MANAGEMENT OF ENDOCRINE DISEASE

Immune check point inhibitors-induced hypophysitis

Frédérique Albarel¹,², Frédéric Castinetti¹,² and Thierry Brue¹,²

¹Aix-Marseille Université, Institut National de la Santé et de la Recherche Médicale (INSERM), U1251, Marseille Medical Genetics (MMG), Marseille, France and ²Assistance Publique-Hôpitaux de Marseille (AP-HM), Department of Endocrinology, Hôpital de la Conception, Centre de Référence des Maladies Rares de l’hypophyse HYPO, Marseille, France

Abstract

In recent years, the development of immunotherapy has constituted a revolution in the therapy for many cancers, with a specific toxicity profile including endocrine immune-related adverse events. Immune check point inhibitors (ICI)-induced hypophysitis is a common endocrine side effect, particularly with CTLA-4 antibodies and combination therapy, with frequent hormonal deficiencies at diagnosis. It can be difficult to evoke such diagnosis as the initial clinical symptoms are not specific (headache, asthenia...); thus, patients receiving such immunomodulatory therapies should be closely monitored by systematic hormone measurements, especially in the first weeks of treatment. Usually, hormonal deficiencies improve, except for corticotroph function. Despite a lack of large prospective studies on ICI-induced hypophysitis, some detailed longitudinal cohort studies have focused on such cases of hypophysitis and allow for optimal monitoring, follow-up and management of patients with this immune-related adverse event. In the case of ICI-induced hypophysitis, patients need long-term multidisciplinary follow-up, with specific education for those patients with corticotropin deficiency to allow them to be autonomous with their treatment. In this review, based on a clinical case, we detail the most relevant and novel aspects related to the incidence, diagnosis, treatment, evolution and management of hypophysitis induced by immunotherapy, with a focus on possible mechanisms and current recommendations and guidelines. Lastly, we emphasize several key points, such as the absence of indication to systematically treat with high-dose glucocorticoid and the pursuit of immunotherapy in such hypophysitis. These points should be kept in mind by oncologists and endocrinologists who treat and monitor patients treated by immunotherapy.

Invited Author's profile

Thierry Brue MD, PhD, is Professor of Endocrinology at Aix-Marseille University, Marseille, France, Head of the Department of Endocrinology at Conception University Hospital and Coordinator of the National and European (ERN) Rare Disease Reference Centre for Pituitary Disorders (HYPO). His research activities focusing on neuroendocrinology comprise clinical research in pituitary disorders, including multicentre clinical trials; experimental research as leader of the research team ‘Differentiation and Proliferation of Neuroendocrine ‘Tissues’ (DIPNET) in the Marseille Medical Genetics AMU-INSERM Laboratory of Nicolas Lévy; coordination of a research network on genetically determined pituitary hormone deficiency (GENHYPOPIT).
Case report (1st part)

A 52-year-old man called the dermatology department because 6 days earlier, he experienced major headaches that began at 11:00 h, as well as having asthenia and nausea. He tried to rest and took an anti-nausea medication, as directed by his doctor, but he was still very tired, had no appetite and had lost 3 kg over the last 5 days. He was scheduled to receive his third dose of immunotherapy the following day for a metastatic melanoma (stage 4 melanoma, with hepatic and pulmonary metastases, ipilimumab 3 mg/kg), and he was uncertain if he should come to the hospital to receive his treatment. In the end, he presented to the hospital with major dizziness and vomiting. His blood pressure was very low (80/40), he was very weak with muscle pain, headaches, nausea and was no longer capable of walking; he also described sexual dysfunction (low libido and erectile dysfunction) during the last 15 days. The physician in charge suspected hypophysitis.

Is hypophysitis a common adverse event with immunotherapy?

