JOURNAL OF EDUCATION, HEALTH AND SPORT
eISSN 2391-8306 · Open Access · Peer-reviewed
apcz.umk.pl/JEHS·Nicolaus Copernicus University in Toruń

Cite as: GRABOWSKA, Julia, JĘDRYSIAK, Joanna, KOLANKO, Magdalena, KOLASA, Wiktoria, KORZENIOWSKA, Anna, KOSIDŁO, Patrycja, LELONKIEWICZ, Martyna, MIKÓŁKA, Karolina, SZELIGA, Katarzyna and STOŁECKA, Greta. Hypophysitis During Immune Checkpoint Inhibitor Therapy: Epidemiology, Clinical Manifestations and Treatment Considerations. 2026;94:73736. https://doi.org/10.12775/JEHS.2026.94.73736

ARTICLE TIMELINE
Received: 28.05.2026 Revised: 02.07.2026
Accepted: 02.07.2026 Published: 09.07.2026

INDEXING & EVALUATION
MEiN points: 40 Unique ID: 201159
Disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

The journal has been awarded 40 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32318). Unique Journal Identifier: 201159. Scientific disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

Punkty Ministerialne z 2019 – aktualny rok 40 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Hypophysitis During Immune Checkpoint Inhibitor Therapy: Epidemiology, Clinical Manifestations and Treatment Considerations

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Abstract

Background. Immune checkpoint inhibitors (ICIs) have substantially improved outcomes in modern oncology; however, their increasing use is associated with immune-related adverse events, including endocrine complications. Among them, ICI-induced hypophysitis represents a clinically important condition that may result in hypopituitarism and potentially life-threatening hormonal deficiencies. **Aim.** This narrative review summarizes current evidence regarding the epidemiology, pathophysiology, clinical presentation, diagnostic approach, and management of ICI-induced hypophysitis.

Material and methods. A structured PubMed search was conducted between March and April 2026. Studies published within the last 10 years evaluating hypophysitis, hypopituitarism, or pituitary insufficiency associated with ICI therapy in humans were included. Additional cohort studies and clinical trials reporting incidence data were analyzed descriptively. **Results.** Eleven studies involving 8,310 patients were included in the epidemiological analysis. The incidence of grade ≥3 hypophysitis ranged from 0-6% with PD-1 inhibitors, reached up to 13.6% with ipilimumab, and ranged from 1.9-19.1% with combination therapy. Earlier onset was observed in CTLA-4-based regimens, whereas PD-1 inhibitor-associated hypophysitis tended to occur later during treatment. Clinical manifestations are frequently nonspecific, which may delay diagnosis and increase the risk of clinically significant adrenal insufficiency.

Conclusions. ICI-induced hypophysitis is a clinically significant endocrine adverse event whose incidence and timing depend on the therapeutic regimen used. Because symptoms are often subtle and nonspecific, early recognition requires increased clinical awareness supported by hormonal evaluation and imaging studies. Prompt diagnosis and appropriate hormone replacement therapy are essential to reduce complications and improve patient outcomes.

Key words: immune checkpoint inhibitors, hypophysitis, hypopituitarism.

1. Introduction

Immune checkpoints are key regulators of immune homeostasis and self-tolerance, expressed on the surface of immune cells where they modulate immune responses and maintain immune balance.

CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) is expressed on T lymphocytes and mediates inhibitory signals that attenuate T-cell activation. In contrast to CTLA-4, CD28

exerts a stimulatory effect on T-cell activity. Both of these immune checkpoints bind the same ligands, CD80/CD86 (B7 proteins), which are expressed on antigen-presenting cells (APCs). However, CTLA-4 exhibits a higher affinity for these ligands.

PD-1 (programmed cell death protein 1) is expressed not only on T cells but also on B cells, macrophages, and certain dendritic cells. Unlike CD28, PD-1 does not share ligands with other checkpoints but instead binds its specific ligands, such as PD-L1. These ligands are expressed, for example, on tumor cells and tumor-infiltrating macrophages, and their interaction with PD-1 induces T-cell exhaustion, thereby enabling tumor cells to evade immune surveillance.

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that exert their effects by blocking CTLA-4 or the PD-1/PD-L1 axis, thereby enhancing T-cell activation and proliferation and ultimately augmenting the anti-tumor activity of the immune system (Byun et al., 2017; Cardona et al., 2023; Chang et al., 2019; Quandt et al., 2021; Wright et al., 2021). The first ICI approved for clinical use in 2011 was ipilimumab (anti-CTLA-4). Over time, additional antibodies have been approved for therapeutic use: anti-CTLA-4 tremelimumab, anti-PD-1: nivolumab, pembrolizumab, cemiplimab, dostarlimab, retifanlimab, toripalimab, tislelizumab, penpulimab, anti-PD-L1: atezolizumab, avelumab, durvalumab and cosibelimab. These agents are used, among others, in the treatment of melanoma, small cell lung carcinoma, non-small cell lung cancer, renal cell carcinoma, colorectal cancer, gastric cancer, Merkel cell carcinoma, head and neck cancers and urothelial carcinoma (Chamorro-Pareja et al., 2024).

The application of ICIs in oncological therapy is diverse and involves their use as monotherapy, as combination therapy with other ICIs or conventional chemotherapy as either first-, second-, third-line therapy or in adjuvant or neo-adjuvant settings (Husebye et al., 2022).

