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ENDOCRINE DYSFUNCTION INDUCED BY IMMUNE CHECKPOINT INHIBITORS

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Abstract Since their approval in 2011, immune checkpoint inhibitors (ICPis) are increasingly used to treat several advanced cancers. ICPis target certain cellular molecules that regulate immune response resulting in antitumor activity. The use of these new agents needs careful monitoring since they brought a whole new spectrum of adverse events. In this review, we aim to describe different endocrine dysfunctions induced by ICPis and to underline the importance of diagnosing and managing these adverse effects. Immune-related endocrine toxicities include thyroid dysfunction, hypophysitis and, less frequently, type 1 diabetes, primary adrenal insufficiency and hypoparathyroidism. Diagnosis of endocrine adverse events related to ICPis therapy can be challenging due to nonspecific manifestations in an oncological scenario and difficulties in the biochemical evaluation. Despite the fact that these endocrine adverse events could lead to life-threatening consequences, the availability of effective replacement treatment enables continuing therapy and together with an interdisciplinary approach will impact positively on survival.

Key words: immune checkpoints inhibitors, immune-related adverse events, hypophysitis, thyrotoxicosis, hypothyroidism, autoimmune diabetes

Resumen ***Disfunción endocrina inducida por inhibidores de los puntos de control inmune.*** Desde su aprobación en 2011, el uso de los inhibidores de los puntos de control inmunes (ICPis) se ha extendido para el tratamiento de diversas neoplasias en estadios avanzados. Los ICPis tienen como blanco ciertas moléculas de las células que regulan la respuesta inmune favoreciendo una actividad antitumoral. El uso de estos nuevos agentes requiere un monitoreo específico, ya que se han vinculado con un amplio y nuevo espectro de efectos adversos. El objetivo de esta revisión es describir las diferentes disfunciones endocrinas inducidas por los ICPis y destacar la importancia del diagnóstico y manejo oportuno de estos efectos adversos. Los efectos adversos inmunes endocrinos incluyen disfunción tiroidea, hipofisitis y con menor frecuencia, diabetes tipo 1, insuficiencia suprarrenal primaria e hipoparatiroidismo. El diagnóstico de eventos adversos endocrinos relacionados con la terapia ICPis es un desafío debido a su presentación clínica inespecífica en un escenario oncológico y a las dificultades en la evaluación bioquímica. Estos eventos adversos endocrinos podrían tener consecuencias potencialmente letales, pero la disponibilidad de un tratamiento de reemplazo eficaz permite continuar la terapia y, junto con un enfoque interdisciplinario, generar un impacto positivo en la supervivencia.

Palabras clave: inhibidores de puntos de control inmune, efectos adversos inmunes, hipofisitis, tirotoxicosis, hipotiroidismo, diabetes autoinmune

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KEY POINTS

- Endocrine immune-related adverse events related to ICPis can occur during immunotherapy or after withdrawal.
- Thyroid dysfunctions are the most frequent, mainly associated with anti-PD-1 or combined blockade. Thyrotoxicosis related to silent thyroiditis evolves usually to hypothyroidism, requiring long-term replacement.
- Hypophysitis is associated with anti-CTLA-4 or combined blockade. Fatigue and headache should trigger biochemical and imaging evaluation. Glucocorticoid treatment should be immediately initiated.
- Autoimmune diabetes evolves rapidly to ketoacidosis needing urgent treatment with insulin analogs.
- Education regarding IRAEs is of utmost importance to ensure notification and early diagnosis.
- Multidisciplinary approach is the milestone to improve quality of life and oncological outcomes.

In recent years, immunotherapy has modified the therapeutic approach to cancer with the development of immune checkpoint inhibitors (ICPis) targeted to increase the immune response against tumor cells. Since the approval by FDA of ipilimumab (anti-CTLA-4 agent) in 2011, for the treatment of advanced melanoma, other ICPis are increasingly used to treat several advanced cancers[1].

ICPis are monoclonal antibodies (mAbs) that target certain cellular molecules that regulate immune response, such as cytotoxic T-lymphocyte-antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand-1 (PD-L1), resulting in T-cell activation and antitumor activity[2].

However, native immune checkpoints also play a role in maintaining immunological self-tolerance and preventing autoimmune disorders; therefore, ICPis therapy can also trigger autoimmune adverse effects[1].

The use of these new agents needs careful monitoring since they brought a whole new spectrum of toxicities for healthcare practitioners to manage, including the risk of developing endocrinopathies[3].