Prior to the recent development of immune checkpoint inhibitors (ICI), which constitute a revolution in cancer therapy, hypophysitis used to be a rare disease (1). These treatments, based on modulation of immunity, promote an enhanced anti-tumor response by targeting and blocking T-cell-inhibiting receptors or ligands (2). The first molecule to be approved, in 2011, by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) was ipilimumab, a human monoclonal antibody (Ab) directed against the cytotoxic T lymphocyte antigen 4 receptor (CTLA-4 Ab). CTLA-4 is a molecule expressed on the surface of most activated T lymphocytes during the initial activation phase in lymphatic tissue, inhibiting the activation of T lymphocytes through the CD28/B7-mediated co-stimulatory pathway. Therefore, CTLA-4 downregulates the T-cell activation pathway and can thus potentiate tumor development. Thus, by blocking the inhibition induced by the CTLA-4 receptor, ICI promotes anti-tumor activity and also enhances immunity (3, 4). Since 2011, five other ICIs have been approved by the FDA for use in numerous solid and hematological cancers (melanoma, non-small-cell lung cancer, renal carcinoma, urothelial carcinoma, head and neck carcinoma, Hodgkin’s lymphoma): two of these antibodies target the programmed death receptor-1 (PD-1; nivolumab and pembrolizumab) and three of the antibodies target its ligand PD-L1 (atezolizumab, durvalumab and avelumab). PD-1 is a co-inhibitory membrane receptor expressed in T cells activated during the effector phase in peripheral tissues. Binding of PD-1 to its ligands PD-L1 and PD-L2, expressed in tumor cells and tissue macrophages, causes an inhibition of T lymphocyte activation and proliferation and a decrease in the production of pro-inflammatory cytokines (ILM-2, IFN gamma). Consequently, PD-1 and PD-L1 Abs also stimulate T-cell activation, modulating tolerance at a more peripheral level (5, 6) (Fig. 1). These treatments can be used as monotherapy or in a combination regimen that may enhance their efficacy in some cancers (7).

The oncological benefit afforded by these molecules is associated with an enhanced immunological activity which leads to an increase in autoimmunity. Through their mechanism of action, ICIs have a specific toxicity profile with adverse effects affecting multiple organ systems. These immune-related adverse events (IRAEs) can affect the skin, gastrointestinal tract, liver and also the endocrine system (8). Endocrine IRAEs (hypophysitis, thyroid dysfunction, insulinitis, adrenalitis, hypoparathyroidism, pituitary ACTH-dependent Cushing’s syndrome...) have been frequently reported with ICI treatment, depending on the type of immunotherapy molecules involved (9, 10, 11). In a recent meta-analysis, hypothyroidism was estimated to occur in 6.6% of patients treated with ICIs, especially in patients receiving PD-1 inhibitors or a combination regimen. In the same study, the incidence of hyperthyroidism was estimated to be 2.9%, with an increased incidence in the case of PD-1 inhibitors, especially pembrolizumab. The occurrence of hypophysitis was less frequent with PD-1 or PD-L1 Ab treatment than with ipilimumab treatment: 0.4% with PD-1 inhibitors, less than 0.1% with PD-L1 vs 3.4% with anti-CTLA-4. Therefore, patients treated with PD-1 inhibitors or PD-L1 inhibitors appear to more frequently develop thyroid dysfunction than hypophysitis. In this study, it is worth noting that combination treatments enhanced the prevalence of all types of endocrine IRAEs and that these also occurred earlier (12, 13). The incidence of confirmed primary adrenal insufficiency is very low (case reports) and can occur with both anti-CTLA-4 and PD-1 inhibitors (12). ICI-induced insulin-deficient diabetes is also rare, reported to be 0.9% in a recent study, and it has only been described with PD-1 or PD-L1 inhibitor treatment, not with anti-CTLA-4 treatment (14).

Depending on the study and the year of publication, immunotherapy-induced hypophysitis seems to occur in between 0.5 and 22% of patients (9, 15, 16).
Indeed, in historical studies endocrine IRAEs were probably underestimated, these being only based on clinical evaluation. Though endocrine clinical signs can be nonspecific and hormonal evaluation was not systematically performed as it is today, hypophysitis was probably underdiagnosed. Interestingly, in the recent review of Barroso-Sousa et al., patients receiving combination therapy (anti-CTLA-4 and anti-PD-1 or PD-L1) had a greater risk of developing hypophysitis than those on monotherapy (6.4 vs 3.4% with CTLA-4 inhibitors and 0.4% with PD-1 inhibitors and less than 0.1% with PD-L1 inhibitors; \( P = 0.0001 \)) (10). From the earliest studies, the incidence of hypophysitis appeared to be dose dependent (3, 17, 18) with a recent randomized trial in patients with advanced melanoma showing double the rate of hypophysitis in the 10mg/kg treatment group compared to the 3mg/kg group (6.6 vs 3.3%, respectively) (19). In a study that we have conducted in our French center, in collaboration with the dermatological department of Timone hospital, Marseille, on patients treated with Ipilimumab for a melanoma, we found a 11.5% incidence of hypophysitis before the study was unblinded (15 cases of hypophysitis in a maximum of 131 patients receiving ipilimumab) and already observed an incidence of 3.2% (2/62) at a dose of 3mg/kg and 25% (11/44) in patients who potentially received 10mg/kg (20). After unblinding the study, only 20 of 44 patients had in fact received 10mg/kg of ipilimumab and the real incidence of hypophysitis in the 10mg/kg group was thus 55% (11/20) with an overall final incidence of hypophysitis of 14% (Albarel et al., unpublished data).

