Anti-CTLA-4 Monoclonal Antibodies Induced Hypophysitis: Case Report and Literature Review

Jaafar Jaafar* and Jacques Philippe
Division of Endocrinology and Diabetology, Geneva University Hospitals and Faculty of Medicine, Switzerland

Abstract
Treatment with Anti-CTLA-4 Monoclonal Antibodies (mAb) has become a common choice in advanced melanoma and is under evaluation for many other types of cancer. These antibodies inhibit the interaction between CTLA-4 (Cytotoxic T Lymphocyte-Associated Antigen 4) receptors on the T cell surface and the antigen presenting cell surface molecules B7, leading to the activation or enhancement of T cell immune responses. The oncologic beneficial effects of Anti-CTLA-4 mAb are marred by many immune related adverse effects, including Ipilimumab-Induced Hypophysitis (IIH). We, herein, report an illustrative case with a literature review. Based on this research, the incidence of IIH was between 1.75% and 13%. Presenting symptoms were predominantly headache and fatigue. Pituitary enlargement was the main radiologic sign on MRI. The thyrotrophic and adrenocorticotropic axes were the most commonly affected followed by gonadotropic, somatotropic and lactotropic axes, respectively. Time to hypophysitis onset varied between 5 and 40 weeks after starting ipilimumab and treatment withdrawal due to hypophysitis was largely variable. Finally, thyrotropin and gonadotropin axes recovered more frequently than other anterior pituitary axes.

Introduction
The emergence of new antitumor drugs called Immune Check-Points Inhibitors (ICIs) in the management of melanoma, Non-Small Cell Lung Cancers (NSCLC) and other cancers led to the development of new forms of adverse effects called Immune Related Adverse Effects (irAEs), as compared to conventional chemotherapy. These new multisystem adverse effects include dermatologic, gastrointestinal, pulmonary, and endocrine effects. Endocrinologists are increasingly facing the diagnosis and management of the endocrine irAEs on the thyroid, pituitary, adrenal glands and pancreas, which was, up until recently, not indexed in endocrine diseases. The nowadays admitted and used ICI are essentially anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) antibodies, anti-programmed cell death-1 (PD-1) antibodies and anti-Programmed death-ligand 1 (PD-L-1) with other check-point inhibitors currently under investigation. Ipilimumab (Ipi-) is an anti-CTLA-4 antibody which showed a beneficial effect in advanced melanoma, but these beneficial effects are tainted by several undesirable effects including hypophysitis. Here we report a case of ipilimumab induced hypophysitis with a literature review of the incidence, diagnosis, treatment and follow-up of this condition.

Case Presentation
A 62-year-old Caucasian male patient diagnosed 6 years ago with non-metastatic right thigh melanoma was treated by tumour excision with inguinal lymph node dissection. His past medical history includes an ischemic stroke due to dissection of the left vertebral artery. Two years ago, he presented a metastatic relapse with a subcutaneous nodule on the anteromedial face of the right thigh with hepatic metastasis rapidly progressive within 2 months, bone metastasis and left adrenal metastasis, without adrenal insufficiency. The patient was started on intravenous (i.v) ipilimumab (Ipi-) 3mg/kg every 21 days. The patient underwent a pre-treatment thyroid assessment which was normal and subsequently serial TSH measurements before every Ipi- injection. Twenty days after the forth injection of Ipi- he presented a mild headache and fatigue. Biological tests showed central hypothyroidism with TSH at 0.1mU/l and free T4 at 11.7 pmol/l (N: 12-22pmol/l), low testosterone 1.27µg/l (N: 2.73-8.16µg/l) with low LH, a surprisingly high level of IGF-1 at 244 µg/l and a normal cosyntropin stimulation test. However, two months later, the cortisol level was reduced to 2µmol/l (Figure 1). A 18F-FDG PET scan showed a high pituitary uptake compared with a previous PET scan (Figure 2), and a Gadolinium-injected pituitary MRI done 10 days later showed hypertrophic and heterogenic pituitary with diminished spontaneous posterior pituitary intensity (Figure 3). The...
The patient was started on levothyroxine and high-dose prednisone with subsequent progressively decreasing doses, as well as replacement treatment with testosterone. The clinical course was rapidly favorable whereas biologically, he recovered the thyrotrophic axis within 52 weeks but till today, the patient needs corticosteroid and testosterone replacement therapy. Ipi- was stopped at the diagnosis of hypophysitis but the patient had already received 4 doses. A new treatment with pembrolizumab 2mg/kg i.v every 21 days was started 5 weeks after the last dose of Ipi- because of disease progression in the liver, internal and external right iliac lymph nodes along with a global increase in almost all known bone and left adrenal metastases.