Immune-related endocrine toxicities are irreversible in 50% of cases, and include thyroid dysfunctions, hypophysitis, type 1 diabetes, primary adrenal insufficiency and hypoparathyroidism[4, 5]. Adverse events are usually managed by oncologists, but endocrinologists must liaise closely with them to provide optimal care for this patient group.

In this review, we aim to describe the different endocrine dysfunctions induced by ICPis and to underline the importance of diagnosing and managing these adverse effects.

Pharmacological mechanisms of action and pathophysiology

The immune system has the capability to recognize and destroy non-self or cancer cells: T cells recognize and interact with an antigen-class II major histocompatibility complex on the membrane of the antigen-presenting cells[4]. Immune checkpoints are small molecules present on the cell surface of T-lymphocytes crucial for regulating the immune response (both its activation and inhibition) and maintaining self-tolerance, preventing it from attacking cells in a random manner[2]. Some of them mediate stimulatory signals to enhance T-cell activity (CD28, ICOS, CD137, OX40, and CD27), and others mediate inhibitory signals to blunt T-cell activity, such as cytotoxic T-lymphocyte-associated-4 (CTLA-4) and programmed cell death protein 1 (PD-1)[1].

In an active immune response, binding of B7 protein on the APC with CD28 receptor on T-cell surface is a second signal required for the activation of T-cell, promoting interleukin 2 (IL-2) production, clonal expansion, anergy avoidance and effector function[1]. T-cell activation induces CTLA-4 expression during the initial activation phase in lymphatic tissue. This receptor on the surface of cytotoxic T cells competes with CD28, and binds B7 with higher affinity[6]. This new interaction leads to abortion of T-cells activation, providing the balance in the immune response[7, 8]. The inhibitory effects of CTLA-4 seem to depend on the presence and availability of its ligands, CD80 (B7-1) and CD86 (B7-2)[1].

Besides, PD-1 receptors are part of immunoglobulin superfamily and are expressed on the surface of activated T lymphocytes, B lymphocytes, and monocytes. Ligands for PD-1 (PD-L1 and PD-L2) are present on the surface of APC and non-lymphoid cells such as beta cells in islets of Langerhans, thyrocytes, endothelial cells, cardiomyocytes and cancerous cells[2]. Binding of PD-1/PD-L1 inhibits the activation and proliferation of activated T lymphocytes, and binding of PD-1/PD-L2 decreases the production of pro-inflammatory cytokines (IL-2, interferon gamma)[9].

Cancerous cells are capable of modifying the expression or effect of these pathways (CTLA-4, PD-1, PD-L1) to avoid lymphocyte activation and to favor tolerance of the tumor cells[2]. Thus, the objective of immunotherapies is to block molecules that have an inhibitory effect to allow reactivation of the immune response and favor destruction of the tumor cells.

ICPis are monoclonal antibodies (mAbs) that target certain immune checkpoints, such as CTLA-4, PD-1 and PD-L1, resulting in T-cell activation and antitumor activity. Thus, the binding of anti-CTLA-4 mAbs, such as ipilimumab, to CTLA-4 prevents B7 binding and leads to upregulation of T-cell activity[8]. Anti-PD-1 (pembrolizumab, nivolumab) and anti-PD-L1 (atezolizumab, durvalumab, avelumab) block the binding between these receptor and ligand, and let the immune system detect and destroy tumor cells[9].

As mentioned before, the inhibitory signals of these immune checkpoints are important to prevent autoimmune disorders. While blocking these pathways may lead to a loss of activity of T lymphocyte regulators and reduced self-tolerance; it may increase the levels of pre-existing antibodies. These antibodies are responsible for certain immune effects, enhancing cytotoxicity directed against self-antigens and releasing new auto-antigens, which are targets for T lymphocytes. All these phenomena cause positive feedback, increasing the immune reaction[2, 10].

ICPis belong to different IgG subclasses, which may have a role in the pathophysiological mechanisms involved. IgG1 subclass (ipilimumab, durvalumab, atezolizumab and avelumab) induces antibody-dependent cell-mediated cytotoxicity (ADCC) and activation of the classical complement pathway. IgG4 subclass (nivolumab, pembrolizumab) has relatively less potency than IgG1 in activating ADCC and cannot activate the complement pathway[1]. However the precise mechanisms underlying the autoimmune side effects of ICPis are not completely understood[2].

Clinical scenarios

ICPis therapy has shown anti-tumoral efficacy in indications as varied as advanced melanoma and non-small-cell lung cancer, changing the prognosis. These agents are progressively becoming the standard of care in the treatment of many tumor types[1].