It is important to note that ICI-induced hypophysitis occurs more frequently in men over the age of 60 years (2–5x greater risk than in women) (21). In any case, these data need to be taken with caution, because the age of occurrence and the sex ratio can be very different from one cancer to another (melanoma or non-small-cell lung cancer for example). The median time to occurrence is, as in this case report, between 2 and 4 months (range 4 weeks to 19 months) with anti-CTLA-4 (20, 22, 23, 24), from 3 to 6 months with PD-1 or PD-L1 (25, 26) and earlier for those on combination treatment (30 days on average) (13). It should also be noted that the development of autoimmune disease has been shown to correlate with a better response to ipilimumab therapy, especially in grade 3/4 IRAEs (6, 27, 28). Faje et al. suggested a correlation between hypophysitis and survival in metastatic melanoma (22) that was confirmed by a recent large study, conducted on 98 patients with an ipilimumab-induced hypophysitis in a melanoma context, showing a better overall survival and time to treatment failure in these patients (29).

**What do we know about the mechanism of ICI-induced hypophysitis?**

Such a significant incidence of hypophysitis with immunotherapy, and especially with anti-CTLA-4 or combination treatments, raises several questions.
Though the precise mechanisms of ICI-induced hypophysitis remain unclear, recent studies have suggested that multiple pathways might be involved in its development. Studies by Iwama et al. have suggested a specific immunological activation at the pituitary level. These authors developed a murine model of anti-CTLA-4-induced hypophysitis, by injecting CTLA-4-blocking antibody into mice and showed that the mice developed a pituitary-specific mononuclear cell infiltration (pituitary lymphocytes and macrophages). They then showed, in these mice, the presence of complement deposition on prolactin- and TSH-secreting cells, which could implicate a type II hypersensitivity reaction with the activation of the classical complement pathway and secondary development of hypophysitis. The activation of this pathway could be explained by an ‘ectopic’ pituitary expression of CTLA-4 antigens that was found predominantly on prolactin and TSH-secreting cells in mice pituitary glands, at both the mRNA and protein levels (30, 31). Direct binding of anti-CTLA-4 to pituitary cells could also activate antibody-dependent cell-mediated cytotoxicity (32). CTLA-4 expression has also been found in normal human pituitary glands and pituitary adenomas, with variability in the expression levels that could influence the risk of developing anti-CTLA-4-induced hypophysitis from one person to another (33). It is noteworthy that ipilimumab and tremelimumab are anti-CTLA-4 IgG1 and IgG2 monoclonal antibodies respectively, which can activate the classical complement pathway and antibody-dependent cell-mediated cytotoxicity, while conversely nivolumab, pembrolizumab and anti-PD-L1 treatments, which are IgG4 antibodies, should be less effective in these pathways (34, 35). Moreover, Iwama et al. showed the development of circulating anti-CTLA-4 antibodies (directed against prolactin or ACTH- secreting cells) in mouse serum after anti-CTLA-4 injections. They also searched for pituitary antibodies in patients treated with ipilimumab for a cancer and found the presence of pituitary antibodies (directed against TSH, FSH or ACTH cells) only in patients presenting a hypophysitis (30).

Interestingly, a recent autopsy study on a subject with hypophysitis after injection of CTLA-4 inhibitors showed strong CTLA-4 expression in the pituitary and data in favor of type II and immunoglobulin IV (T lymphocyte-dependent) hypersensitivity reactions (36). As IgG4 cannot activate the complement pathway and is less effective for antibody-dependent cell-mediated cytotoxicity, the pathogenesis of the few anti-PD-1 or PD-L1-induced cases of hypophysitis is not clear. PD-1 could be expressed in pituitary cells or lymphocytes, as PD-L1 is expressed in pituitary adenomas (37) or as these antibodies are IgG4, they should share the same mechanism as IgG4-related hypophysitis (38).

