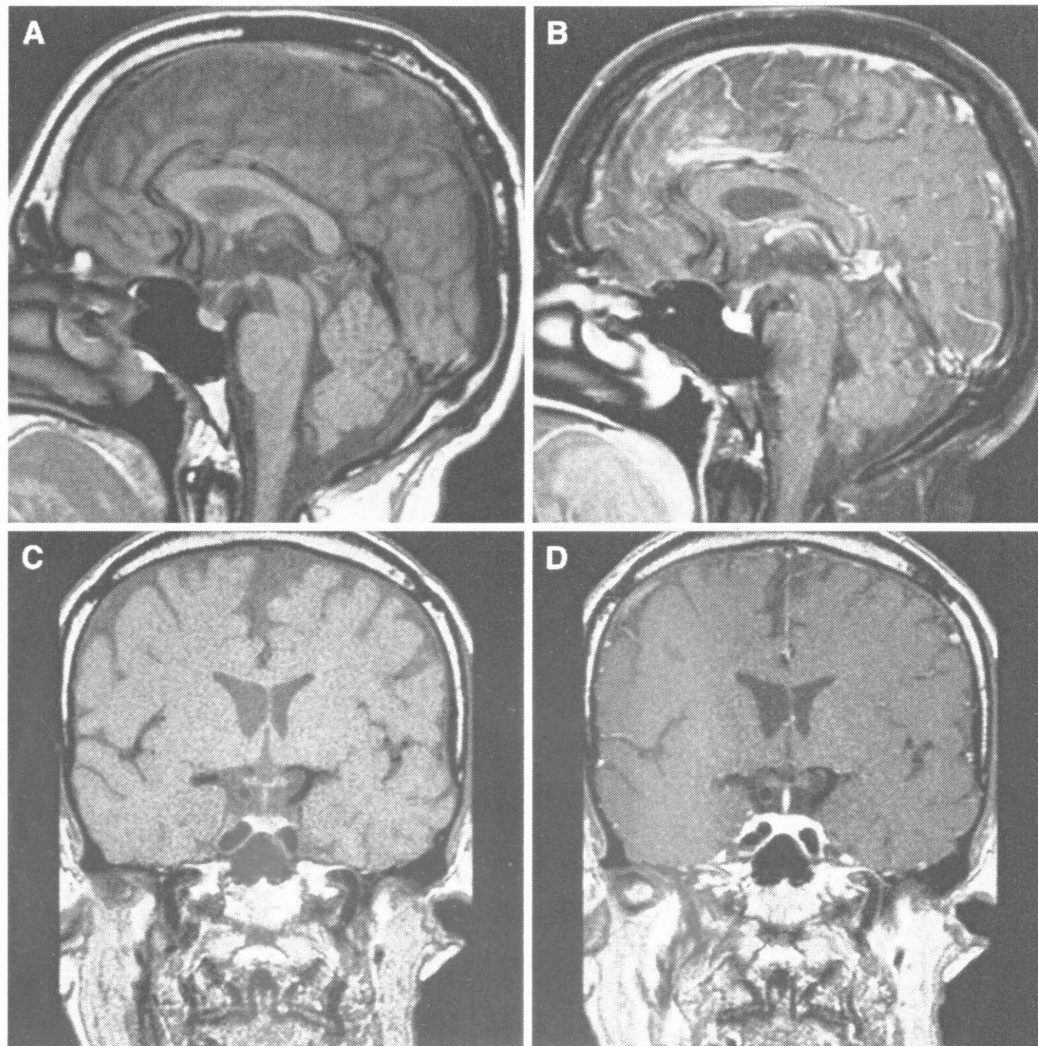


Fig. 3 Case 2 MR images 3 weeks after high-dose glucocorticoid therapy. Sagittal T1-weighted pre-contrast (a); sagittal T1-weighted post-contrast (b); coronal T1-weighted pre-contrast (c) and coronal

T1 weighted post-contrast (d) show only mild heterogeneity of the pituitary gland without radiographic evidence of hypophysitis

improvement in symptoms. This reflects our current treatment strategy. With the increased number of available clinical trials, endocrinologists should be aware of the potential endocrine toxicities that may occur in patients treated with these novel immunotherapies. Given the consistency with which autoimmune hypophysitis and endocrinopathies are seen across patient populations treated with anti-CTLA-4 antibody therapy, research protocols should also incorporate appropriate screening and algorithms for early therapeutic intervention.

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