With the expanding clinical use of ICIs across multiple tumor types and treatment settings, the spectrum and clinical relevance of treatment-related toxicities have also increased. The Common Terminology Criteria for Adverse Events (CTCAE) was developed to assess the severity of adverse events associated with anti-cancer therapy, including immune-related adverse events (irAEs), among them endocrine events. CTCAE categorizes adverse events into five grades: grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening), and grade 5 (death) (Chang et al., 2019).

ICIs stimulate immune system activity- T lymphocytes to fight against cancer cells, but it can trigger autoimmunological reactions in different organ systems and reduce self-tolerance, what is referred to as irAEs. The whole spectrum of irAEs may occur, including enterocolitis, hepatitis, pancreatitis, pneumonitis, myocarditis, pericarditis, cardiomyopathy with reduced systolic function, rash, vitiligo, endocrine adverse events and others. The endocrine adverse events are among the most common and

include hypophysitis, thyroid dysfunction, primary adrenal insufficiency, diabetes mellitus and hypoparathyroidism (De Camilli & Fischer, 2023; Deligiannis et al., 2021; Hattersley et al., 2021).

Hypophysitis is an inflammation of the pituitary gland. This process can affect the anterior pituitary (adenohypophysitis), infundibulum and posterior pituitary (infundibulo-neurohypophysitis), or the entire pituitary (panhypophysitis). Hypophysitis can be classified etiologically as primary or secondary. Primary hypophysitis is well identifiable etiological agent, whereas secondary hypophysitis is associated with systemic conditions, infections, neoplastic processes and medications (including ICI agents). From a histopathological perspective, primary hypophysitis is divided into five types: lymphocytic hypophysitis (infiltration of lymphocytes), granulomatous hypophysitis (infiltration of histiocytes and giant cells), xanthomatous hypophysitis (infiltration of foamy histiocytes), necrotizing hypophysitis, and IgG4 plasmacytic hypophysitis (Bellastella et al., 2016; Chang et al., 2019; Langlois et al., 2022).

2. Research materials and methods

This study was conducted as a narrative review. A structured literature search was performed to identify publications addressing the pathophysiology, clinical presentation, diagnosis, and management of ICI-related hypophysitis. Study selection for the main review process was summarized using a PRISMA flow diagram (Figure 1). The review process was carried out between March 15, 2026, and the end of April 2026. A literature search was conducted using the PubMed database. PubMed was chosen as the primary database because of its comprehensive biomedical indexing. The following search strategy was applied: ("immune checkpoint inhibitors" OR immunotherapy) AND (hypophysitis OR hypopituitarism).

Studies were included if they reported data on hypophysitis, pituitary dysfunction, or pituitary insufficiency associated with ICIs therapy in humans. The following exclusion criteria were applied: publication date older than 10 years from the search date, non-English language publications, bibliometric reviews, case reports, animal studies without reference to human data, studies for which full text was unavailable, studies lacking sufficient clinical or endocrine data relevant to hypophysitis. Data extraction and study selection were performed by a single reviewer. Formal risk-of-bias assessment was not performed due to the narrative design of the review.

In addition to the primary search, a separate targeted search was conducted to identify studies suitable for descriptive comparison of hypophysitis incidence across ICIs classes. For this purpose, clinical trials and cohort studies published within the last 10 years were screened. Studies reporting extractable incidence data on severe hypophysitis (grade ≥3) were selected for inclusion in the comparative table. These supplementary studies were used exclusively for epidemiological comparison and were not part

of the PRISMA selection process for the narrative review. Comparative data in Table 1 were synthesized descriptively and not subjected to meta-analysis.