It is interesting to note that some authors have recently suggested another way in which this susceptibility of pituitary cells to immunotherapy and CTLA-4 expression in pituitary cells and adenomas could be applied. They reported the case of a treatment-refractory aggressive ACTH-secreting pituitary carcinoma, which responded to combination treatment (ipilimumab and nivolumab), which could suggest a potential role for immunotherapy in treatment of such carcinomas (39).

Case report (2nd part)

At the hospital, biochemical and hormonal evaluations were assessed in the afternoon and showed decreased natremia (125 mmol/L), low cortisol (10 nmol/L) with low ACTH (3 pg/mL). Free T4 was also low (7 pmol/L) with a low TSH (0.2 mUI/L), concerning the gonadotropin axis, testosterone was low (400 pg/mL) with low LH and FSH (0.1 U/L) and prolactin level was 0.4 ng/mL. At the previous hormonal evaluation (performed at the last infusion, 3 weeks prior), the only abnormality found was a free T4 level of 11.9 pmol (N >12 pmol/L), with a normal TSH (but showing a decrease from 2.4 mUI/L at the beginning of treatment 9 weeks prior to 0.5 mUI/L at the last infusion).

What are the keys for diagnosis?

As observed in this case report, the initial clinical symptoms are not specific, consisting mainly of headaches, asthenia, nausea and dizziness with moderate symptoms related to mass effect and, exceptionally, visual disturbance (6, 16, 40). Thus, it can be difficult to evoke such a diagnosis and it is important to search for it, by regular clinical examination and biochemical evaluation. The question of performing systematic MRI (magnetic resonance imaging) during immunotherapy treatment has been raised, as some authors have reported a progressive pituitary enlargement before hypophysitis (22) and even pet-TDM has also been suggested, as these could be sensitive early tools (41). In any case, biochemical follow-up of hormone levels seemed to be more pertinent and a wiser approach in terms of screening. However, an incidental finding of a pituitary morphological abnormality makes it necessary to rule out hypopituitarism, since it has been shown by some authors that abnormal neuroimaging could precede symptoms of hypophysitis (33). Regular biochemical profiling in the
first 12 weeks of treatment can result in early detection of endocrinopathies, even those that are asymptomatic, especially in those undergoing monotherapy treatment (65% diagnosed with clinical symptoms in monotherapy vs 83% with combination treatment in the Scott et al. study), thus minimizing morbidity (13). As is the case in autoimmune hypophysitis, diagnosis of ICI-induced hypophysitis is presumptive, with no pathological confirmation needed, as no biopsy or surgery is required in this disease (42).

Patients with ICI-induced hypophysitis present with pituitary deficiencies, usually affecting several hormones, especially thyrotropin (84%), corticotropin (80%) and gonadotropin (76%), as reported by the four main detailed longitudinal cohort studies, which focused on ICI-induced hypophysitis (Table 1). Abnormal prolactinemia (elevated in 6% or collapsed in 61%) or somatotropin deficiencies (29%) are less frequent. A low level of prolactin at diagnosis could predict a lack of recovery of pituitary function (21). Although in these four studies no case of diabetes insipidus was found, a few cases have been described in the literature (being transitory and/or partial), with anti-CTLA-4 and also anti-PD-1 or PD-L1 therapy. Thus, most of the cases of ICI-induced hypophysitis involve only the anterior pituitary (40, 43, 44, 45).

It is noteworthy that an early progressive reduction in TSH, over a few weeks, can precede hypophysitis, as in our case report, so this could be an early marker of the occurrence of ICI-induced hypophysitis. Interestingly De Sousa et al. only reported a fall in TSH but no variation in cortisol levels before such development of hypophysitis (46). This was also highlighted by Faje et al. who found a progressive decline in TSH values prior to diagnosis and appearance of symptoms in patients with ipilimumab-induced hypophysitis (33). We also recently examined TSH levels in our French cohort and found a fall in TSH in 4/15 patients with ipilimumab-induced hypophysitis, at the time of the infusion before diagnosis of hypophysitis (3 weeks prior) (Albarel et al., unpublished). It is common to find hyponatremia at diagnosis, possibly linked to hypocortisolism or hypothyroidism, which is rapidly reversible after treatment (13, 22, 23).