Ipilimumab, a human monoclonal antibody directed against CTLA-4 was first approved in 2011 by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for advanced melanoma. Since then five other ICPis have been approved by the FDA for use in numerous solid and hematological malignancies (melanoma, non-small-cell lung cancer, renal carcinoma, urothelial carcinoma, squamous cell head and neck carcinoma, Hodgkin lymphoma): two of these antibodies target the programmed death receptor-1 (PD-1; nivolumab and pembrolizumab) and the other three target its ligand PD-L1 (atezolizumab, durvalumab and avelumab)[6, 7, 11].

The different ICPis available and their main indications are shown in Table 1[12].

TABLE 1.– *Types of checkpoint inhibitors*

Immune checkpoint target	Drug name	IgG class	Malignancy	
CTLA-4	Ipilimumab	IgG1	Colorectal Melanoma	Renal cell
	Tremelimumab	IgG4	Colorectal Gastric and esophageal Melanoma	Mesothelioma NSCLC
PD-1	Pembrolizumab	IgG4	Cervical Colorectal Esophageal Endometrial Hodgkin lymphoma Hepatocellular Gastric Melanoma	Mediastinal large B-cell lymphoma Merkel cell NSCLC SCLC Renal cell Urothelial
	Nivolumab	IgG4	Colorectal HNSCC Hepatocellular Hodgkin lymphoma Melanoma	NSCLC Renal cell SCLC Urothelial
PD-L1	Atezolizumab	IgG1	Breast cancer (triple negative) NSCLC	Urothelial
	Avelumab	IgG1	Merkel cell Renal cell	Urothelial
	Durvalumab	IgG1	Urothelial	
Combination	Ipilimumab and nivolumab		Melanoma	Renal cell

HNSCC: head and neck squamous cell cancer; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer

Data adapted from[12]

Immune checkpoint inhibitors related adverse events - epidemiology

In contrast to the adverse effects caused by other cancer therapies, like immunosuppression with conventional cytotoxic chemotherapy, the toxic effects related to ICPis are due to an increase of the immune response and therefore called immune-related adverse events (IRAEs). The adverse events related to ICPis are shown in Figure 1.

Most frequent IRAEs involve skin (maculopapular rash, vitiligo, psoriasis), gastrointestinal tract (enterocolitis, celiac disease, gastritis), liver (hepatitis), as well as endocrine system. Less common immune toxicities can affect cardiovascular system (myocarditis, vasculitis), lungs (pneumonitis, pleural effusion), kidney (interstitial nephritis, glomerulonephritis), pancreas (pancreatitis), bone marrow (pancytopenia, neutropenia, thrombocytopenia, hemolytic anemia), musculoskeletal system (inflammatory arthritis, myositis, polymyalgia like-syndrome) and even immune sanctuaries as the nervous system (aseptic meningitis, Guillain-Barré syndrome, peripheral neuropathy, encephalopathy) or the ocular system (uveitis, conjunctivitis, choroiditis, orbital myositis)[5, 7, 11].

The global incidence of IRAEs varies between 15 and 90%[10]. The incidence of IRAEs depends on agent type: it is higher with anti-CTLA-4 (53.8%) than with anti-PD-1 (26.5%) and anti-PD-L1 (17.1%)[11]. It is not established if IPCis present later-term toxicity or if prolonged use results in higher incidence of IRAEs. Treatment of oncological patients at earlier stages will expand the data and may outline the answer[13].

These adverse events are often mild to moderate (grade 1-2), but 0.5-13% of patients can present more severe grades of IRAEs (grade 3-4). Most IRAEs occur within 3-6 months of initiation of ICPis, although delayed manifestations after years of treatment have been reported[14]. Severe IRAEs tended to occur soon after treatment initiation with monotherapy (median of 40 days) and even earlier with ICPis combination (median of 14 days)[10].

Combination therapy of CTLA-4 and PD-L1 blockade has shown promising results; however, it has been associated with a higher prevalence of IRAEs than monotherapy (61.1%), with up to 55% of patients with grade 3 or 4 adverse events, in particular diarrhea, colitis and elevated aminotransferase levels[15,16].

The prevalence of endocrinopathies during immune checkpoint therapy are shown in Table 2[17]. The incidence was reported to reach 10% in a meta-analysis of 38 studies that included a total of 7551 patients under ICPis[18].