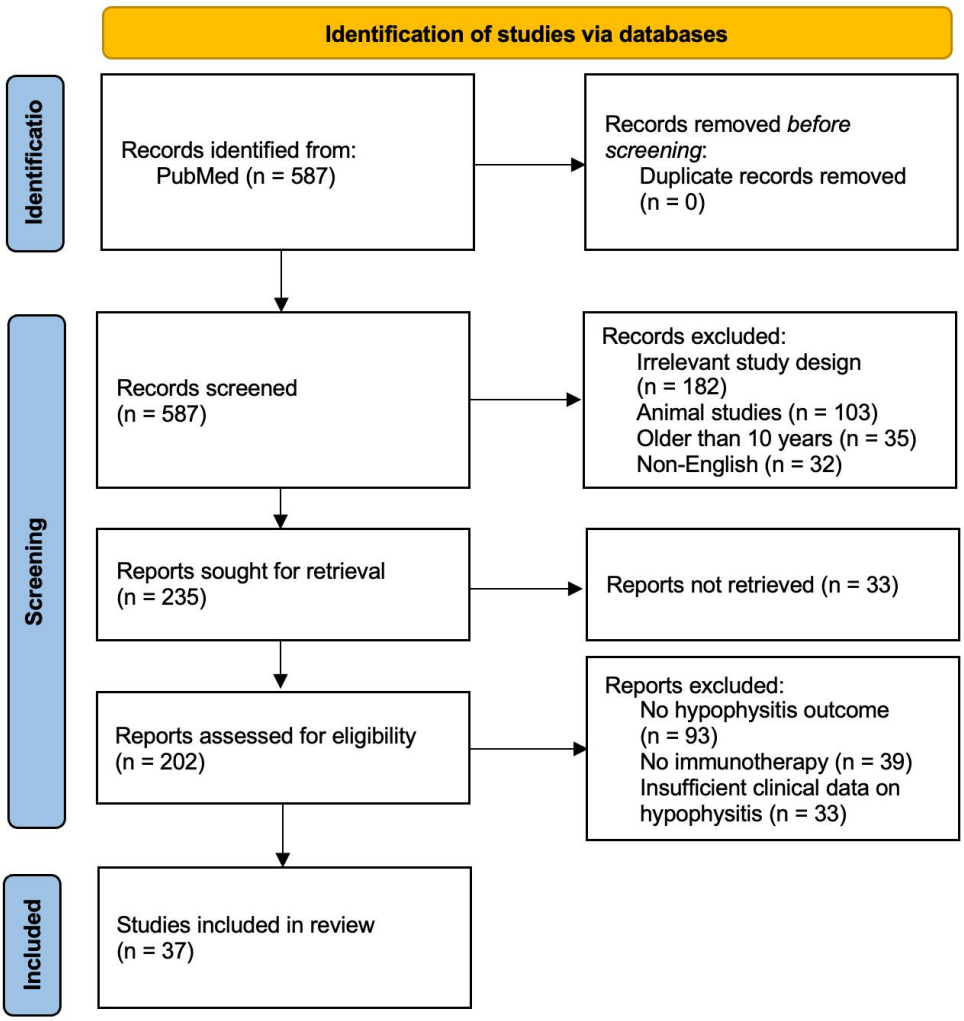

Figure 1. PRISMA flow diagram of the study selection process.

3. Epidemiology and Incidence of ICI-Induced Hypophysitis

To better illustrate differences in the reported frequency and timing of hypophysitis across treatment regimens, a comparative summary of selected studies is presented in Table 1. A total of 11 studies comprising 8,310 patients were included in the analysis. The median sample size across the included studies was 250 patients. The incidence of grade ≥3 hypophysitis varied substantially across studies, ranging from 0% (nivolumab alone) to 19.1% (combination therapy with ipilimumab plus nivolumab).

Study	Study type	Cancer	Drug	N	Hypophysitis (n)	Incidence (%)	Median time to onset and range (weeks)
(Zhang et al., 2025)	retrospective cohort study	non-small cell lung cancer (NSCLC)	pembrolizumab (anti-PD1)	380	9	2.4%	42.6 (25.1 - 62.3)
(Jessel et al., 2022)	prospective cohort study	melanoma, renal cell carcinoma (RCC), merkel cell carcinoma	anti-PD-1	212	12	6%	16.4
(Luke et al., 2024)	phase 3 clinical trials	melanoma, NSCLC, RCC	pembrolizumab (anti-PD1)	2060	11	0.5%	29.6 (0.6 - 60.3)
(Kotwal et al., 2022)	retrospective cohort study	not reported (NR)	nivolumab (anti-PD1)	250	0	0 %	NR
(Kotwal et al., 2022)	retrospective cohort study	NR	pembrolizumab (anti-PD1)	406	7	1.7 %	NR
(Faje et al., 2019)	comprehensive cohort analysis	NR	nivolumab (anti-PD1)/pembrolizumab (anti-PD1)	3522	17	0.5%	25.8 (18.4 - 44.0)
(Sul et al., 2016)	clinical trial	NSCLC	pembrolizumab (anti-PD1)	550	1	0.2%	NR
(Faje et al., 2019)	comprehensive cohort analysis	NR	ipilimumab (anti-CTLA4)	250	34	13.6%	9.3 (7.2 - 11.1)
(Hodi et al., 2016)	phase 2 trial	melanoma	ipilimumab (anti-CTLA4)	46	2	4%	NR
(Jessel et al.,	prospective	melanoma,	ipilimumab	277	53	19.1%	11.2

2022)	cohort study	RCC, merkel cell carcinoma	(anti-CTLA4) plus nivolumab (anti-PD1)				
(Tykodi et al., 2022)	phase 3b/4 trial	RCC	nivolumab (anti-PD1) plus ipilimumab (anti-CTLA4)	52	1	1.9%	18.7
(Tawbi et al., 2021)	phase 2 trial	melanoma	nivolumab (anti-PD1) plus ipilimumab (anti-CTLA4)	119	5	4.2%	NR
(Emamekhoo et al., 2022)	phase 3b/4 trial	RCC	nivolumab (anti-PD1) plus ipilimumab (anti-CTLA4)	28	1	3.6%	8.4
(Heppt et al., 2019)	retrospective, multi-center study	melanoma	ipilimumab (anti-CTLA4) in combination with a PD-1 inhibitor	64	5	7.8%	NR
(Hodi et al., 2016)	phase 2 trial	melanoma	nivolumab (anti-PD1) plus ipilimumab (anti-CTLA4)	94	2	2%	NR

Table 1. Incidence and time to onset of hypophysitis associated with ICIs across selected studies.

The lowest incidence was observed in patients treated with PD-1 inhibitors, including pembrolizumab and nivolumab, where rates ranged from 0% to 6%. In contrast, treatment with the CTLA-4 inhibitor ipilimumab was associated with reported incidence reaching a maximum of 13.6%. Combination therapy with nivolumab plus ipilimumab demonstrated intermediate to high incidence rates, ranging from 1.9% to 19.1% across clinical trials. Time to onset of hypophysitis varied across treatment regimens. For ipilimumab monotherapy, the median time to onset reported in a single study (Faje et al., 2019) ranged from 7.2 to 11.1 weeks. In patients treated with PD-1 inhibitors, later onset was observed, with reported median time to onset ranging from 16.4 to 42.6 weeks across studies. Combination therapy demonstrated intermediate timing, with reported median time to onset ranging from 8.4 to 18.7 weeks across studies. Overall, these findings indicate a clear association between the type of ICI and both the incidence and timing of hypophysitis, with CTLA-4 based therapies and combination regimens carrying a higher risk compared to PD-1 inhibitor monotherapy.