It is important to perform imaging, if possible MRI, to confirm the diagnosis but also to eliminate differential diagnoses such as abscess, pituitary apoplexy, infiltration-related pathology and especially, in this oncological context, a pituitary metastasis (47). Typically, MRI shows moderate enlargement of the pituitary gland, global contrast enhancement, with convex aspect of the gland. It can sometimes show an enlargement of the infundibulum

<table>
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<tr>
<th>Table 1</th>
<th>Longitudinal cohort case studies of ICI-induced hypophysitis.</th>
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<tr>
<td><strong>Characteristics</strong></td>
<td><strong>Albarel et al. (20)</strong></td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>33.6</td>
</tr>
<tr>
<td>Hypophysitis, n (%)</td>
<td>15 (14%)</td>
</tr>
<tr>
<td>Mean age at hypophysitis (years)</td>
<td>55.5</td>
</tr>
<tr>
<td>Median time to diagnosis after ICI start (weeks)</td>
<td>9.5</td>
</tr>
<tr>
<td>Clinical symptoms (main)</td>
<td>Headache, fatigue</td>
</tr>
<tr>
<td>Pituitary hormone abnormalities</td>
<td></td>
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<tr>
<td>Corticotropin deficiency</td>
<td>11/15</td>
</tr>
<tr>
<td>Thyrotropin deficiency</td>
<td>13/15</td>
</tr>
<tr>
<td>Gonadotropin deficiency</td>
<td>12/14</td>
</tr>
<tr>
<td>Somatotropin deficiency</td>
<td>2/8</td>
</tr>
<tr>
<td>Low prolactinemia</td>
<td>3/9</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>1/9</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>0/15</td>
</tr>
<tr>
<td>Visual disturbance at diagnosis</td>
<td>0/15</td>
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<tr>
<td>Last follow-up hormone status</td>
<td></td>
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<tr>
<td>Corticotropin deficiency</td>
<td>13/15</td>
</tr>
<tr>
<td>Thyrotropin deficiency</td>
<td>2/15</td>
</tr>
<tr>
<td>Gonadotropin deficiency</td>
<td>2/15</td>
</tr>
<tr>
<td>Somatotropin deficiency (low IGF1)</td>
<td>1/11</td>
</tr>
<tr>
<td>Low/elevated prolactinemia</td>
<td>1/11, 1/11</td>
</tr>
<tr>
<td>Abnormal MRI at diagnosis</td>
<td>12/14</td>
</tr>
<tr>
<td>Resolution of MRI pituitary enlargement</td>
<td>12/12</td>
</tr>
</tbody>
</table>
Pituitary MRI can also be normal or ‘normalized’, the enlarged inflammatory aspect of the pituitary being rapidly reversible (23, 33, 48, 49), even in a few days, as was recently illustrated in a study by Faje et al. (29). In a recent review, of pituitary imaging of 167 patients with ICI-induced hypophysitis, 108 (65%) showed pituitary abnormalities (10). Therefore, physicians should be careful not to eliminate an ICI-induced hypophysitis based on normal imaging, and management should be based on clinical and biochemical evaluation (50).

**Case report (3rd part)**

Intravenous glucocorticoids were immediately initiated (100 mg hydrocortisone) followed by continuous perfusion of 100 mg over 24 h thereafter and an analgesic. The patient felt rapidly better and his blood pressure increased; his nausea and vomiting stopped and his headaches decreased. The patient underwent a pituitary and cerebral MRI in the evening that showed a moderately enlarged pituitary, far from the optic chiasm, with an enhanced convex aspect.

The next day, natremia normalized and the patient was able to take hydrocortisone orally (60 mg a day taken in three doses); his immunotherapy treatment was rescheduled to the following week. He returned home 3 days later on a daily hydrocortisone treatment of 30 mg taken in three doses and received education on adaptation and injection of hydrocortisone before leaving the hospital.

The following week, he came to the dermatological department for his immunotherapy treatment and felt much better. Hormonal evaluation showed a collapsed cortisol (<10 nmol/L) and ACTH (1 pg/mL) at 8:00 h before hydrocortisone treatment, free T4 was still low (6 pmol/L) with low TSH (0.03 mUI/L); testosterone and prolactin levels were increasing (1000 pg/mL and 4 ng/mL respectively). One month later, he still had a complete corticotropin deficiency, free T4 was still low (5 pmol/L) with a low TSH (0.02 mUI/L); testosterone and prolactin were still increasing (1800 pg/mL and 9 ng/mL respectively). He experienced asthenia along with a progressive weight gain of 5 kg; therefore, it was decided to begin treatment with levothyroxine (50 µg a day).