**Discussion**

**CTLA-4 Immune Check-point Inhibition**

The role of CTLA-4 was clearly evoked by Linsley et al. [1] in 1991 and 1992, who showed a suppression of T cell-dependent antibody responses to sheep erythrocytes or keyhole limpet hemocyanin, by CTLA4 Immunoglobulin (Ig) treatment in vivo. Simultaneously, Lenschow described a long-term survival of xenograft tumors expressing CTLA-4Ig, thus emphasizing the immunosuppressive role of this cell surface protein [2]. Chambers described in 2001 the CTLA-4-mediated inhibition in regulation of T cell responses [3]. T cell activation require recognition and binding of T Cell Receptor (TCR) to antigen-bound Major Histocompatibility Complex (MHC) present on the Antigen-Presenting Cell (APC) with simultaneous co-stimulatory interaction between CD28 on the T cell and members of the B7 family on the APC [4].

Given the inhibitory effect of CTLA-4 in the T cell response, it was proposed that blockade of CTLA-4 might overcome the CTLA-4-mediated suppression and enhance pre-existing or induced immune responses to cancer. This finding was clinically proven in two phase III studies [8-10]. This allowed Ipilimumab (Ipi-), which is a fully human IgG1 Monoclonal Antibody (mAb), to be approved by the Food and Drug Administration (FDA) and by the European Medicine Agency (EMA) in 2011 as the first anti-CTLA-4 mAb for the treatment of advanced malignant melanoma. Ipilimumab is currently being assessed by several trials in lung, renal, prostate, pancreas, liver and ovarian cancer, in addition to lymphoma, leukaemia, and other haematological disorders and solid tumours [11].

Despite its clinical benefits, treatment with anti-CTLA-4 mAb is associated with multiple organs irAEs, which are different from conventional chemotherapy. These adverse effects include dermatological toxicities, colitis, diarrhoea, hepatotoxicity, as well as endocrine, ocular, renal and neurologic immune Adverse Events (AEs) [12]. Endocrine AEs (eAEs) were essentially hypophysitis or hypopituitarism, thyroiditis with hyper and hypothyroidism and adrenalitis. In general, eAEs occur in the first 6 months of treatment, especially during the induction period. In a phase III follow-up study...
Table 1: Phase I, II, III, IV trials of anti-CTLA-4-mAb, with essential endocrine AEs.