4. Patophysiology

The mechanisms responsible for ICI-induced hypophysitis are not yet fully understood. ICIs enhance the activity of CD4+ and CD8+ T lymphocytes against malignant cells. However, this may also lead to a loss of immune tolerance and the development of uncontrolled autoimmune responses. The pathophysiology of anti-CTLA-4–induced hypophysitis likely differs from that associated with anti-PD-1/anti-PD-L1 therapies. CTLA-4 is predominantly expressed on regulatory T cells and effector T cells, but it may also be expressed on other cell types, including pituitary cells, with variable expression levels observed among different individuals (Caturegli et al., 2016; Di Dalmazi et al., 2019).

ICI-induced hypophysitis most likely results, at least in part, from a type II hypersensitivity reaction, in which antibody binding leads to the formation of antigen-antibody complexes, thereby activating the classical complement cascade, phagocytes, and B lymphocytes. This process may also trigger antibody-dependent cell-mediated cytotoxicity (ADCC), ultimately leading to the destruction of pituitary cells. In addition, type IV hypersensitivity reactions involving autoreactive T cells are also believed to contribute to the pathogenesis (Chang et al., 2019; Tateno et al., 2025).

In the study by Caturegli et al., autopsy findings of the pituitary glands from six patients treated with anti-CTLA-4 therapy were analyzed. In one patient with clinically confirmed hypophysitis, autopsy examination revealed near-complete destruction of the anterior pituitary gland, attributable to extensive necrosis and fibrosis, while the posterior pituitary remained unaffected. Histopathological examination demonstrated diffuse lymphocytic infiltration, predominantly composed of CD4+ T cells and CD20+ B cells. In addition, the pituitary tissue was infiltrated by CD68-positive macrophages. IgG2 and complement factor C4d deposition were also detected on selected pituitary cells. In another patient with no clinical or radiological signs of hypophysitis, autopsy showed extravascular presence of lymphocytes scattered throughout the pituitary parenchyma, at times clustered in groups of three to five cells. These findings may indicate the involvement of both type II and type IV hypersensitivity mechanisms in the development of hypophysitis (Caturegli et al., 2016). However it should be taken into consideration that the available data are insufficient to draw definitive conclusions.

The detection of anti-pituitary antibodies in patients with ICI-induced isolated adrenocorticotropic hormone (ACTH) deficiency and ICI-induced hypophysitis, as demonstrated by Kobayashi et al., might support the contribution of humoral immunity to disease pathogenesis (Kobayashi et al., 2021).

In one study involving patients diagnosed with ICI-induced hypophysitis, two autoantibodies were identified: anti-GNAL (guanine nucleotide-binding protein G subunit alpha) and anti-ITM2B (integral membrane protein 2B). Both GNAL and ITM2B are expressed in pituitary tissue. GNAL appears to be involved in the synthesis and secretion of thyroid-stimulating hormone (TSH), whereas ITM2B may play a role in the stimulation and release of ACTH (Tahir et al., 2019) . However, the precise

significance of these autoantibodies in the pathophysiology of ICI-induced hypophysitis remains to be elucidated and requires further investigation, particularly given the small patient cohort included in the study.

Certain malignancies may demonstrate ectopic expression of Pit-1, a key transcription factor required for the differentiation of anterior pituitary cells. ICIs are thought to promote the development of autoantibodies, including anti-Pit-1 antibodies, potentially leading to immune-mediated pituitary injury (Tateno et al., 2025).

ICIs are monoclonal antibodies, and they differ with respect to their immunoglobulin subclass, which may partly explain why some agents are more frequently associated with hypophysitis than others. Each subclass possesses a distinct capacity to mediate ADCC and to activate the classical complement pathway. This potential is greatest for IgG1 antibodies, such as ipilimumab, whereas it is substantially weaker for IgG4 antibodies, including anti-PD-1 agents such as nivolumab. Moreover, IgG4 lacks the ability to efficiently activate complement (Chang et al., 2019).

There are differences in the specific pituitary cell populations affected depending on the type of ICI used. In both anti-CTLA and anti-PD-1/anti-PD-L1 induced hypophysitis, corticotrophs are the predominantly affected cell type, leading to secondary adrenal insufficiency due to ACTH deficiency. In anti-PD-1/anti-PD-L1-induced hypophysitis, this is often the only affected hormonal axis, whereas anti-CTLA-4-associated hypophysitis more commonly involves additional deficiencies, including central hypothyroidism and secondary hypogonadism, reflecting injury to thyrotrophs and gonadotrophs.

The mechanisms underlying PD-1/PD-L1 inhibitor-mediated hypophysitis remain less clearly defined and may involve a more indirect stimulation of autoimmune responses compared with CTLA-4 blockade. Posterior pituitary involvement is exceedingly rare, and diabetes insipidus remains an uncommon manifestation of ICI-induced hypophysitis (Di Dalmazi et al., 2019; Schönberger et al., 2025) .

4. Clinical Presentation

ICI-induced hypophysitis results in inflammatory infiltration and damage to pituitary cells, predominantly in the anterior lobe, disrupting the secretion of pituitary hormones and ultimately leading to hypopituitarism. Clinical manifestations arise directly from the insufficiency of the affected hormonal axis or axes, as well as from pituitary enlargement (Esteves-Ferreira & Rosinha, 2023; Langlois et al., 2022). Three principal pituitary axes may be affected: the adrenal, thyroid, and gonadal axes. Most patients present with involvement of two or three hormonal axes simultaneously (Tan et al.,

2019) . Secondary insufficiency of the adrenal, thyroid, and gonadal axes is reflected by decreased peripheral hormone levels corresponding to each axis.

