IPILIMUMAB – A NOVEL IMMUNOMODULATING THERAPY

CAUSING AUTOIMMUNE HYPOPHYSITIS: A CASE REPORT AND REVIEW

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ABSTRACT

Ipilimumab (Yervoy, Medarex and Bristol-Myers Squibb) is a human monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA-4), which enhances co-stimulation of cytotoxic T lymphocytes, resulting in their proliferation and an anti-tumour response. It is licensed for the treatment of unresectable or metastatic malignant melanoma, while multiple clinical trials using this medication in the treatment of other malignancies are ongoing.

As a clinical response to ipilimumab results from immunostimulation, predictably it generates autoimmunity as well, causing immune-related adverse events in the majority of patients. Of those, endocrinopathies are frequently seen, and in particular autoimmune lymphocytic hypophysitis with anterior panhypopituitarism has been reported a number of times in North America.

We present a case of a male referred to our department with manifestations of anterior panhypopituitarism after his 3rd dose of ipilimumab for metastatic malignant melanoma, and we discuss the management of his case in the light of previous reports. We also review the published literature on the presenting symptoms, time to presentation, investigations, imaging, treatment and follow-up of ipilimumab-induced autoimmune lymphocytic hypophysitis.
INTRODUCTION

Activation of a cellular immune response involves the interaction of T-cell receptors on T-lymphocytes with Major Histocompatibility Complex (MHC) molecules on antigen-presenting cells (APC). This requires co-stimulation, whereby ligand B7 on APC binds to CD28 on T lymphocytes and in turn triggers T cell proliferation. A negative co-stimulation signal is transduced by Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) which is present on T-cells, interaction of which with the same B7 ligand inhibits T-lymphocyte activation and proliferation ¹ (Fig. 1).

Monoclonal antibodies against CTLA-4, such as ipilimumab (Yervoy, Medarex and Bristol-Myers Squibb) or tremelimumab (Pfizer, New York), block CTLA-4 and therefore promote activation of cytotoxic lymphocytes and augment an immune-mediated anti-tumour response. Following recently completed clinical trials, ipilimumab was approved by the Food and Drug Administration (FDA) in February 2011 and by the European Medicines Agency (EMA) in July 2011 for use in advanced (unresectable or metastatic) malignant melanoma in patients not responding to chemotherapy, with or without previous exposure to immunotherapy². NICE guidelines are expected to follow in February 2012, and currently, patients in England can access ipilimumab via the Cancer Drugs Fund. Furthermore, to the present, 47 clinical trials including ipilimumab as a treatment of malignant melanoma, renal cell carcinoma, small and non-small cell lung cancer, prostate cancer, pancreatic adenocarcinoma, liver cancer, and graft versus host disease have
been registered on the National Cancer Institute website. Two significant Phase III clinical trials of ipilimumab in patients with unresectable/metastatic malignant melanoma have been published in the last 2 years. In the first, ipilimumab 3mg/kg alone or in combination with peptide vaccine gp100 significantly improved overall patient survival from 6.4 to 10 months, compared with gp100 vaccine alone. In the second, ipilimumab 10mg/kg in combination with dacarbazine significantly improved survival rate at 3 years, from 12.8% to 20.2%, compared with dacarbazine alone.  

The dose of ipilimumab used in clinical trials ranged from 0.3mg/kg to 10mg/kg. There was no clinical response observed with the lowest dose. Significant, objective clinical responses, and an overall survival benefit, were demonstrated with the dose of 3mg/kg. On the other hand, the dose of 10mg/kg was associated with a significant increase in the incidence of adverse events. An induction course of this therapy consists of a total of 4 doses administered as an intravenous infusion every 3 weeks. In some patients, maintenance therapy may continue with additional infusions at longer intervals.

As might be expected from immunostimulatory therapy, anti-CTLA-4 antibodies were associated with multiple autoimmune adverse events grade 1-4 (References to NCI Common Toxicity Criteria) in 61-77% of patients, and which were dose-dependent. The most commonly reported immune–related side effects were enterocolitis, rash, including vitiligo and hepatitis. The most common
endocrinopathy was hypophysitis with hypopituitarism in 0-17%, followed by hypo- and hyperthyroidism secondary to thyroiditis in 2.7% and 0.3% respectively, and adrenal insufficiency in 2.1% \(^4\). Less then 1% of patients were diagnosed with nephritis, pneumonitis, meningitis, myocarditis, vasculitis, pericarditis, uveitis, iritis, Guillain-Barre syndrome or haemolytic anaemia. The autoimmune side effects appear to be dependent on co-administered medications, as adding dacarbazine to the 10mg/kg dose of ipilimumab resulted in a different pattern of immune-related adverse events with fewer cases of enterocolitis but an increased frequency of hepatitis \(^3\). In this study by Robert et al. no cases of hypophysitis were reported.

We present the case of a patient with presumed ipilimumab-induced hypophysitis and we review the diagnosis and management of this increasingly common condition in the light of this and other recent case studies.