<table>
<thead>
<tr>
<th>Study phase</th>
<th>Authors</th>
<th>Pathology</th>
<th>Treatment</th>
<th>Number of patients</th>
<th>All eAEs</th>
<th>Hypophysitis or hypopituitarism</th>
<th>Thyroiditis</th>
<th>Hyper-thyroidism</th>
<th>Adrenitals</th>
<th>Diabetes</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Scott Antonia [18]</td>
<td>Advanced non-small-cell lung cancer (NSCLC)</td>
<td>Durvalumab (Anti-PD-L1) with anti-CTLA-4 antibody tremelimumab</td>
<td>102</td>
<td>0%</td>
<td>0%</td>
<td>18%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>I</td>
<td>Wolchok [19]</td>
<td>Unresectable, stage III or IV melanoma</td>
<td>Nivolumab (PD-1 checkpoint inhibitor) and ipilimumab (concurrent and sequenced treatment)</td>
<td>53</td>
<td>13%</td>
<td>2%</td>
<td>2%</td>
<td>4% hypo-thyroidism</td>
<td>0%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>II</td>
<td>Maker [15]</td>
<td>Stage III-IV melanoma</td>
<td>CTLA-4 blockade + immune-activating stimulus, interleukin (IL)-2</td>
<td>36</td>
<td>17%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>II</td>
<td>Yang [20]</td>
<td>Metastatic renal cell cancer</td>
<td>Ipilimumab, 10mg/kg, iv on day 1 plus sargramostim, 250 μgsc, on days 1 to 14 of a 21-day cycle (n = 123)</td>
<td>61</td>
<td>32.7%</td>
<td>(only grade≥3 reported)</td>
<td>3.27%</td>
<td></td>
<td>1.6%</td>
<td></td>
<td>Double arm open label study</td>
</tr>
<tr>
<td>II</td>
<td>F. Stephen Hodi [21]</td>
<td>Unresectable stage III or IV melanoma, at least 1 prior therapy</td>
<td>Ipilimumab 10mg/kg, iv on day 1, plus sargramostim, 250 μgsc, on days 1 to 14 of a 21-day cycle (n = 123)</td>
<td>123/122</td>
<td>3.4% Vs 7.5%</td>
<td>NR</td>
<td>0% vs 3%</td>
<td>NR</td>
<td>1% vs 2%</td>
<td></td>
<td>RCT</td>
</tr>
<tr>
<td>II</td>
<td>C. Lebbé [22]</td>
<td>Advanced melanoma treated with ipilimumab in prior phase II studies</td>
<td>Ipilimumab retreatment, extended maintenance therapy, or follow-up for survival only</td>
<td>248</td>
<td>15.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Evan M. Hersh [23]</td>
<td>Unresectable, metastatic melanoma in chemotherapy-naive patients</td>
<td>Ipilimumab at 3 mg/kg every 4 weeks for four doses either alone or with up to six 5-day courses of DTIC at 250 mg/m²/day</td>
<td>72</td>
<td>0% vs 2.8%</td>
<td></td>
<td></td>
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<tr>
<td>II</td>
<td>S. J. O'Day, [24]</td>
<td>Previously treated, unresectable stage III/IV melanoma</td>
<td>10 mg/kg ipilimumab every 3 weeks for four cycles (induction) followed by maintenance therapy every 3 months</td>
<td>165</td>
<td>5.8%</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>II</td>
<td>Richard E. Royal [25]</td>
<td>Locally Advanced or Metastatic pancreatic adenocarcinoma</td>
<td>Ipilimumab IV intravenous (3.0mg/kg every 3wk; 4 doses/ course) for a maximum of 2 courses</td>
<td>27</td>
<td>3.7%</td>
<td>3.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>S. F. Slovin, [27]</td>
<td>Metastatic castration-resistant prostate cancer</td>
<td>Ipilimumab 10 mg/kg + radiotherapy (8 Gyresion)</td>
<td>50</td>
<td>18%</td>
<td>2% hypo-thyroidism</td>
<td>0%</td>
<td>4%</td>
<td>4%</td>
<td></td>
<td>Phase I then expansion to phase II, non-randomized, open-label, multicentre study</td>
</tr>
<tr>
<td>II</td>
<td>Jeffrey Weber [27]</td>
<td>Previously treated and treatment-naïve unresectable Stage III or IV Melanoma</td>
<td>Ipilimumab (10 mg/kg every 3 weeks for four doses) with daily blinded budesonide (group A) or placebo (group B)</td>
<td>115</td>
<td>9.5%</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
II Postow MA [16]
Unresectable, previously untreated stage III or IV melanoma
Nivolumab (PD-1 checkpoint inhibitor) and ipilimumab versus ipilimumab alone
142 34% vs 17.4% 10% vs 3% 2% vs 4% Hypothyroidism 16% vs 15% Hypothyroidism 0% vs 0% NR NR NR NR Double-blinded randomised trial