At the 3-month evaluation, he still presented with a corticotropin deficiency (cortisol <10 nmol/L, ACTH <1 pg/mL), free T4 level was normalized with levothyroxine 50 µg a day and testosterone was normalized with no treatment (4500 pg/mL). MRI re-evaluation showed a decreased pituitary volume with a concave aspect.

At the end of follow-up, 2 and a half years later, the patient had not recovered from the corticotropin deficiency, but his thyrotropin axis had spontaneously normalized (levothyroxine was able to be stopped after 5 months of treatment). His gonadotropin axis and prolactin were normal.

**How to treat and follow-up an ICI-induced hypophysitis**

When such a diagnosis is evoked, searching for a corticotropin deficiency and avoiding an acute crisis (as part of the secondary adrenal insufficiency) is a matter of urgency (51). If a corticotropin deficiency is suspected (nausea, deep asthenia, low blood pressure, hyponatremia…), glucocorticoid (GC) treatment should be immediately commenced (after assaying for plasma cortisol if possible, but in any case without waiting for results) as recommended by guidelines (hydrocortisone by intravenous or oral route, depending on the feasibility in the patient) (52). The question of the type of GC to be administered should also be considered.
Indeed, as the management recommendations of IRAEs in clinical trials were for utilization of high-dose GCs, the first cases of hypophysitis appeared and were treated following these modalities. The use of GCs should also be discussed in the light of the mechanism of action of immunotherapy, which could be negatively affected by an immunosuppressive treatment such as high-dose GCs. In this respect, the first reported studies were reassuring, as they did not appear to show any deleterious effects of high-dose GC therapy in cases of IRAEs, in terms of ICI anti-tumor responses and the duration of tumor response (28, 53, 54). Interestingly, a recent study conducted on 98 patients with melanoma presenting with an Ipilimumab-induced hypophysitis, treated with either low- or high-dose GC showed a significantly higher overall survival and time to treatment failure in the group treated with low-dose GC (29). Moreover, using either low or high-dose GC did not appear to improve the outcome of hypophysitis in terms of frequency and time to resolution of imaging and hormonal abnormalities (23). Complications that may require hospitalization that can follow such high-dose GC treatment, such as glucose tolerance abnormalities or acute corticotropin deficiency, following decrease or stopping of high-dose GC treatment, should be another argument against the systematic use of high-dose GC treatment (55). Therefore, most authors currently recommend that high-dose GC should not be routinely used in patients with ICI-induced hypophysitis but only in cases of serious mass-effect-related symptoms such as severe and refractory headaches, visual field disturbances or if patients present other concomitant autoimmune side effects necessitating such a treatment (20, 29, 55, 56). It is important to note that corticotropin deficiency can have delayed onset and may not recover in the majority of patients (in our French study, no patient recovered after, to date, more than 7 years of follow-up in some patients). Thus, prolonged treatment is, in general, required and patients need to receive an appropriate education to make them autonomous in hydrocortisone adaptation and they should also receive multidisciplinary follow-up (20).

Thyrotropin and gonadotropin deficiencies are also very frequent at diagnosis, but are often reversible, as in our clinical case, with only 45% and 37% respectively of these deficiencies at last follow-up (vs 84 and 76% at diagnosis respectively) reported in the four detailed longitudinal cohort studies which focused on ICI-induced hypophysitis (cited above and shown in Table 1). It is interesting to note that the longer the period of follow-up in the study the better is recovery; for thyrotropin deficiency, only two patients out of 15 had a deficiency after almost 3 years follow-up in the Albarel et al. study compared to 13/17 in the Faje et al. study which had less than 1 year of follow-up. In these same two studies, in terms of gonadotropin deficiency, 2/15 vs 13/17 respectively still had a deficiency at the last follow-up (Table 1). These data underline the importance of regular hormonal evaluation during the follow-up of such patients. It is worth noting that recovery of these deficiencies in the first months following hypophysitis is not rare, so the initiation of treatment for thyrotropin and gonadotropin deficiency is less urgent and can be delayed under close clinical and biochemical follow-up (20, 23). It has even been suggested by some authors that thyroid and gonadal dysfunction may be a result of sickness-induced hypogonadism or hypothyroidism, thus encouraging a delay in the commencement of hormone treatment (57).

