HYPOPHYSITIS

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ABSTRACT

Hypophysitis is an inflammation of the pituitary gland and is a rare cause of hypopituitarism. It can be primary (idiopathic) or secondary to sella and parasellar lesions, systemic diseases, or drugs (mainly immune checkpoint inhibitors). Primary hypophysitis has five histologic variants: lymphocytic, granulomatous, xanthomatous, IgG4-related, and necrotizing. Lymphocytic hypophysitis is the most common form; it is likely an autoimmune disease and is more frequently observed in females during pregnancy or postpartum. Granulomatous hypophysitis is the second most common variant and possible secondary causes of granulomatous infiltration of the pituitary should be excluded before concluding that a case of granulomatous hypophysitis is idiopathic. Xanthomatous, necrotizing, and IgG4-related hypophysitis are very rare and the latter is often the manifestation of a systemic disease with multi-organ involvement (IgG4-related disease). Immune checkpoint inhibitors are monoclonal antibodies increasingly used for the treatment of solid and hematological malignancies. They cause a T-lymphocyte activation and proliferation that lead to the anti-tumor response, and may cause autoimmune manifestations known as part of what is called “immune-related adverse events”. A significant number of patients treated with immune checkpoint inhibitors develop immune-related hypophysitis and require prompt diagnosis and treatment. Regardless of the etiology, patients with hypophysitis present with various signs and symptoms caused by the pituitary inflammation that can lead to hypopituitarism and compression of sella and parasellar structures. Contrary to other causes of hypopituitarism, adrenocorticotropic hormone and thyroid-stimulating hormone deficiencies are very frequent in the early stages of hypophysitis and must be identified immediately. The diagnosis of hypophysitis is based on clinical, laboratory, and radiological data; while pituitary biopsy is the gold standard test for diagnosing primary hypophysitis, it should be reserved only for selected cases. Magnetic resonance imaging is the technique of choice for suspected hypophysitis, and the main differential diagnoses are pituitary adenomas in adults, germinomas, and Langerhans cell histiocytosis in adolescents, and metastases in those receiving immune checkpoint inhibitors. The mainstay of treatment of patients with hypophysitis is pituitary hormone replacement. Those with severe signs and symptoms of sella compression should be treated with high-dose glucocorticoids, which usually cause an excellent initial response, although relapse of the pituitary inflammation is common. Pituitary surgery should be considered in patients who do not respond to glucocorticoids and have progressive and debilitating symptoms. Pituitary fibrosis and atrophy often develop in the late stage of the disease, with persistent hypopituitarism.

INTRODUCTION

Hypophysitis is a generic term that includes a variety of conditions that cause inflammation of the pituitary gland. It is an infiltrative cause of hypopituitarism and

can cause symptoms related to sella compression and pituitary hormone deficiencies.

Hypophysitis can be classified according to the anatomic location of pituitary involvement (adenohypophysitis, infundibulo-neurohypophysitis, or panhypophysitis) and the cause (primary or secondary forms) (Table 1) (1-4). The primary forms are characterized by an idiopathic inflammatory process confined to the pituitary gland, while the secondary forms are triggered by a definite etiology (drugs and intracranial or systemic diseases). Five histologic variants of primary hypophysitis have been described: lymphocytic, granulomatous, xanthomatous, IgG4-related, and necrotizing (Table 1). Lymphocytic hypophysitis is the most common form of hypophysitis and occurs most commonly in women during late pregnancy and the postpartum period. However, thanks to the increasing use over the last two decades of monoclonal antibodies inhibiting immune checkpoints for the treatment of several solid and hematological malignancies, new immune-related adverse events have emerged, with hypophysitis being a relatively common occurrence.

Table 1. Classification of Hypophysitis
CAUSE: PRIMARY AND SECONDARY HYPOPHYSITIS
Primary hypophysitis:
Isolated
Associated with autoimmune diseases:
Polyglandular autoimmune syndromes
Autoimmune thyroiditis (Hashimoto thyroiditis)
Autoimmune adrenalitis
Type 1 diabetes mellitus
Lymphocytic parathyroiditis
Idiopathic inflammatory myopathy
Systemic lupus erythematosus
Sjogren's syndrome
Rheumatoid arthritis
Primary biliary cirrhosis
Atrophic gastritis
Optic neuritis
Myocarditis
Temporal arteritis
Bechet's disease
Retroperitoneal fibrosis
Erythema nodosum
Idiopathic thrombocytopenic purpura
Dacryoadenitis
Autoimmune thrombocytopenia
Autoimmune encephalitis
Secondary hypophysitis:
Drugs:
Immune checkpoint inhibitors
Interferon-α
Ribavirin

Ustekinumab *Sella and parasellar diseases*:* Germinoma Rathke's cleft cyst Craniopharyngioma Pituitary adenoma Primary pituitary lymphoma *Systemic diseases*: IgG4-related disease** Sarcoidosis Granulomatosis with polyangiitis (Wegener's granulomatosis) Langerhans cell histiocytosis Erdheim-Chester's disease Rosai-Dorfman disease Inflammatory pseudotumor Tolosa-Hunt syndrome Takayasu's arteritis Cogan's syndrome Crohn's disease *Thymoma and other malignancies (anti-Pit-1 antibody syndrome)* *Infections:* Bacteria (*Mycobacterium tuberculosis*; *Treponema pallidum*; *Tropheryma whipplei; Borrelia*; *Brucella*) Viruses (*Cytomegalovirus*; *Herpes simplex*; *Varicella-zoster virus; Influenza viruses*; *Coronavirus; Enterovirus; Coxsackie; Tick-Borne encephalitis virus; Hantavirus*) Mycoses (*Aspergillus*; *Nocardia*; *Candida albicans*; *Pneumocystis jirovecii*) Parasites (*Toxoplasma gondii*)
ANATOMIC LOCATION OF PITUITARY INVOLVEMENT
Adenohypophysitis: the inflammation involves the anterior pituitary. It accounts for ~65% of cases of primary hypophysitis Infundibulo-neurohypophysitis: the inflammation involves the posterior pituitary and the stalk. It accounts for ~10% of cases of primary hypophysitis Panhypophysitis: the inflammation involves the entire gland. It accounts for ~25% of cases of primary hypophysitis
HISTOPATHOLOGY FORMS OF PRIMARY HYPOPHYSITIS
Lymphocytic hypophysitis (68%) Granulomatous hypophysitis (19%) IgG4-related (plasmocytic) hypophysitis (8%)** Xanthomatous hypophysitis (4%) Necrotizing hypophysitis (<1%) Mixed forms (lymphogranulomatous; xanthogranulomatous)

* The infiltrate focuses around the lesion rather than diffuse in the entire gland. This secondary form of pituitary infiltration is generally a histopathological finding and patient's signs and symptoms are otherwise related to the primary sella and parasellar mass.
** IgG4-related hypophysitis can be isolated, but is often a manifestation of systemic disease with the involvement of multiple organs.

PRIMARY HYPOPHYSITIS

Primary hypophysitis is a rare disease, with just over 1300 published cases so far (5). The incidence is estimated to be ~1 in 9 million/year (4,6), and hypophysitis accounts for ~0.4% of pituitary surgery cases (2). Five histologic variants of primary hypophysitis have been described, and there are mixed forms as well. Table 2 summarizes the epidemiological and histopathological features of these variants (2,5,7-9). Primary hypophysitis, apart from the rare IgG4-related and necrotizing variants, occurs more frequently in young females. The clinical manifestations of all forms of primary hypophysitis are similar and are linked to the degree of pituitary involvement and the associated hormonal deficiencies.

Table 2. Characteristics of the Various Forms of Primary Hypophysitis

	Lymphocytic	**Granulomatous**	**IgG4-related**	**Xanthomatous**	**Necrotizing**
Prevalence	The most common subtype (68%*).	The second most common subtype (19%*).	Rare (8%*). Higher prevalence in Japan and Korea.	Very rare (4%*).	Extremely rare (<1%).
Gender predominance	Female, ~3:1	Female, ~3:1	Male, ~2:1	Female, ~3:1	Male, ~2:1
Association with pregnancy	Yes. ~70% of patients present during pregnancy or postpartum.	No	No	No	No
Mean age at presentation	4th decade (women). 5th decade (men).	5th decade	7th decade (men). 2nd-3rd decade (women).	4th decade	Six cases reported (aged 12, 20, 33, 39, 40, and 52).
Histopathology	Diffuse lymphocyte infiltration (primarily T cells) of the pituitary gland. Lymphoid follicles can be observed and	Large numbers of multinucleated giant cells and histiocytes with granuloma formation.	Extensive gland infiltration by plasma cells with a high degree of IgG4 positivity. Storiform fibrosis is observed**.	Foamy histiocytes (lipid-rich macrophages) without the presence of granulomas. Plasma cells and small round mature lymphocytes are	Diffuse non-hemorrhagic necrosis with surrounding lymphocytes, plasma cells and eosinophils.

	occasional plasma cells, eosinophils, and fibroblasts may also be present. Pituitary fibrosis and atrophy may occur in later stages of the disease.		Pituitary fibrosis and atrophy occur in later stages of the disease, if not treated.	also observed. Pituitary fibrosis may be seen in later stages of the disease.	