II Lynch [14]
Stage IIIb/IV non-small-cell lung cancer
Iplimumab in combination with paclitaxel and carboplatin as first-line treatment
204 (136 in ipilimumab arm) 2.76% (only hypophysitis and hypopituitarism are reported) 0% 2.76% 0 0 0 0 0
Randomized, double-blind, international, multicenter phase II study

III J. Larkin [17]
Previously untreated patients with unresectable stage III or IV melanoma
Nivolumab alone or Nivolumab and ipilimumab or ipilimumab alone
945 14.4%-30%-34% 0.3%-6.1%-2% 0.3%-1.6%-1.9% Hypothyroidism 8.6%-14.7%-4.2% Hyper T: 4.2%-8.9%-1% Hypothyroidism 0%-0.3%-0% hyperT: 0%-1%-0% NR NR NR NR RCT, double blinded

III F. Stephen Hodi [8]
Unresectable stage III or IV melanoma, whose disease had progressed while they were receiving therapy for metastatic disease
Iplimumab plus gp100 (403 patients), ipilimumab alone (137), or gp100 alone (136)
876 0.8%-1.5%-0% 1%-3.1%-0% HyppT: 1.3%-1.5%-1.5% hypot: 0.3%-0%-0% 0.3%-1.5%-0% 0.5%-0%-0% NR NR NR
Randomized, double-blind, phase 3 study, with patients of 125 centres in 13 countries

RCT: randomized control trial; IV: intravenous
gp100: glycoprotein, is a cancer vaccine derived from the melanosomal protein.

of ipilimumab (with or without gp100) pre-treated patients with stage IV melanoma who progressed under treatment, retreatment with anti-CTLA-4 mAb (ipilimumab) did not confer new types of toxicity and most events were mild to moderate [13]. Table 1 shows the result of a data research that we did in October 2016 of phase I, II, III and IV human trials, available in full English text, with CTLA-4 blockade. We found 139 studies. All abstracts were reviewed and studies with ≤20 patients were excluded. IIH incidence was between 2.76% [14] and 17% [15]. This incidence was greater when Ipilimumab was associated with anti-PD-1 antibodies compared with ipilimumab alone [16,17].

CTLA-4-mAb induced hypophysitis

Hypophysitis is an inflammation of the pituitary gland characterized pathologically by mainly lymphocytic infiltration and destruction of endocrine cells. It could be primary (idiopathic) or secondary by clearly a traceable triggering cause. Since the arrival of anti-CTLA-4 mAb, hypophysitis had emerged as one of the numerous irAEs. One of the first cases was described in 2003 by Phan in a patient with advanced melanoma treated with ipilimumab [18]. Blansfield then reported 8 cases of hypophysitis out of 163 patients with advanced melanoma or renal cell cancer treated by anti-CTLA-4 mAb with an incidence of hypophysitis of 4.9% [19].

The incidence of Ipilimumab Induced Hypophysitis (IIH) was reported by recent studies to be between 0.5% and 17.2% when used alone in advanced melanoma, with a higher incidence when using high compared to low doses [14,20-22]. Time to onset varies between 3.6 and 40 weeks [20,22-24], and when hypophysitis occurs, Ipi-discontinuation is 24-35% [25]. Ipi-discontinuation did not appear to affect the outcome of hypophysitis [26]. The main symptoms were fatigue and headache [25]. In a phase II study comparing ipilimumab to placebo in add-on therapy to Paclitaxel and carboplatin in 204 patients with stage III/IV NSCLC, the incidence of hypophysitis and hypopituitarism in the active arm was 2.76 % [14]. The association of ipilimumab with other ICIs like anti PD-1 was associated with 2%-12% of all hypophysitis grades in advanced stage melanoma patients [25]. The relation between dose and immune toxicity of Anti-CTLA-4-mAb in patients with metastatic melanoma was clearly demonstrated, with increasing grade III/IV irAEs incidence (35%) after a dose escalating of ipilimumab form 3 or 5 mg/kg to 9 mg/kg every 3 weeks [21] compared with an incidence of 25% in patients who received 3 mg/kg of antibody plus a peptide vaccine [27].