Central adrenal insufficiency can be life-threatening and requires urgent treatment. Typical manifestations of chronic or evolving ACTH deficiency include fatigue, weakness, nausea, weight loss, hyponatremia, and hypotension (Barroso-Sousa et al., 2018; Di Dalmazi et al., 2019; González-Rodríguez & Rodríguez-Abreu, 2016). In more severe cases, patients may present with adrenal crisis, a life-threatening endocrine emergency characterized by profound hypotension or shock, vomiting, abdominal/flank, back or lower chest pain, fever, lethargy, confusion, coma, and electrolyte disturbances. In patients with impairment of this axis, ACTH levels are low or inappropriately normal in the presence of low or low-normal cortisol (Barroso-Sousa et al., 2018).

In hypopituitarism, reduced cortisol production leads to increased hypothalamic secretion of corticotropin-releasing hormone (CRH), which subsequently stimulates antidiuretic hormone (ADH) release. Elevated ADH promotes water retention, resulting in dilutional hyponatremia. It is important to note that hyponatremia is a frequent complication of chemotherapy and may also occur as a result of syndrome of inappropriate antidiuretic hormone secretion (SIADH) related to malignancy (De Camilli & Fischer, 2023).

In central hypothyroidism, circulating free T4 is typically low or low-normal, despite an inappropriately low or normal TSH, reflecting impaired pituitary stimulation. Symptoms of central hypothyroidism include fatigue, hair loss, mild cognitive deficits, dysthymia, neuropsychiatric symptoms, weight gain, constipation, cold intolerance and dry skin.

Similarly, in hypogonadotropic hypogonadism, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels are low or inappropriately normal, leading to sex-specific hormonal deficiencies: low testosterone in men, low estradiol in premenopausal women. In postmenopausal women, physiological gonadotropin elevation is normally expected; therefore, low or normal FSH and LH in combination with low estrogen levels may indicate pituitary dysfunction. Among the most significant symptoms of hypogonadotropic hypogonadism are: erectile dysfunction, amenorrhea or other menstrual disturbances and reduced libido (Oliveira et al., 2024).

In their study, Kurokawa et al. described patients with malignant melanoma treated with ICIs (ipilimumab or ipilimumab plus nivolumab) who were clinically diagnosed with ICI-induced hypophysitis. Magnetic resonance imaging (MRI) of the pituitary in these patients revealed enlargement and hypoenhancing lesions in the anterior lobe (Kurokawa et al., 2020) . Symptoms resulting from mass effect, such as visual deficits due to impingement of the optic chiasm, are rare, reflecting the generally mild degree of pituitary enlargement. Another symptom resulting from pituitary enlargement is headache.

Rare manifestations of ICI-induced hypophysitis include central diabetes insipidus, hypoprolactinemia, and growth hormone (GH) deficiency, which occur much more frequently in primary hypophysitis. The prevalence of GH deficiency in ICI-induced hypophysitis remains unclear. Accurate confirmation of adult GH deficiency requires dynamic endocrine testing, including procedures such as the insulin tolerance test, glucagon stimulation test, or arginine-based stimulation protocols. In routine oncology practice, these tests are performed infrequently because they are time-consuming, resource-intensive, and may be unsuitable for frail patients or those with significant comorbidities.

Diabetes insipidus results from a deficiency of ADH, secreted by the posterior pituitary, and is characterized by polyuria, low urine specific gravity, hypernatremia, and polydipsia (Chang et al., 2019; Di Dalmazi et al., 2019; Langlois et al., 2022; Tateno et al., 2025). Some symptoms are highly nonspecific and can be difficult to distinguish from manifestations related to the underlying malignancy or other treatments.

5. Diagnostic

Nguyen H et al. (2021) propose the following diagnostic criteria for immune-related hypophysitis:

Criteria 1 include evidence of central adrenal insufficiency, defined as low serum cortisol (<5 µg/dL) with low or inappropriately normal ACTH, or an abnormal cosyntropin stimulation test (peak serum cortisol <18 µg/dL either before or after administration of low-dose (1 µg) or high-dose (250 µg) cosyntropin), in the absence of exogenous glucocorticoid therapy. Alternatively, central hypothyroidism may be used as a diagnostic criterion, defined as a decreased free T4 level with a low or inappropriately normal TSH, without thyroid hormone replacement exceeding 1.6 µg/kg/day of levothyroxine or an equivalent dose. These hormonal abnormalities must be accompanied by MRI findings consistent with immune-related hypophysitis.

Criteria 2 consists of the simultaneous presence of both central adrenal insufficiency and central hypothyroidism, together with non-specific clinical symptoms such as headache or fatigue, in cases where MRI findings are absent or not available.

MRI is considered suggestive of immune-related hypophysitis when at least two of the following features are present: increased pituitary gland height (>2 mm change from baseline), suprasellar bulging, pituitary stalk thickening, heterogeneous contrast enhancement, or parasellar extension (Nguyen et al., 2021).

5.1 MRI

MRI is the imaging modality of choice for the evaluation of pituitary gland pathology due to its superior soft tissue resolution and ability to accurately assess both gland size and surrounding structures.