* Prevalence derived by published cases after excluding those where the pathologic variant is unknown. Forty-one cases with mixed histology findings have been published.
** Storiform fibrosis: dense, wire-like strands of fibrotic collagen deposition radiating outward from a central point.

Lymphocytic Hypophysitis

Lymphocytic hypophysitis is the most common histologic variant of primary hypophysitis (4,5,8). It shows a striking temporal association with pregnancy, with ~70% of cases in women presenting during pregnancy or postpartum. Most patients present in the last month of pregnancy or in the first 2 months after delivery (4). Lymphocytic hypophysitis is believed to have an autoimmune etiology. This is supported by the lymphocytic infiltration of the pituitary, the link with pregnancy, the frequent association with other autoimmune diseases (Table 1), the frequent finding of pituitary antibodies in these patients (see below), the association with particular human leukocyte antigen alleles (1), the improvement of symptoms in response to immunosuppressive drugs, and animal models of primary hypophysitis (10).

Granulomatous Hypophysitis

Granulomatous hypophysitis is the second most common subtype of primary hypophysitis and its etiology is unknown. Before concluding that a case of granulomatous hypophysitis is "primary" (i.e., idiopathic), known possible causes of granulomatous infiltration of the pituitary should be excluded. Possible secondary causes of granulomatous hypophysitis include tuberculosis, sarcoidosis, syphilis, Langerhans' histiocytosis, granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis), and Rathke's cleft cyst rupture (see "Hypophysitis secondary to sella and parasellar disease" and "Hypophysitis secondary to systemic disease" below). (11).

IgG4-related Hypophysitis

IgG4-related hypophysitis can be isolated (primary hypophysitis) but is often a manifestation of systemic disease with involvement of multiple organs (14,15). Some authors include IgG4-related hypophysitis among the histologic variants of primary hypophysitis, while others report this among the secondary forms of hypophysitis. Considering that the diagnosis and management does not change according to the classification used, we will discuss the features of IgG4-related hypophysitis in this section.

The etiology of this disease is poorly understood and may involve autoimmunity and/or an abnormal tolerance to unspecified allergens and infectious agents (16,17). IgG4-related disease is diagnosed more frequently in older males and is characterized by a dense lymphoplasmacytic infiltration with a predominance of IgG4-positive plasma cells in the affected tissue and storiform fibrosis in the more advanced stages of the disease (Table 2). One or (more frequently) multiple organs can be affected

including lymph nodes, pancreas, liver, salivary and lacrimal glands, retroperitoneum, aorta, pericardium, thyroid, lungs, kidneys, skin, stomach, prostate, ovaries, and the pituitary gland (17-19). Overall, the prevalence of pituitary involvement in IgG4-related disease is believed to be low (2-8%) (20). Nonetheless, a recent cohort study from Japan screened 27 patients with IgG4-related pancreatitis via pituitary MRI and found 1 case of hypophysitis with hypopituitarism and 4 cases of empty sella (21). Patients with pituitary abnormalities were more likely to have multi-organ disease. If confirmed by large-scale studies, these findings would advocate for screening for hypophysitis especially in patients with multiple IgG4-related organ involvement.

IgG4-related disease is considered a rare cause of hypophysitis, although a Japanese group reported a strikingly high prevalence of IgG4-related hypophysitis in 170 consecutive patients with hypopituitarism/central diabetes insipidus and a clinical diagnosis of hypophysitis (4% and 30% respectively) (22). Moreover, Bernreuther *et al.* reviewed retrospectively 29 cases of biopsy-proven primary hypophysitis previously diagnosed as "lymphocytic" or "not otherwise specified, non-granulomatous" and found that 41.4% of cases fulfilled the criteria for IgG4-related hypophysitis, suggesting that this entity might be more frequent than previously thought (23). Two recent reviews of the literature found that the epidemiology of IgG4-related hypophysitis may differ according to sex: affected men were older, more likely to have systemic disease and higher IgG4 serum levels; women were younger and often presenting with isolated pituitary disease, lower IgG4 serum levels, and a concomitant diagnosis of other autoimmune diseases (24,25).

The diagnosis of IgG4-related hypophysitis is confirmed by characteristic histopathologic findings at pituitary biopsy. However, pituitary biopsy is an invasive procedure and other criteria can be used to establish the diagnosis (Table 3) (26).

Table 3. Diagnostic Criteria for IgG4-related Hypophysitis

Criteria		**Established diagnosis**
Criterion 1	PITUITARY HISTOPATHOLOGY: Mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with >10 IgG4-positive cells/high-power field. *	**CRITERION 1** or
Criterion 2	PITUITARY MRI: Sella mass or thickened pituitary stalk.	
Criterion 3	OTHER INVOLVEMENT: Biopsy-proven involvement in other organs.	**CRITERIA 2 + 3**
Criterion 4	SEROLOGY: Serum IgG4 level >140 mg/dL (1.4 g/L).	
Criterion 5	RESPONSE TO TREATMENT: Shrinkage of the pituitary mass and symptom improvement with corticosteroids.	or **CRITERIA 2 + 4 + 5**

* Low level of infiltration may be seen if the patient is receiving treatment with glucocorticoids (27)

It should be considered that patients with IgG4-related hypophysitis have multi-organ involvement in 60-90% of cases. Therefore, they should receive an extensive evaluation for establishing the extent of the disease after the initial diagnosis. The diagnostic work-up should include physical examination, laboratory evaluation, and whole-body imaging (19).

Xanthomatous Hypophysitis

The pituitary shows cystic-like areas of liquefaction infiltrated by lipid-rich macrophages. It has been suggested that many cases of xanthomatous hypophysitis may represent an inflammatory response to components of a ruptured Rathke's cleft cyst (see

"Hypophysitis secondary to sella and parasellar disease" below) (12,13).

Necrotizing Hypophysitis

Necrotizing hypophysitis has been reported in six patients (of which only five histology-proven) (28-30). Five patients presented with diabetes insipidus and some degree of anterior pituitary dysfunction was described in all reported cases. Frontal headache at presentation was reported in three patients (28,29). One patient presented with photophobia (29). Five patients were treated surgically and all but one had persistent postoperative panhypopituitarism and central diabetes insipidus (28-31).

Clinical Presentation of Primary Hypophysitis

The signs and symptoms at diagnosis, as well as the pituitary hormone abnormalities depend on the degree of pituitary involvement (Table 4) (4,5,8).

Primary hypophysitis more frequently involves the anterior pituitary and patients typically present with severe headaches, visual disturbances due to chiasmal compression, and symptoms of adrenal insufficiency. Contrary to other causes of hypopituitarism, impaired adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH) secretion is very frequent in the early stages of primary hypophysitis, putting these patients at increased risk of life-threatening adrenal insufficiency. A large case series from Germany has highlighted that secretion of gonadotropins is also impaired very frequently in these patients (32). Growth hormone (GH) deficiency and hyperprolactinemia can also occur.

Less frequently, the inflammation can involve primarily the posterior pituitary and the stalk. Patients with infundibulo-neurohypophysitis typically present with diabetes insipidus and other pituitary hormone deficiencies are less common. As expected, signs of both anterior and posterior pituitary involvement coexist in panhypophysitis (that is, inflammation of the entire gland).