Fig. 1.– Immune checkpoint inhibitors related adverse events

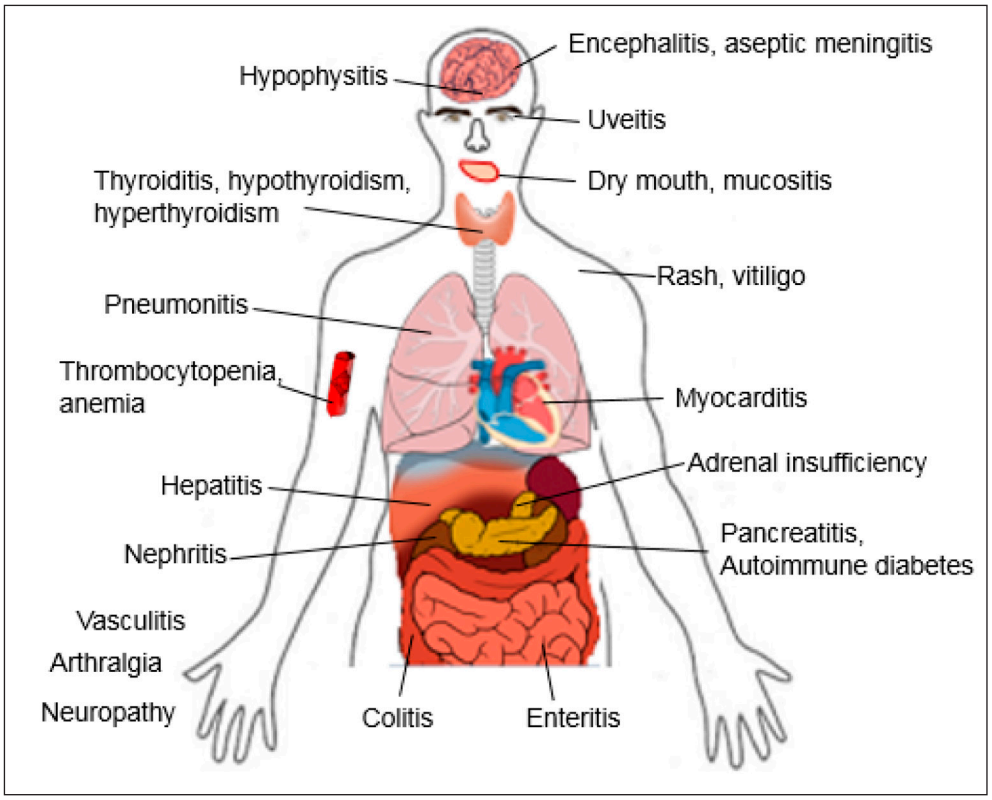


TABLE 2.- *Prevalence of endocrinopathies during IPCis therapy*

Target	Drug	Hypothyroidism	Thyrotoxicosis	Pituitary dysfunction	Primary adrenal insufficiency	Type 1 diabetes
CTLA4	Ipilimumab	3.8%	1.4%	5.6%	1.4%	–
	Tremelimumab	–	–	1.8%	1.3%	–
PD-1	Nivolumab	8%	2.8%	0.5%	2%	2%
	Pembrolizumab	8.5%	3.7%	1.1%	0.8%	0.4%
PD-L1	Atezolizumab	6%	–	–	–	1.4%
	Durvalumab	4.7%	–	–	–	–
	Avelumab	5.5%	2.3%	–	1.1%	1.1%
CTLA4 + PD-1	Combination	10-15%	10%	8-10%	5-7%	2%

Data adapted from Ref.[17]

It remains unclear why the endocrine effects induced by these autoimmune mechanisms are more frequently associated with the pituitary and thyroid. An explanation for this could be that both organs have rich vascularization, making them more susceptible to contact with activated T lymphocytes[2]. Furthermore, pituitary gland expresses CTLA-4, predominantly in prolactin- and TSH-secreting cells, making it a direct target for anti-CTLA-4 agents. The blockade of CTLA-4 molecules, involved in initial T-cell deactivation, may cause antibody-dependent cell-mediated cytotoxicity and activation of the complement pathway, leading to hypophysitis[6, 19, 20]. On the other hand, PD-1 and PD-L1 are expressed in the thyroid and could explain the more frequent involvement of these targets with ICPis[19, 20].

General approach to immune-related adverse events

Globally, grade 1-2 IRAEs can be managed symptomatically without dose omission, however grade 3-4 require suspension of medication and treatment with glucocorticoids[14].