**CASE REPORT**

A 54 year-old man presented to the oncology clinic with a one week history of headaches and severe lethargy following his third course of ipilimumab for recurrent metastatic malignant melanoma. On direct questioning, he admitted to the recent onset of poor libido and erectile dysfunction, which he linked to stress related to his principal disease and chemotherapy. He denied nausea, vomiting, visual symptoms, polydipsia or polyuria. For his melanoma, he was initially treated
surgically, then started on chemotherapy on developing pulmonary metastases. He had stable disease on chemotherapy based upon docetaxel, but relapsed soon after this was completed. He did not have other co-morbidities or family history of endocrine problems or malignancy.

As metastatic brain disease or hypophysitis were suspected, a brain MRI scan was arranged: this showed a pituitary swelling consistent with hypophysitis (Fig. 2A-B). Hormonal investigations demonstrated anterior pan-hypopituitarism (random cortisol 10 nmol/L [reference range 180-620], testosterone <4nmol/L [8.4-28.7] with a low-normal LH and FSH, TSH < 0.01mU/L [0.35-5.5] and fT4 9.4pmol/L [10.5-20.5]). There was no diabetes insipidus, his prolactin was less the 7 mU/L [45-375mU/L], and the serum IGF-1 was normal [13.5nmol/L, normal range 10.5-35 nmol/L]. He was started on dexamethasone 8mg twice daily and three days later L-thyroxine 75mcg daily and testosterone replacement were added. These resulted in rapid resolution of his symptoms. The dose of dexamethasone was gradually decreased over 3 weeks and replaced with physiological hydrocortisone replacement of 10/5/5mg daily. A pituitary MRI scan performed 2 weeks after initiation of corticosteroid treatment did not show any significant change in the size of the pituitary. However, the pituitary swelling had resolved completely on MRI three months later (Fig. 2C-D).

He currently remains stable on his hormonal replacement therapy, and this will be periodically reviewed. Since hormonal replacement was started, the patient has
received his 4\textsuperscript{th} course of ipilimumab. Follow-up CT scans have demonstrated a response to treatment, with shrinkage in his pulmonary disease.

\textbf{DISCUSSION}

We present a patient with presumed autoimmune hypophysitis secondary to ipilimumab therapy, and note the increasing frequency of this diagnosis. Lymphocytic hypophysitis is a rare inflammatory condition of the pituitary gland whose pathogenesis is probably autoimmune and is associated with other autoimmune disorders in about 25\% of the patients. It has generally shown a strong female preponderance, often in or around the peri-partum period\textsuperscript{7}. However, it appears to be increasing in frequency following the use of immunomodulating medications, such as ipilimumab, which in turn tends to confirm its probable autoimmune pathogenesis.

Lymphocytic hypophysitis has been reported in 0-17\% of patients involved in ipilimumab trials \textsuperscript{3, 4, 8-10}. Table 1 summarizes main studies reporting on ipilimumab-induced hypophysitis. Most patients were diagnosed with hypopituitarism after receiving 3mg/kg of ipilimumab and developed relevant symptoms after a median 11 weeks, i.e. before the 4\textsuperscript{th} dose, suggesting a possible cumulative effect \textsuperscript{4}. Min \textit{et al.} reported a similar time to the onset of symptoms in 8 patients receiving 10mg/kg of ipilimumab who developed hypopituitarism at a
median time of 9.4 weeks (range 6-12 weeks) \(^8\). In a trial involving prostate cancer treatment with 10mg/kg of ipilimumab, hypophysitis symptoms occurred after 4 weeks in one patient and after 16 weeks in a second \(^{11}\).

The presenting symptoms relate to a pituitary mass effect and hormonal deficiencies. Most patients presented with headache, fatigue, asthenia, lethargy, nausea, loss of libido or (rarely) visual disturbances; only 2 patients have been described with visual field defects, which is understandable as pituitary enlargement is usually modest \(^{12}\).

In autoimmune hypophysitis secondary to ipilimumab, ACTH and TSH seem to be invariably lost (100%), usually confirmed by low ACTH, cortisol, TSH and fT4 levels \(^{11,12}\). The majority of male patients (83%-87%) had hypogonadotrophic hypogonadism; in addition, in the recent report by Min et al. 3 out of 5 patients had low levels of serum IGF-1 \(^8\). There is also a single case report describing diabetes insipidus \(^{11}\) and one case of hyponatraemia secondary to SIADH \(^{13}\). Serum prolactin may be elevated (2 out of 8 cases from the National Cancer Institute data) or low (2 out of 8 patients from the case series reported by Blansfield et al. \(^{12}\)).

MRI imaging of the pituitary in patients with histologically confirmed lymphocytic hypophysitis usually shows a uniformly enlarged and homogeneously enhancing gland, often with loss of posterior pituitary signal intensity on pre-contrast images and variable enlargement of the infundibulum \(^{14}\). Similar changes are often seen in
patients with ipilimumab-associated hypopituitarism, but appear to be of a lesser magnitude and in some cases the MRI has been regarded as within normal limits. The pituitary enlargement, when it occurs, shows an increase in the height of the pituitary gland in the sagittal plane of the MRI scan from baseline 3.4-6mm to 7.7-11.8mm, which is relatively modest. Such expansion decreases gradually on glucocorticoid treatment. In the case series by Min et al. only one out of 8 patients had typical hypophysitis MRI findings, which resolved after one month. Another case described by Phan et al. showed a small decrease of pituitary height on the 6 weeks scan although the patient had only replacement doses of corticosteroids. Our patient’s MRI did not change significantly after 2 weeks, but his pituitary gland returned to its pre-ipilimumab treatment size after 3 months.