In a retrospective study of 154 adult patients with metastatic melanoma treated by ipilimumab, male gender and older age were risk factors for IIH, and pituitary enlargement on MRI was a sensitive and a specific sign for IIH, which can precede the clinical diagnosis and resolves rapidly under high steroid dose treatment. In this study, anterior pituitary function recovery was uncommon and the incidence of hypophysitis was positively correlated with improved survival (median survival 19.4 months with and 8.8 months without IIH) [20]. Male gender and older age were found by another team as predictors of hypophysitis in this setting [22]. Nevertheless they were not retained as predisposing factors for IIH in a recent retrospective study [23]. Hypophysitis with panhypopituitarism was described also for the first time in 2009 in two patients with prostate cancer treated with ipilimumab. In one patient, the onset of hypopituitarism was 4 weeks after initiation of Ipilimumab (10 mg weekly) with recovery of the Hypothalamic-Pituitary-Thyroid (HPT) axis after 9 months. The other patients presented hypopituitarism with Diabetes Insipidus (DI), with recovery after 3 days of high dose corticosteroids [11]. It is noteworthy that DI did not occur in large retrospective studies of IIH in patients with melanoma [19,20,24]. Hypophysitis induced by anti-CTLA-4-mAb could affect one, two or more pituitary axes, with typically gonadotrophic and thyrotrophic axes involvement first [28].

Table 2 summarizes several longitudinal studies (mainly retrospective in nature), that investigate the incidence, the clinical, biological and radiological presentation, and follow up of IIH.
### Table 2: Follow-up studies of ipilimumab induced hypophysitis.