Monitoring by pituitary imaging in the first 3 months is necessary to definitively rule out a differential diagnosis, especially a metastasis, with pituitary enlargement resolving in most cases of such hypophysitis (100% in studies by Faje et al., Albarel et al. and Min et al., Table 1). The typical evolution of ICI-induced hypophysitis is an early decrease in pituitary volume, with a concave appearance of the gland, and even in some cases, the appearance of empty sella turcica (33) (Fig. 2D).

It is also essential to note that further treatment with additional cycles of immunotherapy is not contraindicated in patients who develop an ICI-induced hypophysitis, as most authors agree that the benefits of immunotherapy regarding survival, in such an oncological context, greatly outweigh the risks of continuing therapy using an appropriate hormonal substitutive treatment. Sometimes, it may be necessary to suspend the immunotherapy for a few days during the acute phase of hypophysitis, but it can then be continued after replacement therapy is adjusted (23, 58, 59, 60).

To conclude, what can we currently recommend for ICI-induced hypophysitis?

Many guidelines and recommendations have been proposed in the last few years, for the acute management of hypophysitis or more generally on the management of endocrinopathies, based on the CTCAE (common terminology criteria for adverse events) (56, 61) or based only on symptoms, blood and imaging data (62, 63). Some authors have recently proposed detailed follow-up for patients with immunotherapy, to allow for early diagnosis and treatment of ICI-induced hypophysitis. Joshi et al. proposed a complete and common algorithm...
for management of endocrine IRAE, based on CTCAE grade that could make endocrine follow-up easier for oncologists (47). However, we believe that this generalization is open to discussion. Indeed, firstly, the frequencies of endocrine IRAEs are very different from treatment with one immunotherapy molecule to another; thus, close pituitary follow-up is needed with anti-CTLA-4 and combination therapies, but it is less justified in patients treated with anti-PD-1 and anti-PD-L1, as pituitary effects in this case are much rarer. Moreover, we believe that the CTCAE scale is not well adapted for endocrine, and especially pituitary IRAEs, as it could be difficult to distinguish the difference between grade 2 (moderate) and grade 3 (severe) hypophysitis, and the corresponding treatment recommendations are very different: grade 2 being withdrawal of the immunotherapy treatment and resumption when symptoms resolve, GCs only used in case of symptoms persisting after 1 week (0.5–1 mg/kg); while for grade 3, high-dose GCs (1–2 mg/kg) are recommended with withdrawal of the immunotherapy treatment. Moreover, in grade 4 (life-threatening, such as would be the case in an acute crisis during a corticotropin deficiency), the immunotherapy treatment should be definitively contraindicated (57, 64). As mentioned above, immunotherapy could be delayed in severe forms of hypophysitis, but should not be definitively interrupted. Moreover, high-dose GCs should not be routinely recommended. Thus, this scale and the corresponding recommendations do not seem to be applicable for pituitary IRAEs (65). Barroso-Sousa et al. proposed an algorithm, in 2018, based on clinical or biochemical (hyponatremia or low TSH and free T4 level) suspicion of hypophysitis. They then proposed complete biochemical, imaging and infection assessments before commencing hormonal replacement, with replacement doses of corticosteroids prospectively in every patient, and high-dose GC only in patients with life-threatening adrenal crisis, severe hyponatremia or severe headaches (66). French guidelines on endocrine IRAEs of immunotherapy have been recently published, with a specific algorithm for hypophysitis, based on clinical suspicion, then biochemical and MRI evaluation. Regarding treatment, rapid hydrocortisone replacement is recommended and then other deficiencies should be evaluated and substitutive treatment should be considered. The consensus also indicates the possibility of continuing the immunotherapy and details the long-term clinical, hormonal and imaging monitoring after hypophysitis (at each infusion for 6 months, then every 3 months for 6 months and later twice yearly). It was underlined that in case of suspected hypophysitis, corticotroph axis evaluation using 08:00h ACTH and cortisol measurement is important (to eliminate rare cases described of primary adrenal insufficiency); in case of emergency (to avoid acute adrenal crisis), a cortisol level (ACTH only if possible) should be obtained regardless of the time of day just before beginning hydrocortisone treatment. An initial hormonal monitoring before initiation of immunotherapy and hormonal follow-up during immunotherapy, with a common algorithm for all endocrine IRAEs, were also proposed that could allow oncologists to more easily make an earlier diagnosis of ICI-induced hypophysitis (60, 65, 67).