Table 4. Clinical Presentation and Prevalence of Pituitary Hormone Abnormalities at Diagnosis in Patients with Primary Hypophysitis According to the Degree of Pituitary Involvement

SIGNS AND SYMPTOMS AT DIAGNOSIS			
Adenohypophysitis (~65% of cases)	**Infundibulo-neurohypophysitis (~10% of cases)**	**Panhypophysitis (~25% of cases)**	**All forms ***
Headache: 53% Visual disturbances: 43% Adrenal insufficiency: 42% Hyperprolactinemia: 23% Hypothyroidism: 18% Hypogonadism: 12% Lactation failure: 11% Polydipsia/polyuria: 1%	• Polydipsia/polyuria: 98% • Headache: 13% • Adrenal insufficiency: 8% • Hyperprolactinemia: 5% • Hypogonadism: 3% • Visual disturbances: 3% • Hypothyroidism: 0% • Lactation failure: 0%	• Polydipsia/polyuria: 83% • Headache: 41% • Adrenal insufficiency: 19% • Visual disturbances: 18% • Hypothyroidism: 17% • Hyperprolactinemia: 17% • Hypogonadism: 14% • Lactation failure: 5%	• Headache: 48% • Adrenal insufficiency: 38% • Polydipsia/polyuria: 34% • Visual disturbances: 32% • Hypogonadism: 21% • Hyperprolactinemia: 20% • Hypothyroidism: 16% • Lactation failure: 8%

PITUITARY HORMONE ABNORMALITIES AT DIAGNOSIS			
Adenohypophysitis (~65% of cases)	**Infundibulo-neurohypophysitis (~10% of cases)**	**Panhypophysitis (~25% of cases)**	**All forms**
• ACTH deficiency: 56% • TSH deficiency: 44% • FSH/LH deficiency: 42% • GH decreased: 26% • Hyperprolactinemia: 25% • Hyperprolactinemia: 23% *** • ADH deficiency: 0%	• ADH deficiency: 98% • FSH/LH deficiency: 8% ** • Hyperprolactinemia: 5% *** • Hyperprolactinemia: 0% • ACTH deficiency: 0% • TSH deficiency: 0% • GH decreased: 0% **	• ADH deficiency: 95% • GH decreased: 51% • FSH/LH deficiency: 47% • ACTH deficiency: 46% • Hyperprolactinemia: 40% *** • TSH deficiency: 39% • Hyperprolactinemia: 16%	• ADH deficiency: 63% • ACTH deficiency: 60% • FSH/LH deficiency: 55% • TSH deficiency: 50% • Hyperprolactinemia: 39% • GH decreased: 37%

Abbreviations: ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

* Other possible symptoms at diagnosis include weight gain (~20%) and temperature dysregulation (rare) (32,33).

** Some case series have reported a high prevalence of GH and FSH/LH deficiency in patients with infundibulo-neurohypophysitis (34).

*** Hyperprolactinemia may be related to stalk compression (disconnection hyperprolactinemia) or to the immune-mediated destruction of prolactin-secreting cells.

Granulomatous hypophysitis can be associated with more severe symptoms than lymphocytic hypophysitis, with two case series documenting more frequent occurrence of headache, chiasmal compression, and hypopituitarism (32,35). A review of the literature found that the most common symptoms of granulomatous hypophysitis at presentation were headache (61%), visual changes (40%), polyuria/polydipsia (27%) and cranial nerve palsies (27%); panhypopituitarism and diabetes insipidus were found in 49% and 27% of cases, respectively (11). Cases of compression of the cavernous part of the internal carotid artery have also been described (36).

Clinical data regarding xanthomatous and IgG4-related hypophysitis are less robust due to the rarity of these variants. Gutenberg *et al*. found that xanthomatous hypophysitis did not cause chiasmal compression and was associated with a low risk of diabetes insipidus and a less severe anterior pituitary hormone impairment than lymphocytic or granulomatous hypophysitis (FSH/LH and GH deficiencies are more common than TSH and ACTH deficiencies) (35). IgG4-related hypophysitis involves frequently both the pituitary and the stalk (~65%) and causes panhypopituitarism, anterior hypopituitarism and central diabetes insipidus in ~50%, ~25% and ~18% of cases, respectively (37). Cases of intrachiasmal abscess and spreading to the cavernous sinus have also been reported (38,39).

Primary hypophysitis is rare in children, with less than 100 cases reported in the literature of which only a few were biopsy-proven (40-42). The clinical presentation, however, seems to differ from adults. A review of the literature showed that the most common presenting symptoms in children are caused by antidiuretic hormone (ADH) deficiency (85%) (42). GH deficiency is found in 76% of cases, while FSH/LH, TSH and ACTH deficiencies were less common than in adults (32%, 29% and 20%, respectively). Headaches and

visual disturbances were also rarely reported (17% and 8% of cases, respectively) (42). As central diabetes insipidus and growth retardation are the most common presenting symptoms in children with primary hypophysitis, the more frequent intracranial germinomas and Langerhans cell histiocytosis, as well as craniopharyngiomas, have to be considered in the differential diagnosis (43). Moreover, children with a presumptive diagnosis of hypophysitis are at risk of developing germinomas later in life (up to 3 years after the initial diagnosis) and require extended follow-up (42,44). Germinomas are also a documented cause of secondary hypophysitis (see "Hypophysitis secondary to sella and parasellar disease" below).

Imaging and Differential Diagnosis of Primary Hypophysitis

Magnetic resonance imaging (MRI) of the sella region typically shows an enlarged pituitary. In order to avoid unnecessary surgery, primary hypophysitis needs to be differentiated from other sella and parasellar masses (Table 5) (45), with pituitary adenomas being the most frequent differential diagnosis in adults.

Table 5. Differential Diagnosis of Hypophysitis

SELLA AND PARASELLAR MASSES
Pituitary adenomas (including pituitary apoplexy);
Pituitary metastases: the differential diagnosis is particularly important in patients with suspected hypophysitis and malignant tumors receiving immune checkpoint inhibitors;
Other sella and parasellar tumors (e.g., craniopharyngiomas, germinomas, gliomas, lymphomas, meningiomas, pituicytomas, chordomas, teratomas, dermoids and epidermoids);
Rathke's cleft cyst;
Abscesses.
OTHER
Physiological hypertrophy of the pituitary in children and adolescents (especially pubertal females) and perimenopausal women;
Pituitary hyperplasia associated with pregnancy;
Sheehan's syndrome at onset;
Thyrotropic hyperplasia associated with severe, untreated primary hypothyroidism.

Primary hypophysitis typically presents as a homogeneous pituitary enlargement with intense and homogeneous enhancement post-gadolinium and no deviation of the stalk (Figure 1); these and other features can help differentiate between primary hypophysitis and pituitary adenomas at MRI (Table 6) (1,4,46,47). Gutenberg *et al*. developed a score using variables such as age, association with pregnancy, and MRI findings to distinguish hypophysitis from pituitary adenomas with high accuracy (47). Further differential diagnoses, especially for lymphocytic hypophysitis, are the physiologic pituitary enlargement associated with pregnancy and Sheehan's syndrome, although these patients have no history of obstetric hemorrhage (48,49). A cautious balance between radiological, clinical, and laboratory findings is necessary to reach the correct diagnosis and avoid inappropriate treatment (50).

Table 6. Differential Imaging Characteristics of Primary Hypophysitis and Pituitary Adenomas		
MRI	**Primary hypophysitis**	**Pituitary adenoma**
Pre-gadolinium	ACUTE / SUB-ACUTE PHASE: Homogeneous pituitary enlargement with symmetrical suprasellar expansion; Suprasellar extension with compression and displacement of chiasm; Stalk thickened but not deviated; * Loss of bright spot of the neurohypophysis in case of involvement of the posterior pituitary. ** CHRONIC PHASE: Pituitary atrophy; Empty sella.	Microadenoma (<1cm): unilateral, asymmetric endosellar mass; Macroadenoma (>1cm): expanding, not homogeneous pituitary mass with asymmetrical suprasellar expansion; Compression and displacement of chiasm (macroadenoma); Contralateral deviation of the stalk; The bright spot of the neurohypophysis can be usually seen. **
Post-gadolinium	Intense and homogeneous enhancement of the pituitary mass. Cystic areas have been described, especially in the xanthomatous variant; Dural tail sign can be present (thickening of the enhanced dura that resembles a tail extending from a mass). ***	Slight, delayed and not homogeneous enhancement. Cystic and necrotic areas are frequently observed in macroadenomas; Dural tail usually absent. ***

Abbreviations: MRI, magnetic resonance imaging.

* An enlarged pituitary stalk can also be found in other intracranial pathologies (e.g., sarcoidosis, metastases, Langerhans cell histiocytosis, germinoma, craniopharyngioma, astrocytoma, pituitary adenoma, lymphoma, tuberculosis, Erdheim-Chester's disease) (51).