Adverse events grade 4, particularly cardiac, pulmonary or neurologic, force the discontinuation of the treatment, impacting on survival. Exceptions to this rule are endocrine adverse events (adrenal crisis, thyroid storm, severe hypocalcemia or diabetic ketoacidosis). Despite the fact that these could lead to life-threatening consequences, the availability of effective replacement treatment enables continuing therapy after stabilization[5, 21]. Moreover, there is no evidence that anti-inflammatory treatment with high-dose glucocorticoids modifies the evolution of the endocrinopathies and should not be indiscriminately applied[6].

Restarting ICPis after delaying a dose and/or glucocorticoid treatment was not associated with further IRAEs in 50%, while 24% presented recurrence of the initial event and 26% a new one in 38 patients treated with anti-PD-1 or anti-PD-L1. Recurrent or new IRAEs are usually less severe, probably related to closer surveillance[14].

After serious IRAEs with one type of ICPi, the initiation of other type seems to be safe, probably due to specific biologic effects associated with pharmacologic mechanisms of action[22].

Diagnosis and management of endocrine immune-related adverse events

The diagnosis of endocrine dysfunctions during ICPis therapy can be challenging for many reasons. Firstly, most of the symptoms are nonspecific, thus, they may be assumed as part of the oncological disease and not as endocrine IRAEs. Secondly, endocrine tests are not routinely included in the biochemical evaluation. In third place, hormone alterations may be presented in patients with advanced cancer, who are severely ill, for instance non-thyroid illness or central hypogonadism. Finally, glucocorticoids are usually given empirically to attenuate some IRAEs or for pain management, interfering with the endocrine evaluation.

For counteracting the first point it is essential that patients are educated in reporting new signs and symptoms after treatment initiation. For the other three aspects, the interdisciplinary approach will ensue in opportune diagnosis and appropriate management.

Thyroid disorders

Thyroid dysfunctions are the most common endocrine IRAEs of ICPis and are more frequently developed with anti-PD-1 agents or combined treatment, except for the uncommon Grave's disease related to anti-CTLA-4 agents[11]. The main form is represented by silent inflam-

matory thyroiditis, although the spectrum includes both extremes. The reported frequency of ICPis treatment for hypothyroidism varies between 6-13%, for thyrotoxicosis between 3-16% and up to 28 and 22% respectively, when subclinical forms were considered[6, 23]. Median time to occurrence since ICPis initiation ranges from 2 to 4 months[14].

Thyroid dysfunctions related to ICPis are usually mild to moderate and thyroid storm or myxedema coma are extremely rare. The clinical picture mimics the one of endogenous disease: hypothyroidism presents with fatigue, asthenia, constipation, cold intolerance, dry skin and mild weight gain and hyperthyroidism with heat intolerance, diaphoresis, diarrhea, weight loss, tremor and tachycardia[14].

Biochemically the thyroiditis initiates with a thyrotoxicosis phase followed by hypothyroidism, less frequently by euthyroidism, or hypothyroidism from the outset. Whole thyroid profile (TSH, free T4 and total T3) will help in the differential diagnosis. Antithyroid antibodies are not invariable present and should be measured to detect autoimmune thyroiditis[6]. Identifying central hypothyroidism is another key aspect in the diagnosis and should be suspected with normal or low TSH and low free T4. Additionally, rapid decrease of a previous normal TSH over a few weeks is another clue to consider central hypothyroidism and should trigger the evaluation of the corticotroph axis to detect hypopituitarism related to hypophysitis[6, 14, 24]. Thyrotoxicosis with suppressed TSH and high free T4 and T3 levels could be differentiated from euthyroid sick syndrome by the low but not fully suppressed TSH and the normal or low normal levels of free T4 and total T3 in the latter. Hyperthyroidism should be considered in cases where thyrotoxicosis is not spontaneously autolimited, then TRAbs, doppler ultrasound and radioactive iodine uptake scan will clarify the diagnosis[11].

Thyrotoxicosis is usually autolimited and asymptomatic but cases with severe symptoms can be managed with ß-blockers. Rarely, glucocorticoids are needed in severe cases due to anti-inflammatory properties and blockade of T4 to T3 conversion, particularly useful in elderly patients[11].

Treatment of hypothyroidism is similar to the endogenous form and the general state of the patient and comorbidities (especially cardiovascular) should be considered. Clinical and biochemical parameters will guide treatment: confirmed TSH > 10 mUI/l supports levothyroxine replacement. When TSH ranges between 5 and 10 mUI/l, the presence of symptoms or antithyroid antibodies will favour treatment. Starting doses (1-1.6 µg/kg/day) are based on age, comorbidities and prognosis and titrated according to TSH controls[6].