MRI abnormalities are most commonly observed in patients receiving ipilimumab-based immunotherapy. The typical finding is a mild to moderate, diffuse, and symmetric enlargement of the pituitary gland (Chamorro-Pareja et al., 2024; Chang et al., 2019). In a multicenter retrospective study, enlargement of the pituitary gland was observed in 36% of cases (Amereller et al., 2022). Following contrast administration, homogeneous enhancement of the gland is often seen, and a "dural tail" sign may be present, reflecting enhancement of the adjacent dura mater in the post-contrast phase (Castillero et al., 2019) . However, a normal-appearing pituitary gland does not exclude hypopituitarism, making clinical evaluation essential regardless of imaging findings (Chang et al., 2019) . Radiological changes may precede the onset of clinical symptoms in up to 50% of patients (Joshi et al., 2016).

Pituitary enlargement is usually transient and resolves spontaneously in the majority of cases. Progression to significant mass effect, including compression of the optic chiasm due to gland or stalk enlargement, is rare (Chang et al., 2019) . The initial enlargement may be followed by subsequent gland atrophy during the course of the disease (Castillero et al., 2019).

MRI findings are not uniform across all hormonal deficits. In isolated ACTH deficiency, imaging abnormalities are less frequently observed, and features related to mass effect are typically absent (Fukuda, 2023).

Follow-up imaging is generally recommended after approximately three months. Complete or near-complete resolution of previously observed changes supports the diagnosis of hypophysitis, whereas persistent lesions raise suspicion for metastatic involvement (Johnson et al., 2023).

Pituitary metastases most commonly involve the posterior lobe (approximately 69 - 79% of cases) and frequently present with diabetes insipidus due to ADH deficiency, a condition that is exceedingly rare in hypopituitarism secondary to immunotherapy-related hypophysitis (Castillero et al., 2019; González-Rodríguez & Rodríguez-Abreu, 2016).

6. Clinical Approach to ICI -Induced Hypopituitarism

Patients with hypopituitarism secondary to ICI therapy often present with non-specific symptoms, which may delay diagnosis. For this reason, clinicians should maintain a high

index of suspicion in patients undergoing immunotherapy. Symptoms typically do not occur immediately after treatment initiation but develop after several to several dozen weeks (Wright et al., 2021). Patients presenting with symptoms suggestive of pituitary enlargement, such as diplopia or severe headache should undergo neuroimaging, preferably MRI with a dedicated pituitary protocol.

Barroso-Sousa et al. recommend targeted endocrine evaluation in patients who develop new clinical features suggestive of pituitary or adrenal dysfunction, particularly: (1) newly emerging moderate fatigue or headache; (2) recent onset of nausea, vomiting, or diarrhea; (3) lightheadedness, orthostatic symptoms, hypotension, or hyponatremia; and (4) any signs of hemodynamic or cardiovascular instability (Barroso-Sousa et al., 2018) . The initial endocrine evaluation should include assessment of all anterior pituitary axes, namely TSH, LH, FSH, ACTH, prolactin (PRL) and GH. This should be complemented by evaluation of target organ function, including free triiodothyronine (fT3), free thyroxine (fT4), cortisol, testosterone in men, estradiol in women and insulin-like growth factor 1 (IGF-1) (Fukuda, 2023) .

For routine monitoring, a minimal laboratory panel is recommended every 4-6 weeks, ideally prior to each immunotherapy cycle. This should include TSH, fT4, cortisol, glucose, sodium, potassium, and calcium. In patients considered at higher risk of developing hypopituitarism, an extended screening panel is advised. This should additionally comprise ACTH, LH, FSH, estradiol or testosterone, PRL, and glycated hemoglobin (HbA1c) (Husebye et al., 2022) .

It should be kept in mind that opioids, frequently used in cancer patients for pain control, may suppress the hypothalamic-pituitary-adrenal axis and should be considered in the differential diagnosis. When feasible, opioids should be withheld for at least 8 hours before hormonal testing (Barroso-Sousa et al., 2018) . Endocrinology consultation is recommended whenever hypophysitis is suspected, in order to support diagnostic evaluation and appropriate hormonal management.

6.1. Adrenal Axis Dysfunction

As previously mentioned central adrenal insufficiency is defined by low or inappropriately normal ACTH levels in the setting of low or low-normal serum cortisol. Among pituitary hormone deficits, adrenal axis dysfunction is the most clinically significant, as it accounts for the highest mortality risk (Chang et al., 2019) . ACTH deficiency persists in 86% - 100% of cases, making long-term glucocorticoid replacement therapy necessary in most patients (Del Rivero et al., 2020).

When interpreting ACTH and cortisol levels, physiological diurnal variation must be considered, as both hormones peak in the early morning (around 8 a.m.), which represents the most informative time for sampling. A detailed medication history is essential, particularly regarding current or recent oral or topical glucocorticoid use, as this may significantly alter results (Chang et al., 2019; Fukuda, 2023).

Undetectable cortisol levels in the presence of non-elevated ACTH are strongly suggestive of secondary adrenal insufficiency. When cortisol levels are low but still measurable (approximately 3–15 µg/dL), dynamic testing is recommended (Di Dalmazi et al., 2019).

The standard diagnostic tool is the ACTH stimulation test. Following measurement of baseline cortisol, 250 µg of intravenous tetracosactide is administered, with cortisol levels assessed at 30 and/or 60 minutes. A peak cortisol response <18 µg/dL is considered diagnostic of adrenal insufficiency (Chang et al., 2019) . In central adrenal insufficiency due to ACTH deficiency, adrenal atrophy develops gradually; therefore, early in the disease course, the adrenal glands may still respond normally to stimulation, potentially yielding false-negative results. In general, adrenal impairment develops over approximately six weeks, meaning that testing performed shortly after disease onset may remain normal (Fukuda, 2023).