** The bright spot may be absent in up to 20% of healthy subjects (especially the elderly).

*** The dural tail sign is not specific to hypophysitis. It can be observed in meningioma (most frequently) and other intracranial pathologies (e.g. lymphoma, chloroma, metastasis, multiple myeloma, glioblastoma multiforme, aspergillosis, chordoma, schwannoma, pleomorphic xanthoastrocytoma, hemangiopericytoma, granulomatosis with polyangiitis, sarcoidosis, medulloblastoma, eosinophilic granuloma, pituitary adenoma, pituitary apoplexy, Erdheim-Chester's disease) (52)

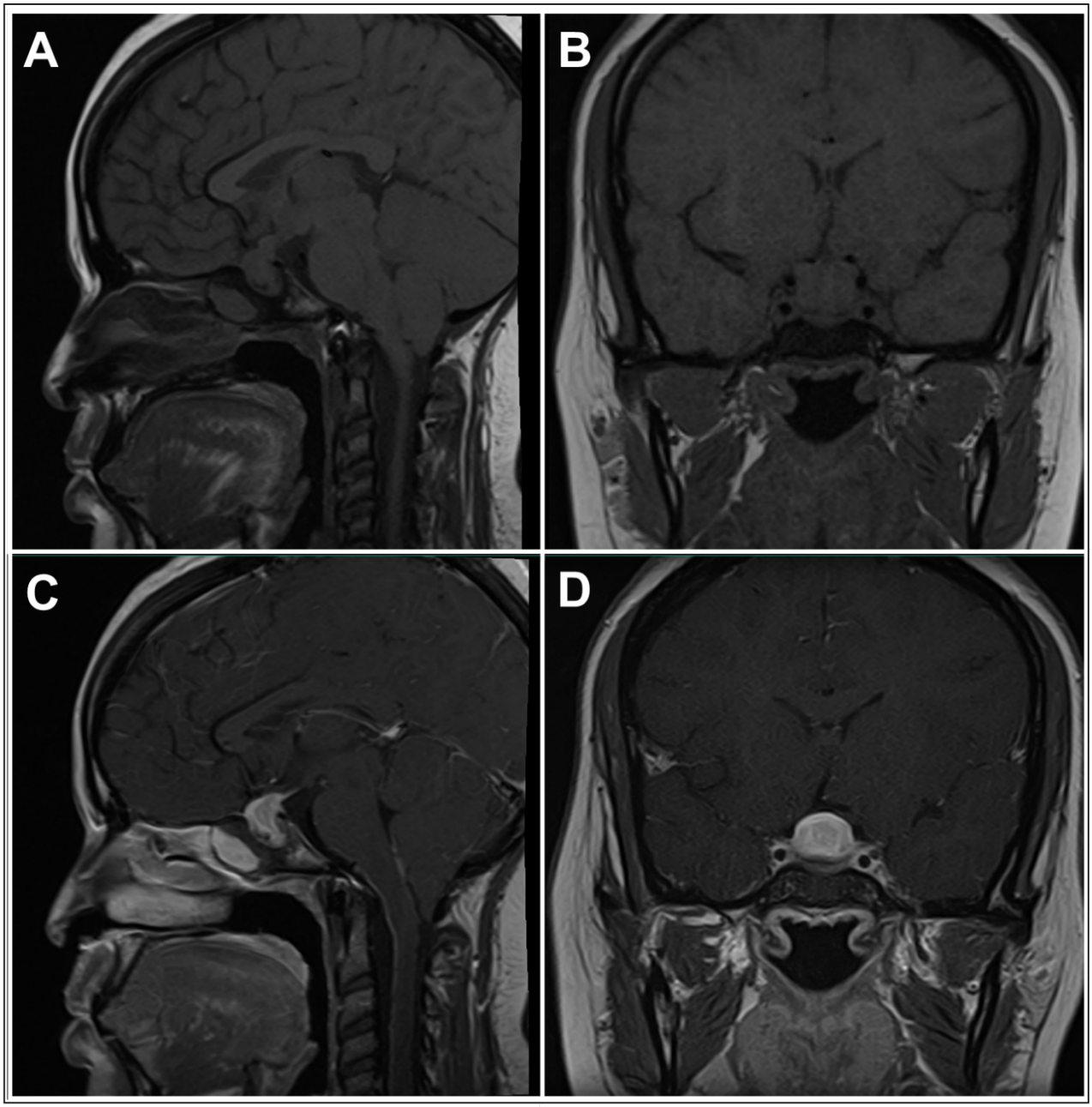

Figure 1. Magnetic resonance imaging findings in a case of primary hypophysitis. Panel A) T1-weighted image, sagittal section. Panel B) T1-weighted image, coronal section. Panel C) T1-weighted image post-gadolinium, sagittal section. Panel D) T1-weighted image post-gadolinium, coronal section. A homogeneous enlargement of the pituitary with thickening of the stalk can be seen. The mass shows intense and homogeneous enhancement post-gadolinium.

Autoantibodies in Primary Hypophysitis

Several authors have assessed the presence and utility of serum autoantibodies (pituitary and/or hypothalamic antibodies) in patients with primary hypophysitis:

- An autoimmune etiology for lymphocytic hypophysitis was suggested by the presence of pituitary antibodies that may recognize α-enolase, GH, the pituitary gland-specific factors 1a and 2 (PGSF1a and PGSF2), regulatory prohormone-processing enzymes commonly produced in the pituitary gland (PC1/3, PC2, CPE and 7B2), secretogranin II, chromosome 14 open reading frame 166 (C14orf166), the corticotroph-specific transcription factor TPIT, and chorionic somatomammotrophin (HCS) (53-61). Several techniques have been used to detect pituitary antibodies in primary hypophysitis (ELISA, radioligand assay, immunoblotting, and immunofluorescence) and the prevalence of antibody-positive hypophysitis is 11-73% depending from the antigen(s) tested and the technique used (7,62). However, the pathogenic role of these autoantibodies is unclear and they are not specific to hypophysitis. For example, pituitary antibodies were identified by indirect immunofluorescence in ~45% of patients with biopsy-proven hypophysitis, but were also found in the serum of patients with isolated central diabetes insipidus (35%), germinomas (33%), isolated anterior hormone deficiencies (29%), prolactinomas (27%), Rathke's cleft cysts (25%), craniopharyngiomas (17%), non-functioning pituitary tumors (13%), GH-secreting pituitary tumors (12%), and healthy subjects (5%) (62-65). They can also be found in patients with autoimmune endocrine disorders, especially Hashimoto thyroiditis (63). However, indirect immunofluorescence using human pituitary gland as a substrate and showing a granular cytosolic staining pattern was most commonly found in patients with hypophysitis and isolated hormone deficiencies (62); therefore, the finding of this staining pattern can be useful to clinicians in establishing a diagnosis of hypophysitis;

- The detection of hypothalamic antibodies targeting corticotropin-releasing hormone (CRH)-secreting cells in some patients with GH/ACTH deficiency but with pituitary antibodies targeting only GH-secreting cells indicates that an autoimmune aggression to the hypothalamus can be responsible for some cases of lymphocytic hypophysitis (66). Consequently, not only pituitary but also hypothalamic autoimmunity may contribute to anterior pituitary dysfunction in a subset of patients with primary hypophysitis;

- A search for ADH antibodies in patients with primary hypophysitis may help identifying patients who are prone to developing autoimmune central diabetes insipidus (67). These antibodies alone are not a good diagnostic marker for posterior pituitary involvement, but may serve as a predictive marker of gestational or post-partum diabetes insipidus (68,69);

- Anti-Rabphilin antibodies have been proposed to be a biomarker for lymphocytic infundibulo-neurohypophysitis (70). Rabphilin is involved in the release of hormones or neurotransmitters and is expressed mainly in the brain, including the posterior pituitary and hypothalamus where ADH is present. Whether anti-Rabphilin antibodies are a *cause* of central diabetes insipidus or a *result* of infundibulo-neurohypophysitis is unknown. However, anti-Rabphilin antibodies are detected in 76% of patients with infundibulo-neurohypophysitis and 11% of patients with lymphocytic hypophysitis. In contrast, these antibodies are absent in patients with sella/suprasellar masses without lymphocytic hypophysitis, suggesting that this antibody may serve as a biomarker for the diagnosis of infundibulo-neurohypophysitis and may be useful for the differential diagnosis in patients with central diabetes insipidus (45);

- Primary hypophysitis can eventually evolve in pituitary fibrosis and atrophy, documented at imaging as an "empty sella". Lupi *et al*. have found pituitary antibodies in 6% of patients with an empty sella not linked to previous head trauma. In this

cohort, the presence of pituitary antibodies also correlated with the presence of hypopituitarism (71);

- Antibodies recognizing GH and one peptide from proopiomelanocortin (POMC) have been described in a patient with IgG4-related hypophysitis (72).