Thyroid abnormalities do not contraindicate continuation of ICPis, nor initiation in cases of preexistent endogenous disease. When more severe IRAEs occur, therapy could be postponed until stabilization. In case of severe orbitopathy, treatment should be considered on an individualized basis[6].

Reversibility of hypothyroidism after ICPis withdrawal is uncertain: resolution was reported in 20-30% of patients with hypothyroidism and in up to 75% of patients with hyperthyroidism[25-27]. Levothyroxine treatment can be progressively tapered after ICPis withdrawal with clinical and biochemical control.

Hypophysitis

The incidence of hypophysitis varies largely among different studies according to treatment protocol, diagnosis criteria and follow-up[28]. It is higher with combined treatment (6.4%) and anti-CTLA-4 (3.4%) than with anti-PD-1 (0.4%) and anti-PD-L1 (less than 0.1%)[18]. It has been reported more frequently in men over the age of 60 years, twice to fivefold greater compared to women[6, 29]. Although it could be attributed to the oncological disease, after controlling for gender (melanoma occurs more frequently in men), the male predominance persists[30, 31]. Furthermore, older age and higher dose of ICPis (mostly ipilimumab) result in higher risk of hypophysitis[30, 32].

The median time to occurrence also depends on the agent: 2 to 4 months with ipilimumab (range between 1 to 19 months), 3 to 6 months with anti-PD-1 or anti-PD-L1 and earlier (less than 1 month) with combined therapy[3, 30, 33].

Diagnosis is based on clinical, biochemical and imaging criteria. The clinical picture is non-specific, including fatigue, weakness and headache. Other symptoms include hypotension, nausea, confusion, amenorrhea and sexual dysfunction. Visual disturbances are rare and diabetes insipidus exceptional, distinguishing from lymphocytic hypophysitis and pituitary metastases[1, 14, 12].

Biochemical deficiencies usually include anterior pituitary axes: thyrotroph (84%), corticotroph (80%) and gonadotroph (76%). New onset of hyponatremia, malaise, and appetite loss should prompt an evaluation for adrenal insufficiency. It has been reported isolated adrenocorticotropic hormone deficiency presented with hyponatremia, even after six month of ICPis withdrawal[34]. Decrease of TSH levels, indicating central hypothyroidism, is an early event in ICPis-related hypophysitis and should be taken into account[6, 14, 24]. Prolactin is more frequently decreased (61%) than elevated (6%), distinguished again from lymphocytic hypophysitis[30, 31, 35, 36]. GH-deficiency is not clearly defined as long as it needs provocative tests for diagnosis confirmation and replacement is contraindicated in active oncological disease[1].

The role of antipituitary antibodies (Abs) in the diagnosis of hypophysitis is controversial. Iwama et al. reported that antipituitary Abs developed in all the patients that presented ipilimumab-related hypophysitis (7/7) but in none of the 13 who did not, although its implication in

pathogenesis and prognosis is unclear[19]. Nevertheless, antipituitary Abs have been detected in patients with other autoimmune conditions, such as celiac disease[37].

Enhanced sellar magnetic resonance image (MRI) is the most sensitive imaging technique for diagnosis: the pituitary is mostly enlarged with heterogeneous enhancement after gadolinium administration[3, 35]. However, some changes can be mild and only noticeable when compared to prior MRI of the patient[31]. Changes in MRI tend to be early and can be rapidly reversed, even before clinical signs appear, explaining why a normal MRI does not rule out the diagnosis. Conversely, in case of abnormal MRI in a patient under ICPis without clinical evidence of hypophysitis, close biochemical monitoring (mainly with basal cortisol, weekly during 1 month) is advised[6, 14]. MRI is also fundamental for ruling out differential diagnosis such as metastasis, infiltrative or infectious pathology, pituitary adenoma or apoplexy[6, 32].

Aim of treatment is physiologic hormone replacement, since the few indications for high-dose glucocorticoids are incapacitating and refractory headache and/or visual impairment. The first axis to replace is the corticotroph, after taking a sample for deferred cortisol measurement, to prevent an adrenal crisis. Initial dose, administration route and dose tapering should be defined according to clinical state, preferably guided by an endocrinologist. Due to exceptional recovery of ACTH sufficiency (0-14%), education of patient, family and oncologist about dose increasing in stressful situations is of utmost importance[6].