<table>
<thead>
<tr>
<th>Study, author and type</th>
<th>Cohort size (M/F)</th>
<th>Pathology</th>
<th>Hypophysitis patient number (%)</th>
<th>Presenting symptoms</th>
<th>MRI</th>
<th>Hormone impairment</th>
<th>Treatment discontinuation due to hypophysitis</th>
<th>Time to onset of hypophysitis</th>
<th>Biological recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Downey [38], retrospective</td>
<td>139 (92/47)</td>
<td>Stage IV melanoma</td>
<td>13 (9%)</td>
<td>Headache and fatigue</td>
<td>Systematically done/ often abnormal (percentage NR)</td>
<td>Low TSH and T4</td>
<td>Low IGF-1 and GH</td>
<td>Low ACTH and cortisol</td>
<td>Low LH FSH (with low T or E2)</td>
</tr>
<tr>
<td>Phan [28] retrospective</td>
<td>14 (11/3)</td>
<td>Stage IV melanoma</td>
<td>1 (7.1%)</td>
<td>Personality changes, memory problems</td>
<td>Done 1/1 Pituitary size at the upper limit if normal</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Blansfield [29] retrospective</td>
<td>163 (128/35)</td>
<td>Advanced melanoma or renal cell cancer</td>
<td>8 (4.9%)</td>
<td>Headache, fatigue, Personality changes, memory problems anxiety, impotence, arthrits</td>
<td>Done 8/8 Enlarged sella 7/8 Empty sella 1/8</td>
<td>8/8</td>
<td>NR</td>
<td>7/8</td>
<td>8/8</td>
</tr>
<tr>
<td>Peter Attia [37] prospective</td>
<td>57</td>
<td>Metastatic melanoma</td>
<td>1 (1.75%)</td>
<td>Personality changes and memory loss</td>
<td>Done 1/1 (no pituitary anomaly)</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Frédérique Albarel [34] retrospective</td>
<td>130</td>
<td>Stage III-IV melanoma</td>
<td>15 (11.54%) 10 M, 5 F</td>
<td>Headache and anhidrosis</td>
<td>Done 12/15 (CT 2/15) Pituitary enlargement (12/15)</td>
<td>13/15</td>
<td>2/8</td>
<td>11/15</td>
<td>12/15</td>
</tr>
<tr>
<td>Alexander T. Faje [30] retrospective</td>
<td>154</td>
<td>Stage III-IV melanoma</td>
<td>17 (11%) 15M, 2F</td>
<td>Headache, fatigue, nausea</td>
<td>Done 17/17 Mild to moderate Enlargement of pituitary 17/17</td>
<td>14/14</td>
<td>1/6</td>
<td>7/14</td>
<td>14/14</td>
</tr>
<tr>
<td>Lucia Brilli [33] retrospective</td>
<td>273 (165/108)</td>
<td>Metastatic prostate cancer and metastatic melanoma</td>
<td>9 (3.3%) 4M,5F</td>
<td>Headache, fatigue and general discomfort</td>
<td>Done in 7/9 pituitary enlargement in 4 patients without chiasm compression, pituitary contractionin one patients, and no abnormalities in two patients</td>
<td>6/9</td>
<td>1/9</td>
<td>9/9</td>
<td>7/9</td>
</tr>
<tr>
<td>Troy Z. Horvat [29] retrospective</td>
<td>208 (162M, 116F)</td>
<td>Metastatic melanoma</td>
<td>17 (5.7%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mabel Ryder [40] retrospective</td>
<td>211 (134M, 77F)</td>
<td>Metastatic or unresectable melanoma</td>
<td>19 (8%) 11M,8F</td>
<td>Headache, nausea, emesis, extreme fatigue, diaphoretic, arthralgia, and/or mental status changes</td>
<td>Done 12/19 Enlarged pituitary 9/12 Normal pituitary 3/12</td>
<td>11/18</td>
<td>NR</td>
<td>16/16</td>
<td>5/12</td>
</tr>
</tbody>
</table>
Le min [36] retrospective 187 (118M,69 F) Metastatic melanoma 25 (19M, 6F) 13.3% (16.1M, 8.7%) Headache, fatigue Done 26/25 Pituitary enlargement 15/25 Normal 10/25 22/25 3/7 22/25 15/20 4/9 0/25 0/25 (24%) Median of 9 weeks (range: 5–36 weeks) 0% ACTH recovery, (64%) TSH recovery, (45%) gonadotropin recovery

T. Lam [32] Case series 10 (9M,1F) Stage III, IV melanoma 10 (9M,1F) Headache, fatigue, lethargy nausea Done in 10/10 4/10 enlarged pituitary 6/10 Normal pituitary including 2 patients with increased uptake on PET scan 5/10 2/6 9/10 5/9 0/6 0/10 0/10 (0%) (2 discontinued due to disease progression) Mean of 10.7 weeks (6–24 weeks) 1 (20%) TSH secretion recovery 3 (60%) gonadotropin recovery no (0%) ACTH recovery

Table 3: Symptoms and signs suggestive of hypophysitis in anti-CTLA-4 mAb treated patients.

Symptoms
- Headache
- Fatigue
- Nausea
- Confusion and behaviour disturbance
- General discomfort
- Loss of appetite
- Loss of libido
- Hot flashes
- Blurry vision, diplopia and other visual disturbances
- Lethargy
- Vomiting

Signs
- Weight loss
- Hypotension
- Fever

According to these studies the incidence of IIH was between 1.75% and 13%. Presenting symptoms were essentially headache, fatigue, personality changes and nausea. When pituitary MRI was done, pituitary enlargement was the main radiologic sign but was not consistently present. No case of DI was reported in all these studies (englobing 1636 patients). The thyrotrophic and adrenocorticotrophic axes were the most commonly affected (probably because they were systemically assayed), followed by gonadotropin, somatotropin and lactotropic axes, respectively. Treatment withdrawal because of hypophysitis was largely variable from 0 to 100% [19,27]. Time to hypophysitis onset after starting Ipi- also varied between 5 and 40 weeks. Thyrotropin and gonadotropin axes recovered more frequently, as compared to other anterior pituitary axes, with also a low rate of adrenocorticotrophic recovery (Table 2).