Natural History of Primary Hypophysitis

Primary hypophysitis can be self-limiting and spontaneous remission may occur (Figure 2). Considering the low prevalence of the disease, however, robust data regarding the natural history of primary hypophysitis are lacking (54). Moreover, most of the literature regards lymphocytic hypophysitis, while data from other histology subtypes are less robust. A review of 76 cases of primary hypophysitis from Germany has shown that patients not receiving any active treatment had improvement, stability or progression of the pituitary involvement at MRI in 46%, 27% and 27% of cases, respectively; pituitary deficiencies improved, remained stable or worsened in 27%, 55% and 18% of patients, respectively (73). A previous study by Khare *et al*. showed that spontaneous resolution of sella compression symptoms occurred in all patients managed conservatively and that 33% had complete or partial recovery of pituitary function (74). Park *et al*. also reported similar findings (75).

Primary hypophysitis frequently evolves to fibrosis and pituitary atrophy in the chronic stages of the disease, which often impair pituitary function (Figure 2). The evolution to empty sella has also been shown in a mouse model of autoimmune hypophysitis (76). Caturegli *et al*. reported that only 4% of patients had spontaneous remission with recovery of pituitary function, while most patients will require long-term replacement of one or more pituitary axes (4,54). Whether medical treatment with glucocorticoids has a positive impact on the natural history of primary hypophysitis is still a matter of debate.

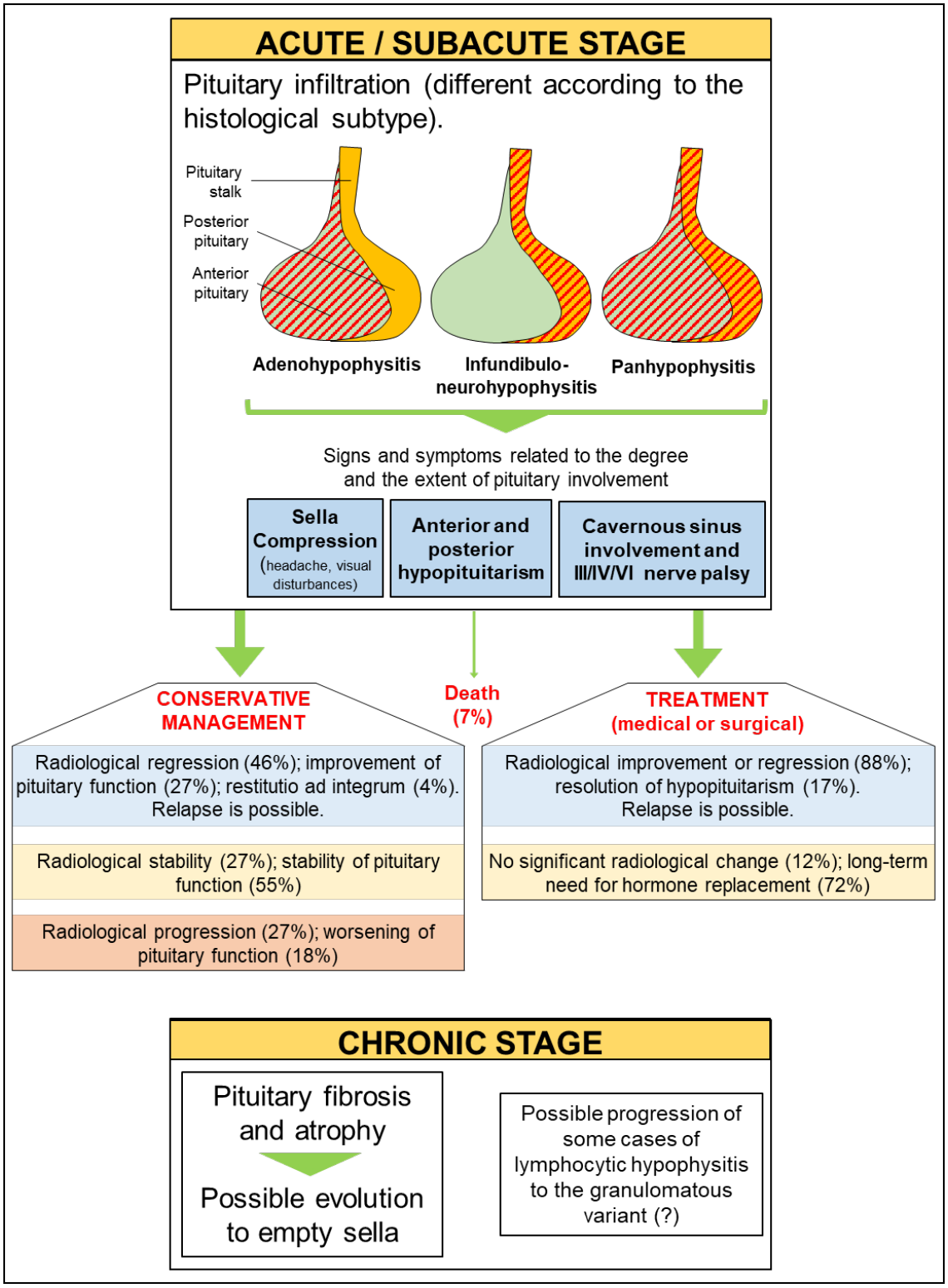

Figure 2. Natural History of Primary Hypophysitis.

Most of the published case series mainly focus on the more frequent lymphocytic hypophysitis. Granulomatous hypophysitis can cause more severe signs and symptoms (headache, chiasmal compression and anterior/posterior hypopituitarism). Xanthomatous hypophysitis seems to cause sella compression and pituitary dysfunction less frequently. IgG4-related hypophysitis can cause various degree of involvement of the anterior pituitary, posterior pituitary and the stalk. Necrotizing hypophysitis is extremely rare and is associated with a high risk of panhypopituitarism and diabetes insipidus. The chronic stage of the disease is most likely related to the extent of damage of the pituitary. Some authors have suggested that some cases of lymphocytic hypophysitis may evolve to the granulomatous form, as mixed forms can rarely be observed. A death rate of 7% has been described in large case series of patients with primary hypophysitis and is probably related to unrecognized acute adrenal insufficiency.

Diagnosis and Treatment of Primary Hypophysitis

Pituitary biopsy is the gold standard to confirm the diagnosis of primary hypophysitis. This procedure, however, should be considered only in equivocal cases and when the outcome of the biopsy is expected to change the therapeutic management, and should be performed by a neurosurgeon with extensive expertise in pituitary surgery.

Due to the rarity of the disease, the management of hypophysitis is controversial. An algorithm in line with the more recent literature is reported in Figure 3. Initial evaluation of patients with suspected hypophysitis involves clinical and laboratory assessment. Patients with a suspicion of hypophysitis based on biochemical results should undergo a pituitary MRI, as well as visual assessment to check visual fields and acuity. Secondary causes of hypophysitis and other sella/parasellar masses should be considered in the differential diagnosis.

The mainstay of treatment of primary hypophysitis is pituitary hormone replacement (77,78). As outlined above, ACTH production is frequently impaired at presentation, and most patients will require glucocorticoid replacement. This should be started before thyroxine replacement (if TSH deficiency is present as well) to avoid precipitating acute adrenal insufficiency.

Conservative management is recommended for primary hypophysitis unless symptoms are severe and progressive. The only exception to this rule is IgG4-related hypophysitis that – like other manifestations of the disease – should be promptly treated to revert symptoms and prevent irreversible fibrosis (79,80). The mainstay of treatment are glucocorticoids, which often cause remission of symptoms within a few weeks. A typical starting dose is prednisone 30-40 mg/day (or equivalent), which should be continued for 2-4 weeks, and then tapered gradually over 2-6 months (19). However, some patients may benefit from long-term maintenance glucocorticoid therapy (with or without a steroid-sparing agent), especially in case of extensive multi-organ involvement. Relapse is possible and multiple courses of high-dose glucocorticoids are often necessary. Rituximab has also been used in patients with poor response to glucocorticoids (19,81,82). A case of IgG4-related hypophysitis successfully treated with azathioprine has also been reported (83).