Thyrotroph and gonadotroph replacement are not urgent and function can be monitored closely to define the necessity of treatment, as long as both axes can be transitory affected due to sickness-induced hypogonadism or hypothyroidism or evolve to spontaneous recovery (64-87% and 57-87% respectively) within the first 10 to 15 weeks[31, 35]. For both therapies, clinical and oncological contraindications should be considered. Follow-up should be done biochemically (including TSH measurement in central hypothyroidism) not only for treatment adjustment, but also for recovery detection and/or additional deficits screening[1,6]. According to a review of the literature (n = 71), patients with low prolactin at diagnosis tended to present lack of recovery of pituitary function ($p = 0.07$)[29].

Imaging abnormalities are expected to reverse in 73-100% of cases and a deferred MRI after 3 months is suggested for certain exclusion of the possible differential diagnoses mentioned before[30, 31, 35].

The diagnosis is rarely confirmed by histopathology, since surgery is only indicated in cases with sustained visual disturbances that do not improve with medical treatment[14].

As previously stated, hypophysitis related to ICPis does not contraindicate immunotherapy, owing to the favorable risk-benefit balance of ICPis on survival. Sometimes it is only necessary to suspend the immunotherapy for a brief period during the acute phase until replacement therapy is adjusted[6, 21].

Autoimmune diabetes

Autoimmune diabetes is an infrequent IRAE reported in patients treated with anti-PD-1 and anti-PD-L1 but not with anti-CTLA-4 blockade, with an overall incidence lower than 1%. It is diagnosed on average 20 weeks after the initiation of treatment, ranging from 1 week to 54 months[1, 11, 38].

Clinical diagnosis is based on signs of insulinopenia: polyuria, polydipsia, weight loss, abdominal discomfort and fatigue, as long as manifestation is more frequently in the form of fulminant diabetes associated with ketoacidosis, accounting for 57-71% of the cases[1, 38]. This abrupt onset warrants the rationale of patient, family and treating physician education regarding clinical signs[6]. Pancreatitis coexists in 42% of the patients[38].

Biochemical evaluation shows hyperglycemia, low C-peptide levels and non-concordant HbA1c due to the rapidity of diabetes development. Antibodies, mainly anti-GAD, are present in half of the patients[38]. Lipase reflects exocrine compromise. No abdominal imaging is needed for diagnosis.

Treatment is based on insulin analogs administered in multiple doses aiming at maintenance of HbA1c below 8% and follow-up is identical to endogenous autoimmune diabetes. Corticosteroid should be avoided, since no efficacy has been proven in diabetes reversal and could also interfere with glucose control. Patients with ongoing diabetes are candidates for ICPis treatment, adjusting capillary glucose monitoring. There is no evidence of diabetes remission after ICPis withdrawal[6].

Adrenal insufficiency

There are only few cases of primary adrenal insufficiency induced by ICPis adequately documented and reliably confirmed in the literature[1, 6]. These were reported with anti-CTLA-4 and anti-PD-1 with a median time of onset between 2.5 to 5 months after treatment initiation, but also occurred after ICPis withdrawal[14, 18].

Clinical signs can evolve rapidly, as adrenal crisis, or more progressively with a subacute course: fatigue, anorexia, weight loss, abdominal discomfort, postural dizziness and orthostatic hypotension[1, 39].

Biochemical assessment shows hyponatremia and the presence of hyperkalemia is characteristic of primary adrenal insufficiency. Low cortisol associated with high ACTH, the latter distinguishing primary etiology, confirms the diagnosis. Additionally, deficiency of the *zona glomerulosa* is evident due to low aldosterone and elevated renin levels. Hypoglycemia is rarely present. Anti-adrenal antibodies have been detected in some patients. Abdomi-

nal images should be conducted to rule-out other primary etiologies: bilateral adrenal metastasis, adrenal hemorrhage or infiltration[1, 6].

Replacement treatment with hydrocortisone should be initiated immediately when diagnosis is suspected, even before confirmation, similar to secondary adrenal insufficiency. Sick-day rules are equally important as in secondary adrenal insufficiency. In primary adrenal insufficiency fludrocortisone should be added to treatment when hydrocortisone dose is titrated below 50 mg daily[1].

Since recovery is unusual but adrenal insufficiency can be effectively replaced, ICPis should not be contraindicated, and treatment could be resumed when clinical stabilization is achieved[6].