In patients receiving chronic glucocorticoid therapy, the cortisol response to ACTH stimulation may be blunted.

Additional dynamic tests include the CRH stimulation test (100 µg CRH) and the insulin tolerance test (ITT), both of which consider a peak cortisol <18 µg/dL as an inadequate response. The ITT is regarded as the gold standard for evaluating the hypothalamic-pituitary–adrenal axis; however, it is contraindicated in patients with seizures, elderly or frail individuals, and is no longer widely recommended due to the risk of severe hypoglycemia (Fukuda, 2023).

Management strategies remain debated. A study by Theiler-Schwetz et al. (2025) demonstrated that high-dose glucocorticoid therapy (prednisolone 1 mg/kg/day for two weeks with tapering and subsequent hydrocortisone maintenance) did not improve adrenal recovery compared with hydrocortisone 20 mg/day alone, while being associated with a higher rate of metabolic adverse effects, particularly impaired glucose control. Given the lack of demonstrated benefit outside emergency settings and the increased risk of infections, hyperglycemia, and other steroid-related complications, routine use of high-dose glucocorticoids is not recommended in patients without adrenal crisis or significant mass effect (Barroso-Sousa et al., 2018; Theiler-Schwetz et al., 2025).

According to European Society for Medical Oncology (ESMO) guidelines, immunotherapy interruption and initiation of prednisone at 1 mg/kg/day (or equivalent glucocorticoids) are recommended only in cases of symptomatic pituitary enlargement (e.g., headache or visual impairment) or adrenal crisis. Once the patient is stabilized, immunotherapy may be resumed (Haanen et al., 2022).

In most remaining patients, physiologic replacement with hydrocortisone is preferred. Long-term management often requires ongoing glucocorticoid replacement therapy, typically hydrocortisone 15–20 mg per day in divided doses, although some patients may require dose adjustment based on symptoms and clinical response. Patients should also be educated regarding dose escalation during intercurrent illness, during which the maintenance dose should be increased two- to three-fold (Barroso-Sousa et al., 2018; Schönberger et al., 2025).

6.2. Thyroid Axis Dysfunction

Thyroid axis dysfunction is one of the most frequently observed endocrine abnormalities in patients treated with ICIs (Chang et al., 2019; Fukuda, 2023).

It is recommended to assess TSH and fT4 levels prior to initiation of immunotherapy and subsequently monitor them regularly, ideally at each treatment visit for at least the first five cycles (Chang et al., 2019).

In cases of confirmed central hypothyroidism, levothyroxine replacement therapy is required. An initial dose of approximately 0.8 µg/kg/day is generally recommended. Importantly, if concomitant adrenal insufficiency is present or suspected, glucocorticoid replacement should be initiated prior to thyroid hormone therapy, as levothyroxine administration in untreated adrenal insufficiency may exacerbate symptoms and precipitate adrenal crisis (Barroso-Sousa et al., 2018).

The therapeutic goal is to maintain fT4 levels within the mid- to upper-normal range. As immune-related thyroid dysfunction may be transient and potentially reversible, a conservative initial dosing strategy is preferred. Thyroid function should be reassessed approximately four weeks after initiation of therapy, with dose titration as needed. In some patients, higher replacement doses of up to 1.6–1.8 µg/kg/day may be required.

In elderly patients and those with coronary artery disease, lower starting doses (12.5–25 µg/day) are recommended, with close monitoring of fT4 levels.

Dose adjustments should primarily be guided by fT4 concentrations, although serial TSH measurements may also be useful in detecting potential recovery of hypothalamic–pituitary function over time (Chang et al., 2019).

This condition is often transient, and in most cases thyroid axis function returns spontaneously without the need for long-term treatment (Paschou et al., 2021) . TSH deficiency remains in approximately 13% - 36% of cases (Del Rivero et al., 2020).

6.3. Gonadal Axis Dysfunction

Gonadal axis involvement presents as hypogonadotropic hypogonadism. In men, evaluation should include measurement of total testosterone together with LH and FSH. Because testosterone secretion

follows a circadian rhythm, serum testosterone should preferably be measured in the early morning (approximately 8–10 a.m.), when concentrations are highest (Wright et al., 2021).

Interpretation of gonadal hormones should always take clinical context into account, as chronic systemic illness, malnutrition, or severe stress may suppress gonadotropin secretion independently of structural pituitary disease.

Sex hormone replacement therapy should be considered only in symptomatic patients, after confirmation of persistent deficiency and careful evaluation of risks and contraindications.

In men, testosterone therapy should be avoided or postponed in patients actively pursuing fertility in the near term, as exogenous testosterone may suppress spermatogenesis. Additional contraindications include known or suspected prostate or breast cancer, unexplained prostate abnormalities requiring urological assessment, elevated hematocrit, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, recent myocardial infarction or stroke, and known thrombophilia.

In women, estrogen replacement should be avoided in those with a history of breast cancer, endometrial cancer, or other estrogen-dependent neoplasms, previous venous or arterial thromboembolic disease, thrombophilia, unexplained vaginal bleeding, significant liver dysfunction, or pregnancy.

Particular caution is warranted in women with diabetes mellitus, asthma, gallbladder disease, hypertriglyceridemia, migraine with aura, systemic lupus erythematosus, epilepsy, increased cardiovascular risk, or elevated risk of breast cancer. The decision to initiate gonadal hormone replacement should therefore be individualized, balancing symptom burden, age, fertility plans, comorbidities, and long-term risks (Chang et al., 2019).