High-dose glucocorticoids are the first-line treatment to improve the swelling of the pituitary and improve the symptoms related to significant sella compression. Anterior pituitary function can recover after pulse corticosteroid therapy, although >70% of patients will require long-term replacement with one or more hormones (4); central diabetes insipidus rarely recovers. Honegger *et al.* documented excellent initial

responses to high-dose glucocorticoids, with radiological improvement, stability and progression in 65%, 31% and 4% of cases, respectively (73). However, these patients carried a higher risk of side effects (weight gain, psychiatric symptoms, peripheral edema, diabetes mellitus and glaucoma) and relapse of the pituitary inflammation was documented in 38% of cases. Relapses occurred 2-17 months after starting pulse steroids and the risk or relapse did not correlate with either initial glucocorticoid dose or treatment duration (73). Hormone deficiencies improved with glucocorticoids only in 15% of patients, while they remained stable or worsened in 70% and 15% of cases, respectively (73). Lupi *et al*. performed a review of the literature and found somewhat better outcomes with medical therapy, reporting pituitary mass reduction in 84% of cases, improving anterior pituitary function in 45%, and restored posterior pituitary function in 41% after high-dose glucocorticoids and/or azathioprine, with a relatively low risk of relapse (14%) (84). Recently, Chiloiro *et al*. found in a small prospective double-arm study that high-dose glucocorticoid treatment – compared with simple observation – was associated with higher rates of hypophysitis resolution and pituitary function recovery (85). The authors also showed that positive pituitary antibodies, a diagnosis of diabetes insipidus and secondary hypogonadism at the time of presentation, and specific MRI findings (a thicker pituitary stalk, a smaller pituitary volume, and the evidence of posterior pituitary involvement at MRI including absent bright spot) predicted better clinical outcomes following glucocorticoid therapy. These findings should be confirmed in a larger prospective cohort.

Whether central diabetes insipidus is an unfavorable prognostic factor for response to glucocorticoids is unclear. The abovementioned study by Chiloiro *et al*. suggests better outcomes in patients with central diabetes insipidus at the time of hypophysitis diagnosis (85); however, Lupi *et al*. found that patients with concomitant anterior and posterior pituitary dysfunction responded poorly to glucocorticoids, which were unable to revert the hypopituitarism (86). Glucocorticoid therapy was also found to be less effective in granulomatous or xanthomatous hypophysitis (35). In glucocorticoid-resistant cases and when high-dose glucocorticoids cause unacceptable side effects, immunosuppressive drugs such as azathioprine, methotrexate, and cyclosporin A have been used successfully. However, the long-term effects are unclear (1). Rituximab has also been employed to treat steroid-refractory hypophysitis (36,87-89).

Surgery should be considered only in cases with serious and progressive deficits of the visual field, visual acuity, or nerve paralysis not responsive to medical treatment. Surgery generally improves sella compression in the short term; however, Honegger *et al*. observed progression/relapse of the disease in 25% of patients after a mean follow-up of 3 years (73). Pituitary function improved only in 8% of patients after surgery, and the rates of resolution of chiasmal compression were also low (73). Further supporting the limited role of surgery in the management of hypophysitis, two small observational studies found that surgery did not impact significantly on the resolution of neurological symptoms or hormonal deficits during follow-up (90,91).

Stereotactic radiotherapy (radiosurgery) has been effectively employed in selected patients who have failed medical treatment or suffer from repeated recurrence of lymphocytic hypophysitis (92,93).

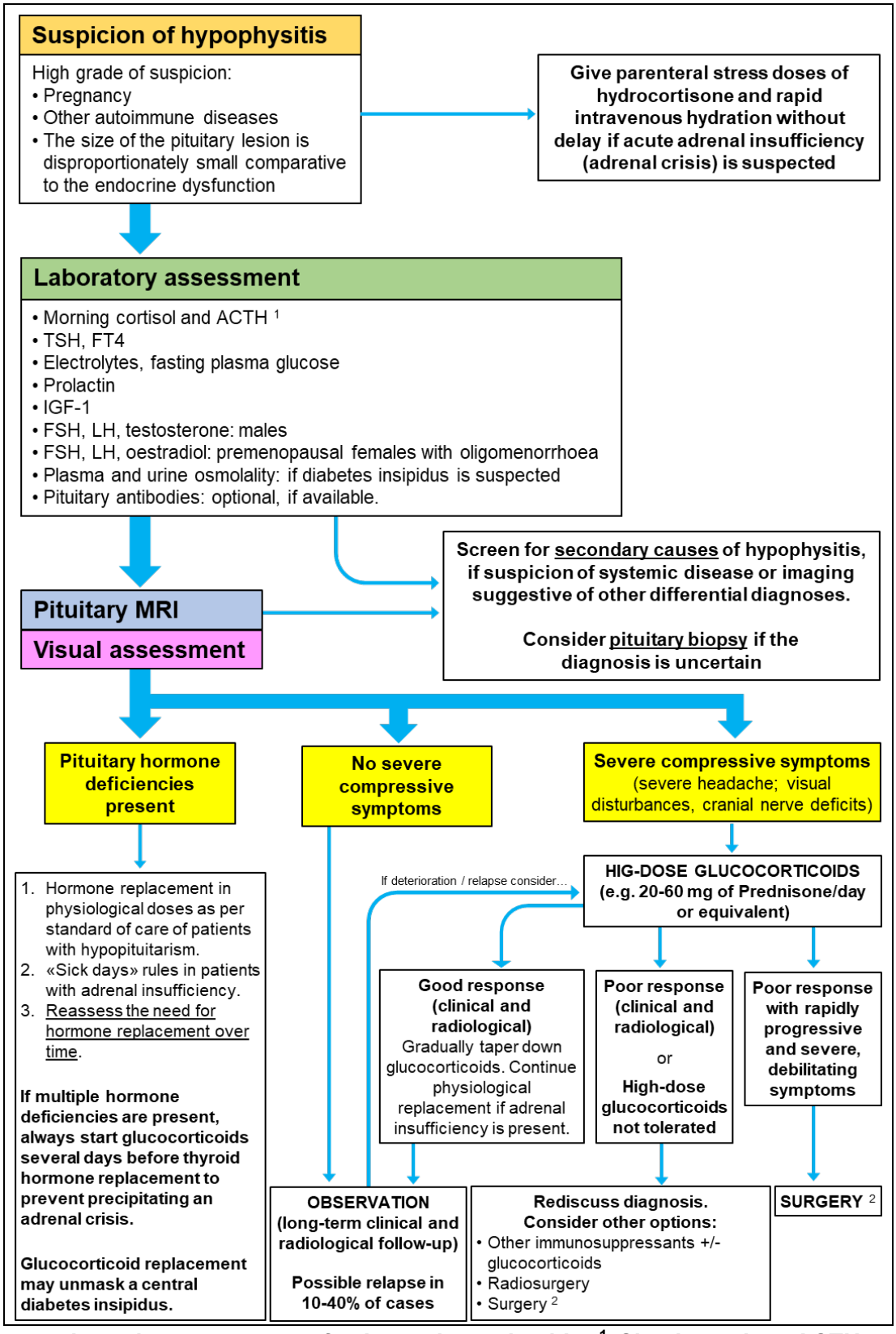

Figure 3. Diagnosis and management of primary hypophysitis. [1] Check random ACTH and cortisol if acute adrenal insufficiency is suspected. Consider confirmatory testing (e.g., Synacthen) if equivocal or

borderline results. The Synacthen test can give false-positive results in the early stages of central adrenal insufficiency. During pregnancy and in patients receiving oral estrogens, the rise of corticosteroid-binding globulin (CBG) leads to falsely elevated cortisol levels and the normal reference ranges and stimulated cortisol cut-offs do not apply. [2] Pituitary surgery can also provide histology for definitive diagnosis.

DRUG-INDUCED HYPOPHYSITIS: IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors are monoclonal antibodies increasingly used for solid and hematological malignancies (94). They block several regulators of the immune activation (immune checkpoints), enhancing the host's immune response to tumor cells (Figure 4). These drugs have shown a favorable toxicity profile and significant anti-tumor activity but, because of their mechanism of action, new typical side-effects have emerged (immune-related adverse events, irAEs) (Figure 4) (95,96).