Hypoparathyroidism

Only a few case reports of hypoparathyroidism with immunotherapy have been documented in the literature. Acute hypocalcemia with inappropriately low PTH levels developed between 1 and 12 months of anti-PD-1 or combination ICPis treatment[40-42].

Some grade of PTH recovery and normocalcemia have been observed under immunosuppressive therapy for colonic IRAE, but relapsed when glucocorticoids and anti-TNF-α were tapered[41]. Patients remain under replacement with calcium and calcitriol during the follow-up, even in the longest one of 3.25 years[43, 44].

Initial testing and monitoring of patients treated with immune checkpoint inhibitors

Clinical suspicion and routine hormone testing are the keys of early diagnosis of immune related endocrinopathies.

Basal determinations before immunotherapy are recommended to state normality: TSH and free T4, morning cortisol (if corticosteroids have not been used), fasting glycemia and ionogram. Given the major risk of endocrine IRAEs development at the beginning of ICPis treatment, closer monitoring should be performed: every course during the first semester, every 2 courses over the next 6 months and less frequently thereafter, guided mainly by clinical suspicion (Fig. 2)[6, 34].

Endocrine IRAEs have been reported even after immunotherapy withdrawal (mainly with nivolumab) warranting prolonged screening, although extension is controversial[34].

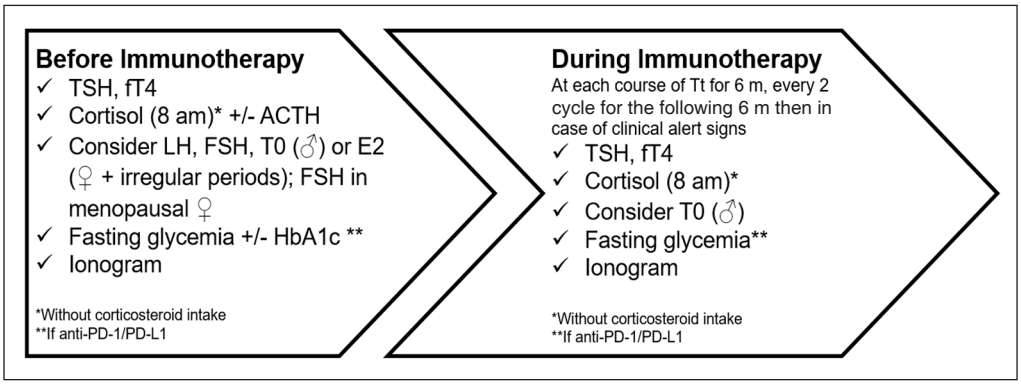
Immune-related adverse events and prognostic implications

There is still no clear evidence that IRAEs are associated with improved oncological outcomes. Some studies suggested that development of hypophysitis may predict better oncological outcomes in advanced melanoma treated with ipilimumab, but advantage is attenuated when treatment with high doses of corticosteroids is needed[24, 30, 45]. Notwithstanding, there is opposite data in melanoma patients reporting that overall survival and time to treatment failure were not affected by the occurrence of IRAEs or the need for systemic immunosuppression[46].

Although several studies suggest positive association between IRAEs and tumor response to ICPis and, consecutively, survival, the whole are retrospective and small studies. No prospective data is available to affirm this tendency, applying also to endocrine IRAEs[1, 47].

To summarize, since the introduction of ICPis as a new option in oncological treatment, IRAEs arise and the endocrine ones are commonly found. Among them, thyroid dysfunctions and hypophysitis prevail and less frequently, autoimmune diabetes, primary adrenal insufficiency and hypoparathyroidism. Each ICPis has a specific spectrum of endocrine IRAEs and combination therapy increases the toxicities significantly. Pathophysiology remains obscure as well as the impact of IRAEs or their treatment on

Fig. 2.– Biochemical evaluation before and during immunotherapy



fT4: free T4; T0: testosterone; E2: estradiol; Tt: treatment; m: months

oncological outcomes. Further research will clarify these uncertainties and may allow the identification of patients at greater risk of developing endocrine IRAEs.

Clinical and hormonal monitoring before and during immunotherapy is strongly recommended. Interdisciplinary approach is advised to achieve early diagnosis and opportune management of immune-related toxicities.

It is crucial to emphasize that under no circumstances endocrine IRAE precludes continuing immunotherapy due to available and effective replacement treatment. Immunosuppressive therapy is typically unnecessary but hormone replacement treatment should be monitored to adjust doses or even withdraw therapy when recovery is stated.

Conflict of interest: None to declare

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