This dysfunction is often transient, and in many cases gonadotropic axis function recovers spontaneously over time (de Filette et al., 2019). Persistent deficiency is observed in 13% - 53% of patients (Del Rivero et al., 2020). Clinicians should actively address the possibility of hypogonadism with patients, as these symptoms are often underreported and may not be spontaneously disclosed (Sznol et al., 2017).

Recovery of the pituitary-gonadal axis after discontinuation of sex hormone supplementation is indicated by testosterone, FSH, LH values within the normal male reference range. In premenopausal women, recovery was evidenced by normalization of basal gonadal hormone levels together with resumption of the menstrual cycle. In contrast, in postmenopausal women, physiological recovery was reflected by low estradiol concentrations accompanied by appropriately elevated gonadotropins (FSH $\geq$ 40 IU/L) (Xiao et al., 2025).

6.4. Growth Hormone Axis Dysfunction

The involvement of the GH axis in ICI-associated hypopituitarism remains uncertain, and the frequency of clinically relevant deficiency has not been clearly established. Circulating IGF-1 concentrations may be decreased, although normal IGF-1 values do not reliably exclude impaired GH reserve (Byun et al., 2017).

Compared with adrenal or thyroid insufficiency, disturbances of the GH axis are usually of lower immediate clinical priority in adults. Furthermore, recombinant GH therapy is generally not considered in patients with active cancer because of theoretical concerns regarding tumor growth or disease recurrence (González-Rodríguez & Rodríguez-Abreu, 2016).

Consequently, GH deficiency in the setting of immune-related hypophysitis has received limited attention in the literature, and neither routine screening nor standard replacement therapy is currently recommended.

6.5. Prolactin Axis Dysfunction

Reduced PRL levels may occur in immune-related hypopituitarism; however, clinically significant PRL deficiency appears to be an uncommon manifestation (Byun et al., 2017). Hipoprolactinemia was more frequently observed in ICI-induced hypophysitis compared with primary hypophysitis (15% vs. 3 %), suggesting a more extensive degree of pituitary dysfunction in the immune-related form of the disease (Amereller et al., 2022).

7. Limitations

Several limitations of this review should be acknowledged. First, the literature search was conducted using a single database (PubMed), which may have resulted in omission of relevant studies indexed exclusively in other sources.

Second, study selection and data extraction were performed by a single reviewer, which may have increased the risk of selection bias or unintentional errors in data interpretation. In addition, a formal risk-of-bias assessment was not undertaken because of the narrative design of the review.

The available evidence itself is also subject to limitations. Several included cohort studies had relatively small sample sizes, which may reduce the generalizability of their findings. Considerable heterogeneity was present across studies with regard to cancer type, ICI regimen, diagnostic criteria for hypophysitis, follow-up duration, and monitoring strategies.

Finally, the comparative epidemiological table did not include studies focused on anti-PD-L1 monotherapy, which limits conclusions regarding this treatment subgroup. Therefore, comparisons between checkpoint inhibitor classes should be interpreted with caution.

8. Conclusions

ICI-induced hypophysitis is an increasingly recognized endocrine irAEs event that reflects the expanding use of immunotherapy in oncology. Although relatively uncommon, its clinical relevance is substantial, as hypophysitis may lead to multiple pituitary hormone deficiencies, with the most clinically dangerous consequence being secondary adrenal insufficiency, which can progress to life-threatening adrenal crisis. The present narrative review confirms that the risk, timing, and severity of hypophysitis are strongly dependent on the type of ICI, with CTLA-4-based regimens and combination therapies demonstrating higher incidence rates and earlier onset compared with PD-1 inhibitors. The pathophysiology of ICI-induced hypophysitis remains incompletely understood. However, both type II and type IV hypersensitivity reactions are thought to contribute to its development.

A key clinical challenge remains the nonspecific and often subtle presentation of hypophysitis, which may delay diagnosis. This underlines the importance of maintaining a high index of suspicion in all patients receiving ICIs, supported by regular hormonal monitoring and timely imaging when indicated.

Management is primarily based on prompt hormone replacement rather than aggressive immunosuppression in most cases. Current evidence does not support routine use of high-dose glucocorticoids outside of adrenal crisis or cases with significant mass effect, as they do not improve endocrine recovery and are associated with increased metabolic and infectious complications. Instead, physiologic hormone replacement remains the cornerstone of therapy, with individualized supplementation of thyroid and sex hormones when clinically indicated.

In summary, ICI-induced hypophysitis represents a clinically important but still incompletely understood toxicity of cancer immunotherapy. Further research is required to elucidate its underlying pathophysiology, identify potential risk factors, and clarify mechanisms of disease development. Future prospective, multicenter studies with standardized diagnostic criteria and long-term endocrine follow-up are also needed to better define its natural history, optimize monitoring strategies, and refine management protocols.

Disclossure:

Author Contributions

Conceptualisation: JG, JJ

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Visualisation: GS, KM, KSZ, MK, PK

Project administration: JG, JJ,

All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable

Informed Consent Statement

Not applicable

Data Availability Statement

This study is based on previously published data. No new data were created or analyzed.

Conflicts of Interest

The authors deny conflict of interest.

In preparing this work, the authors used ChatGPT to enhance linguistic clarity and improve readability. After using this tool, the authors reviewed and edited the text and accepted full responsibility for the content of the publication.

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