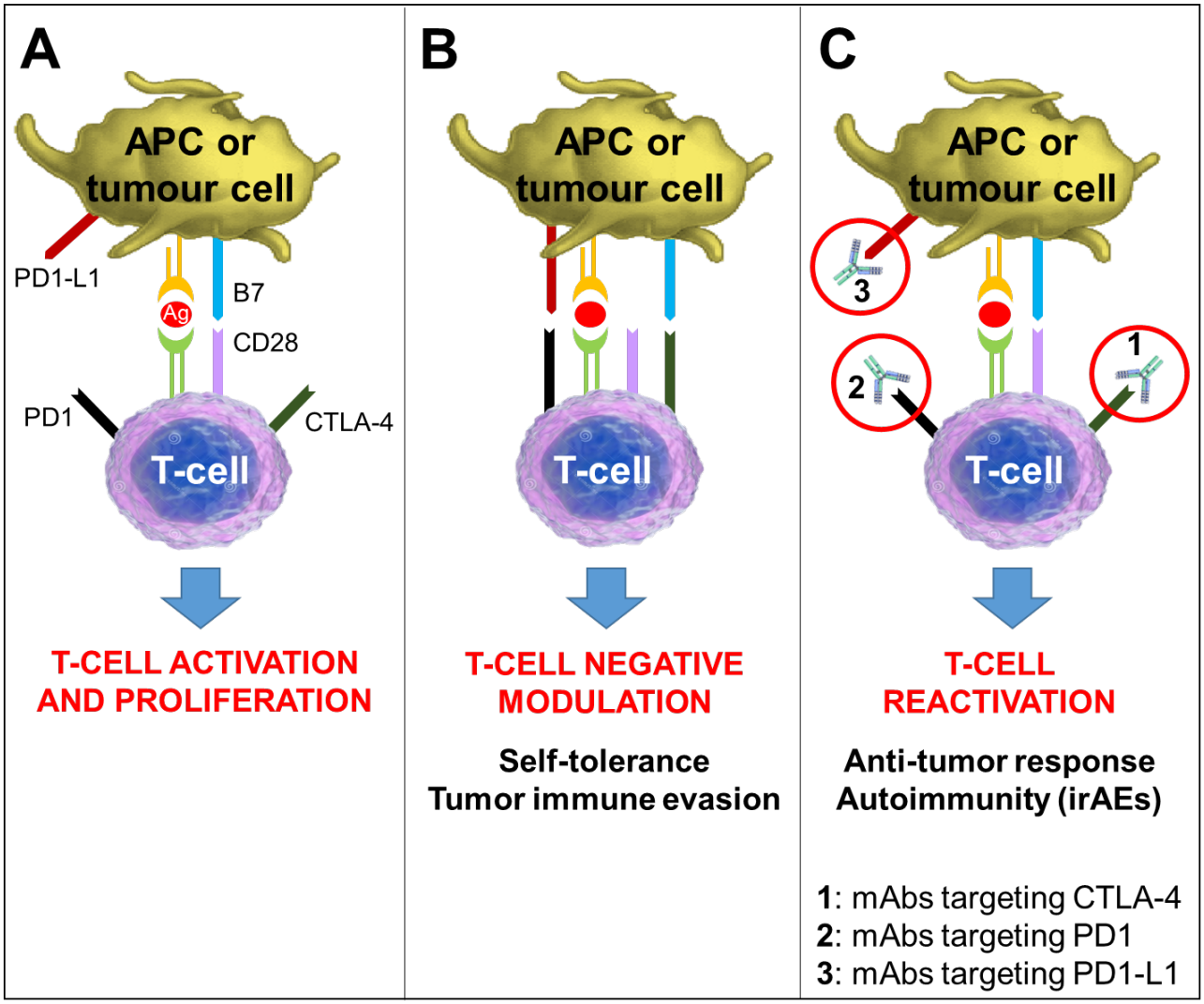

Figure 4. Mechanism of Action of Immune Checkpoint Inhibitors. Tumor antigens are presented to T-cells by antigen-presenting-cells (APCs) via the interaction of the major histocompatibility complex

(MHC) and the T-cell receptors, representing the primary signal for activating T-cells. Another costimulatory signal involving interaction between B7 on APCs and CD28 on T-cells is needed to complete T-cell activation and expansion (Panel A). Several co-receptors act as negative modulators of immune response at different molecular checkpoints. The CTLA-4 is induced in T-cells at the time of their initial response to antigen. CTLA-4 is transported to the cell surface proportionally to the antigen stimulation; it binds to B7 with greater affinity than CD28, resulting in specific T-cell inactivation (Panel B). The PD-1/PD1-L1 pathway is not involved in initial T-cell activation: it regulates inflammatory responses in peripheral tissues sustained by already activated effector T-cells. Activated T-cells up-regulate PD-1 and inflammatory signals in the tissue induce the expression of PD1-L1s, which downregulate the activity of T-cells, protecting normal tissues from collateral destruction; this mechanism is also exploited by tumor cells to evade the immune system response (Panel B). Monoclonal antibodies that block either CTLA-4 or PD1/PD1-L1 increase cytotoxic T-cell activity by expanding T-cell activation and proliferation (Panel C). The eventual T-cell reactivation is responsible for the both anti-tumor response and the immune-related adverse events associated with these drugs.

irAES mirror the immune response reactivation induced by immune checkpoint inhibitors and may predict better survival and response to the treatment of the underlying malignancy (97-100). irAEs can affect multiple organs and systems, including the pituitary and other endocrine glands (Table 7) (101).

Table 7. Immune-Related Adverse Events Associated with Immune Checkpoint Inhibitors

ENDOCRINOPATHIES	OTHER SYSTEMS AND ORGANS
PITUITARY: Hypophysitis.* **THYROID:** Thyroiditis (both hypo- and hyperthyroidism); Euthyroid Graves' ophthalmopathy. **ADRENAL GLANDS:** Adrenalitis.* **PANCREAS:** Insulinopenic diabetes mellitus.	**SKIN:** Rash/inflammatory dermatitis; Bullous dermatoses; Stevens-Johnson syndrome; Toxic epidermal necrolysis; Drug rash with eosinophilia and systemic symptoms syndrome; Drug-induced hypersensitivity syndrome; Acute generalized exanthematous pustulosis; Alopecia areata; Vitiligo; Psoriasis. **GASTROINTESTINAL SYSTEM:** Colitis; Hepatitis; Pancreatitis. **LUNGS:** Pneumonitis. **MUSCOSKELETAL SYSTEM:** Arthritis; Polymyalgia-like syndrome; Myositis; Vasculitis. **KIDNEY:** Nephritis. **CARDIOVASCULAR SYSTEM:** Myocarditis; Pericarditis; Arrhythmias; Heart failure; Vasculitis; Venous thromboembolism. **NERVOUS SYSTEM:** Guillain-Barré syndrome; Myasthenia gravis; Peripheral neuropathy; Autonomic neuropathy; Aseptic meningitis; Encephalitis; Transverse myelitis.

	HEMATOLOGY: Autoimmune hemolytic anemia; Acquired thrombotic thrombocytopenic purpura; Hemolytic uremic syndrome; Aplastic anemia; Lymphopenia; Immune thrombocytopenia; Acquired hemophilia. **EYE:** Uveitis; Iritis; Episcleritis; Blepharitis.

***** Immune checkpoint inhibitors can cause both primary adrenal insufficiency (rarer) and secondary adrenal insufficiency (more frequent).

Epidemiology

Hypophysitis may occur as a complication during treatment with immune checkpoint inhibitors. Ipilimumab, a monoclonal antibody against the cytotoxic T lymphocyte antigen-4 (CTLA-4) is the drug that has been more strongly associated with this immune-related adverse event (Table 8) (5,102-112). The overall incidence of hypophysitis is 12% in patients treated with anti-CTLA-4 antibodies and 0.5% in patients treated with anti-programmed death 1 (PD1) antibodies (113,114).

Table 8. Immune Checkpoint Inhibitors and the Risk of Hypophysitis

Category	Drug	Approved and off-label indications	Incidence of reported hypophysitis in clinical studies
Anti-CTLA-4 (70% of published hypophysitis cases)	Ipilimumab	Unresectable or metastatic melanoma; Adjuvant treatment in melanoma; Relapsed hematologic cancer.	Up to 17.4% (G3-G4: 0.3-17.4%)
	Tremelimumab	Malignant mesothelioma; Hepatocellular carcinoma. This drug is not FDA approved.	0-2.6% (G3-G4: 1%)
Anti-PD1 (24% of published hypophysitis cases)	Nivolumab	Metastatic colorectal cancer; Recurrent or metastatic squamous cell head and neck cancer; Hepatocellular carcinoma; Classical Hodgkin's lymphoma; Unresectable or metastatic melanoma; Adjuvant treatment in melanoma; Progressive, metastatic non-small cell lung cancer; Progressive small cell lung cancer; Advanced renal cell cancer; Urothelial carcinoma; Platinum-resistant ovarian cancer.	0-3% (G3-G4: 0.5%)