In these algorithms, the most important point is the possibility of making an early diagnosis of hypophysitis to avoid the occurrence of an acute adrenal crisis that could be life threatening. This is why a systematic clinical and biochemical evaluation before and during immunotherapy (especially with anti-CTLA-4 and combination treatment) is needed, with particular attention additionally paid in the first 3 months to a possible decrease in levels of the thyrotropin axis (22, 23, 24, 46). If corticotropin deficiency is suspected, hydrocortisone should be given at substitutive dose without waiting for hormonal assay results. High-dose GC can be considered in cases of severe analgesic-refractory headaches, visual disturbances or other IRAEs requiring such treatment (60, 66). Evaluation of other pituitary axes and assessment of pituitary MRI should also be done, but these are not as urgent. Substitutive treatments need to be discussed, since the thyrotropin and gonadotropin axes can recover; the somatotropin axis does not, however, need to be monitored as GH treatment is contraindicated in this oncological context. Another important point that should be underlined in recommendations is that immunotherapy can be postponed but does not need to be interrupted because of a pituitary IRAE. Finally, an essential point is the long-term persistence of the corticotropin deficiency in most of the patients with ICI-induced hypophysitis. These patients need to be ‘hydrocortisone educated’, meaning that they should be capable of adapting the dose of their hydrocortisone treatment to daily life incidents such as stress, infection and so forth, and they should also understand how and when they need to perform a subcutaneous injection of hydrocortisone (68). In our center, we have developed practical educational exercises for such patients, who have a significant increased morbidity and mortality linked to this new ICI-induced corticotropin defect (69).

In conclusion, we can currently state that even though there is a lack of large prospective studies on ICI-induced
Box 1: Key points

- Hypophysitis is a common IRAE in patients undergoing anti-CTLA-4 and combination treatment and appears to be dose dependent.
- Clinical and hormonal monitoring before and during immunotherapy is necessary for an early diagnosis of hypophysitis, especially in the first months of treatment with special attention paid to TSH level (TSH decrease may precede hypophysitis).
- If hypophysitis is suspected, the substitution of a corticotropin deficiency is an emergency.
- MRI must be performed if a hypophysitis is suspected and monitored during the first 3 months, especially to rule out the differential diagnosis of cerebral metastasis.
- Diabetes insipidus and visual disturbance are rare in such cases of hypophysitis.
- In case of hypophysitis, high-dose GC should not be systematically given, only in cases of major tumor syndrome (severe resistant headache or visual disturbance).
- Immunotherapy should not be stopped (can sometimes be delayed) in case of ICI-induced hypophysitis.
- Gonadotropin and thyrotropin defects should recover, unlike corticotropin deficiencies that are in most cases definitive and necessitate education of patients and oncologists on adaptation and injection of hydrocortisone.
- A multidisciplinary long-term follow-up with an endocrinologist and an oncologist is needed in cases of hypophysitis.

hypophysitis, the four major detailed longitudinal cohort studies focused on such cases of hypophysitis allow us to decide on the main points concerning monitoring, follow-up and management of patients with this IRAE (Box 1). Oncologists and endocrinologists must work together in the management of patients treated with immunotherapy since hypophysitis is not a rare IRAE, especially in those treated with anti-CTLA-4 or combination therapy. In the case of ICI-induced hypophysitis, patients need long-term multidisciplinary follow-up and in cases where they present with corticotropin deficiency, need specific education to allow them to be autonomous with the management of their hydrocortisone treatment, including its adaptation or injection.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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References
4 Tivol EA, Borriello E, Schweitzer AN, Lynch WP, Bluestone JA & Sharpe AH. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity 1995 3 541–547. (https://doi.org/10.1016/1074-7613(95)90125-6)
10 Tan MH, Iyengar R, Mizokami-Stout K, Yentz S, MacEachern MP, Shen LJ, Redman B & Gianchandani R. Spectrum of immune checkpoint inhibitors-induced endocrinopathies in cancer patients:


45 Gunawan F, George E & Roberts A. Combination immune checkpoint inhibitor therapy in ipilimumab and nivolumab associated with multiple endocrinopathies. Endocrinology, Diabetes and Metabolism Case Reports 2018 17 146.


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