Mechanism of anti-CTLA-4 mAb induced hypophysitis

To respond to the question why do anti-CTLA-4 mAb, especially ipi-, provoke hypophysitis, Iwama et al. [29] developed a murine hypophysitis model by repeated injections of a CTLA-4 blocking antibody, leading to pituitary lymphocytic infiltration with development of circulating anti-pituitary antibodies. They then followed 20 patients with advanced melanoma or prostate cancer treated with ipi- and found that the 7 patients who developed hypophysitis had all novel anti-pituitary antibodies whereas the 13 patients who did not develop hypophysitis did not have these antibodies. These antibodies mainly recognized thyrotropin-, follicle-stimulating hormone-, and corticotropin-secreting cells. CTLA-4 was expressed at both RNA and protein levels in the pituitary gland, particularly in prolactin- and thyrotropin-secreting cells. It is then hypothesized that the injected anti-CTLA-4 antibody could cause pituitary toxicity if bound to CTLA-4 antigen expressed “ectopically” on pituitary endocrine cells. These cells became the site of complement activation, with deposition of C3d and C4d components leading to an inflammatory cascade similar to that seen in type II hypersensitivity. Conversely, in a recent retrospective study, pituitary antibodies were not found in all 9 patients who developed hypophysitis out of 273 patients with metastatic melanoma who were treated with Ipilimumab [23]. Nevertheless, it remains unclear why some patients but not others develop these antibodies. In one autopsy study of 6 patients treated with ipilimumab for melanoma the expression of CTLA-4 was present in all patients’ pituitary glands but at different levels, with the highest expression level in the patient who had severe hypophysitis. This study included one patient who had clinical and biological hypophysitis and a second with pituitary lymphocytic infiltration without clinical hypophysitis, and four other patients with normal pituitary function and structure. This elevated CTLA-4 expression was associated with high T-cell infiltration and IgG dependent complement fixation and phagocytosis. These findings suggest that a high level of CTLA-4 expression predisposes to hypophysitis through type IV (T-cell dependent) and type II (IgG dependent) immune mechanisms. This may possibly explain why only some patients develop hypophysitis when treated by anti-CTLA-4 mAb.

Diagnosis of anti-CTLA-4 mAb induced hypophysitis

Treating patients with ICIs require a good knowledge about their rAEs, and a low threshold of suspicion to evocate these AEs. In patients who are treated with anti-CTLA-4 mAb, especially ipilimumab, hypophysitis should be suspected in case of new onset headache, fatigue, hypotension, nausea, confusion and other symptoms and signs which are summarized in Table 3 [18-20,23,24,27,30]. Diabetes insipidus is very rare and was described in one patient with prostate cancer treated by Ipi [11]. Clinically, it might be associated with supine or orthostatic hypotension. Hyponatremia is present in some patients but not all.

When possible, before starting treatment, a morning evaluation of pituitary function should be performed, including corticotropin, thyrotropic, and gonadotropin axes, by measuring Thyroid-
Stimulating Hormone (TSH), Free Thyroxine (fT4) and Free Triiodothyronine (fT3), Adrenocorticotropic Hormone (ACTH) and cortisol, testosterone (in male patients) or estradiol (in female patients) with Luteinizing Hormone (LH) and Follicular Stimulating Hormone (FSH). A normal Cosyntropin Stimulation Test (CST) does not exclude an abnormal corticotroph axis due to a still normal adrenal response in a recently damaged pituitary gland. If doubt persists, a Corticotropin-Releasing Hormone (CRH) stimulation test could be done. On the other hand, a normal or high ACTH with a low cortisol or abnormal response to CST indicates primary adrenal damage, which is another possible complication of anti-CTLA-4-mAb. Similarly, a pituitary cause of hypothyroidism will be associated with both low or normal low TSH and low peripheral thyroid hormones (fT4 and fT3), while primary hypothyroidism will show a high TSH with low fT3 and fT4. Pituitary antibodies are not a part of the diagnostic workup.