The recommended treatment for most of grade 3 and 4 immune-related adverse events secondary to anti-CTLA-4 antibodies consists of high-dose glucocorticoids (dexamethasone 4mg every 6 hours, prednisolone 45-60mg daily or methylprednisolone), tapered down gradually over one month. In cases of hypopituitarism secondary to autoimmune hypophysitis, the initial high dose of glucocorticoids is replaced by a physiological dose of hydrocortisone of 15-20mg a day in divided doses. However, it remains to be clarified whether these initial high doses of glucocorticoids are actually needed, or whether from the time of diagnosis patients should be started on close to a physiological replacement dose. Certainly, our patient was treated with high-dose corticosteroids but these were on an ambulatory basis and did not require hospital admission. Thyroxine and
testosterone should be replaced appropriately. Growth hormone was not offered to patients with low IGF-1 and dynamic tests or quality of life questionnaire were not discussed. In all reported cases of ipilimumab-induced hypophysitis, symptoms resolved with glucocorticoids, thyroxine and testosterone replacement.

We query the recommendation that discontinuation of ipilimumab treatment is necessary in anti-CTLA-4 antibody-induced hypophysitis; it is relatively straightforward to replace deficiencies of pituitary hormones, and the ipilimumab is generally prescribed for life-threatening cancers. Therefore, we would suggest that continuation of ipilimumab treatment may well be in patients’ best long-term interest.

To date, there has been only a single case showing recovery of corticotroph function. Most patients remain on glucocorticoid replacement at 2-28 months at the time of reports. Pituitary-thyroid function recovered in 37-50% of patients. In the case series reported by Blansfield et al., 57% of men could discontinue testosterone replacement following normalisation of the pituitary-gonadal axis.

In conclusion, we report a further case of ipilimumab-induced hypophysitis, and note the increasing awareness of this problem. It responds rapidly to normal replacement therapy, but as based on published literature, the expansile nature of the pituitary lesion is usually minor; we question the need for high-dose corticosteroid therapy, and the necessity for cessation of ipilimumab.
Endocrinologists need to be rapidly aware of new immuno-modulating agents used in cancer treatment, as they cause a variety of autoimmune complications, which could be life threatening if unrecognised.

DECLARATION OF CONFLICT OF INTEREST

Authors do not declare any conflict of interest.

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Figure 1. Mechanism of action of CTLA-4 inhibitor:

A: Activation of T-cells requires 2 signals; presentation of antigen to TCR by MHC and interaction between co-stimulatory molecule B7 and CD28. B: T-cell activation upregulates CTLA4, which binds to B7 with greater affinity than CD28 and blocks signal 2, thus down-regulating the T-cell. C: Anti-CTLA4 antibodies bind and block CTLA4, thus allowing resumption of signal 2 and restoration of T-cell activation.

APC – Antigen Presenting Cell, MHC – Major Histocompatibility Complex, TCR – T-cell receptor, Ag – Antigen, B7 – peripheral membrane protein, CTLA4 – Cytotoxic T Lymphocyte Antigen 4, CD – Cluster of Differentiation

Figure 2. MRI scan of the pituitary gland, T2 phase with gadolinium contrast: A - at diagnosis, showing pituitary gland enlargement with contrast enhancement (sagittal plane), B- coronal plane, C – No change 2 weeks after presentation D- complete resolution of pituitary enlargement after 3 months.
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245x109mm (150 x 150 DPI)
Figure 2. MRI scan of the pituitary gland, T2 phase with gadolinium contrast: A - at diagnosis, showing pituitary gland enlargement with contrast enhancement (sagittal plane), B - coronal plane, C - No change 2 weeks after presentation D - complete resolution of pituitary enlargement after 3 months.

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<th>Study</th>
<th>Number of patients (%) with hypophysitis</th>
<th>Hormonal deficiencies</th>
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<th>L-T4/ Testosterone replacement</th>
<th>Hormonal recovery</th>
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<td></td>
<td></td>
<td>ACTH</td>
<td>TSH</td>
<td>LH/FSH</td>
<td>GH</td>
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<td>Hodl et al. 2010</td>
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<td>Downey et al. 2007</td>
<td>13 (9%)</td>
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<td>Merker et al. 2008</td>
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<td>Blansfield et al. 2005</td>
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Table 1. Summary of the studies reporting on ipilimumab induced hypophysitis. Abbreviations: ACTH – adrenocorticotrophin, TSH – thyroid stimulating hormone, ADH – vasopressin, GH – growth hormone, HC – hydrocortisone, T4 – L-thyroxine, N/A – data not available; † - no comments included regarding remaining cases; ‡ - normal pituitary; # - empty sella turcica.