MRI is not crucial for hypophysitis diagnosis and is sometimes normal even when there is clinical and biological evidence of hypophysitis, but when abnormal it confirms this diagnosis and allows exclusion of alternative diagnoses, mainly brain metastasis. Gadolinium injected cerebral MRI focusing on the pituitary gland is the test of choice and in case of hypophysitis it shows a pituitary gland and stalk enlargement and/or heterogeneity with loss of normal posterior pituitary signal intensity on the pre contrast images [31] (Figure 3). Follow up pituitary MRI may show evolution to empty sella [23].

Management of anti-CTLA-4 mAb induced hypophysitis

High-dose corticosteroids to treat hypophysitis was suggested by some studies [11,20,25] but others did not find a clear benefit on the outcome of frequency and time to resolution. Hormone replacement should be introduced in the case of deficiencies [22,23,26]. One study proposes to use high-dose corticosteroids only in severe and persistent mass-effect symptoms [23]. When high-dose corticosteroids are prescribed for treatment of acute hypophysitis, the suggested treatment is intravenous prednisone dose (1mg/kg) followed by the same oral daily dose with a gradual tapering over 4 weeks [28,32]. Thereafter, corticotropin substitution can be achieved using hydrocortisone 10 to 20 mg in the morning and 5 to 10 mg in the beginning of the afternoon or by a single dose of prednisone 5 mg to 7.5 mg in the morning with a thyroid substitution dose of levothyroxine 1.2 to 1.8 mg/kg. There are no recommendations for sex hormone replacement in immune-induced hypophysitis. A case-by-case assessment should therefore be done. In our practice, when a patient is hemodynamically stable without symptoms suggestive of local compression, we use replacement doses for deficient hormones, starting by corticosteroids then levothyroxine and eventually testosterone replacement. GH analogues are contraindicated in oncological circumstances.

Follow-up and reversibility of anti-CTLA-4 mAb induced hypophysitis

Endocrinological long term follow-up after hypophysitis due to anti-CTLA-4 mAb is not standardised and is often dictated by the oncological course. This generates a clinical practice disparity which is appreciated when we observe the heterogeneous results of both prospective and retrospective studies reported here. Generally, the pituitary size normalises on follow-up, but pituitary axes recover variably. Based on long term retrospective studies, the corticoadrenal axis recovery rate varies between 0 and 18.7% [26,33]. However, these values are probably underestimated due to the negative feedback of exogenous corticosteroids which are usually maintained over long periods of time without systematically evaluating the possibility of weaning. The pituitary-thyroid axis recovers between 0 and 100% [23,33] and the gonadotrophic axis recovers between 0 and 83.3% [24,27]. Finally, time to recovery varies from days to over two years.

Conclusion

Ipilimumab-induced hypophysitis has become a frequent immune check-point inhibitors complication, especially when Ipi- is used with other ICIs. Its recognition is based on acknowledgement and familiarity with adverse effects of this treatment and on having a low suspicion threshold. The main clinical presentation is headaches associated with fatigue. The workup includes anterior pituitary axes assessment along with pituitary imaging, preferably MRI. The use of high steroid doses as a treatment of acute phase of hypophysitis remains controversial. Deficient pituitary axes should be replaced and periodic evaluation of eventual pituitary hormone recovery should be done. Some studies suggested that the occurrence of hypophysitis might predict a better response to Ipi-. Finally, the mechanisms of the adverse effects must be better understood to look for preventive measures.

References

5. Linsley PS, Greene IL, Brady W, Bajorath J, Ledbetter JA, Peach R. Human B7-1 (CD80) and B7-2 (CD86) bind with similar avidities but distinct kinetics to CD28 and CTLA-4 receptors. Immunity. 1994; 1: 793–801.
12. Quirk SK, Shure AK, Agrawal DK. Immune-mediated adverse events of anticytotoxic T lymphocyte-associated antigen 4 antibody therapy in