	Pembrolizumab	Metastatic or recurrent locally advanced gastric cancer; Recurrent or metastatic squamous cell head and neck cancer; Relapsed or refractory classical Hodgkin's lymphoma; Relapsed chronic lymphocytic leukemia; Unresectable or metastatic melanoma; Unresectable or metastatic microsatellite instability-high cancer; Metastatic non-small cell lung cancer; Metastatic, non-squamous Non-small cell lung cancer (in combination with Pemetrexed and Carboplatin); Locally advanced or metastatic urothelial carcinoma; Advanced Merkel cell carcinoma.	0-4.8% (G3-G4: 0-2.4%)
	Dostarlimab	Mismatch repair deficient recurrent or advanced endometrial cancer; Mismatch repair deficient recurrent or advanced solid tumors.	No cases published. Hypophysitis is listed as a possible adverse reaction in <10% of treated patients in the product information.
	Cemiplimab	Cutaneous squamous cell carcinoma.	1 case reported
	Toripalimab	Melanoma; several solid malignancies (development stage).	1 case reported
	Geptanolimab (still in development stage)	Peripheral T-cell lymphoma; Alveolar soft part sarcoma; Cervical cancer; Non-Hodgkin's lymphoma; Liver cancer; Colorectal cancer; Non-small cell lung cancer.	1 case reported
Anti-PD1-L1 (2% of published hypophysitis cases)	Atezolizumab	Metastatic non-small cell lung cancer; Locally advanced or metastatic urothelial carcinoma.	1% (G3-G4: 1%)
	Avelumab	Metastatic Merkel cell carcinoma; Locally advanced or metastatic urothelial carcinoma; Advanced non-small cell lung cancer.	1 case reported
	Durvalumab	Advanced non-small cell lung cancer; Locally advanced or metastatic urothelial carcinoma.	1 case reported
Combination therapy (4% of published	Ipilimumab + Nivolumab	Unresectable or metastatic melanoma; Progressive small cell lung cancer; Non-small cell lung cancer; Advanced renal cell cancer; Malignant mesothelioma; Recurrent glioblastoma.	Up to 12.8% (G3-G4: 1.5-8.7%)

hypophysitis cases)	Ipilimumab + Pembrolizumab	Advanced melanoma; Advanced renal cell carcinoma.	0-9.1% (G3-G4: 0-6%)
	Durvalumab + Tremelimumab	Advanced non-small cell lung cancer.	0%

Abbreviations: CTLA-4, cytotoxic T lymphocyte antigen-4; FDA, Food and Drug Administration; G3, grade 3 immune checkpoint inhibitor-induced hypophysitis (see Table 11); G4, grade 4 immune checkpoint inhibitor-induced hypophysitis (see Table 11); PD1, programmed death 1; PD1-L1, programmed death 1 Ligand 1.

Pathogenesis

The pathogenesis of anti-CTLA-4 antibody-induced hypophysitis involves type II and IV hypersensitivity, as well as the humoral immune response (Figure 5). This has been suggested by histopathological findings of patients with hypophysitis following treatment with Ipilimumab (alone or in combination with Nivolumab or Pembrolizumab), evidence of pituitary antibodies in the serum of these patients, association with specific human leucocyte antigens, and animal models of anti-CTLA-4-induced hypophysitis (8,15,115-118).

Evidence regarding the pathophysiology of anti-PD1/PD1-L1 antibody-induced hypophysitis is scant, but immune response reactivation most likely targets ACTH-secreting cells because of the very frequent isolated ACTH deficiency (5). Kanie *et al*. recently postulated that ectopic expression of ACTH in the tumor may contribute to some cases of anti-PD1/PD1-L1 antibody-induced hypophysitis, as a form of paraneoplastic syndrome (119). Furthermore, Bellastella *et al.* identified a higher prevalence of anti-pituitary and anti-hypothalamus antibodies in patients with cancer treated with anti-PD1/PD1-L1 agents (120). In a small longitudinal study, the same group also found that more than half of patients who start anti-PD1/PD1-L1 treatment developed anti-pituitary or anti-hypothalamus antibodies after 9 weeks of treatment, with a concomitant increase prolactin and a reduction in ACTH and IGF-1 levels compared to baseline (120). These preliminary results need to be validated in a larger cohort, but the presence of anti-hypothalamus antibodies would suggest that – at least in some patients – hypothalamic autoimmunity might contribute to the development of anti-PD1/PD1-L1 antibody-induced pituitary dysfunction.

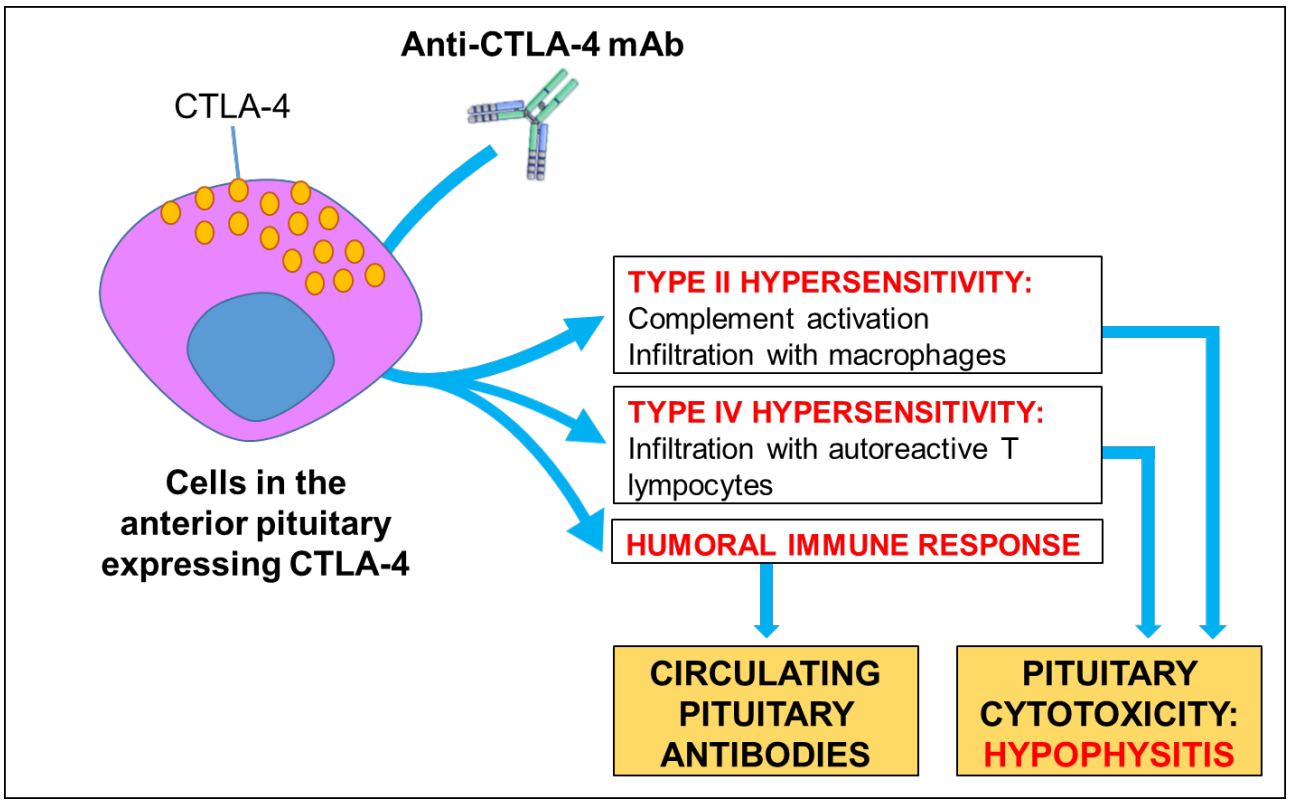

Figure 5. Proposed pathogenesis of anti-CTLA-4 antibody-induced hypophysitis. Anti-CTLA-4 antibody-induced hypophysitis accounts for ~70% of immune-checkpoint induced hypophysitis cases. The CTLA-4 antibody binds to pituitary CTLA-4 antigen, inducing complement activation and infiltration with macrophages and other inflammatory cells, leading to phagocytosis and enhanced antigen presentation. Subsequently, autoimmune type IV hypersensitivity reactions start, with infiltration of the anterior pituitary by autoreactive T lymphocytes that eventually leads to pituitary cytotoxicity and inflammation. Moreover, patients with anti-CTLA-4 antibody-induced hypophysitis develop pituitary antibodies that predominantly recognize TSH- FSH- and ACTH-secreting cells. Pituitary cytotoxicity in anti-PD1/PD1-L1 antibody-induced hypophysitis presumably affects mostly ACTH-secreting cells, as isolated ACTH deficiency is the most common occurrence in these patients.

Clinical Characteristics

There are important differences between primary hypophysitis and immune checkpoint-induced hypophysitis (Table 9) (5,8,103). The latter does not have a female predominance (8,121) and seems to present more frequently with hypopituitarism at diagnosis. Both forms of hypophysitis are more commonly associated with an initial deficit of ACTH, FSH/LH and TSH, but symptoms of adrenal insufficiency and confirmed ACTH deficiency are much more common in patients with immune checkpoint-induced hypophysitis (8,113,114). Central diabetes insipidus can occur in a substantial share of primary hypophysitis cases (i.e., the infundibulo-neurohypophysitis and panhypophysitis variants), while it is extremely rare in immune-checkpoint induced hypophysitis. Pituitary enlargement and visual impairment are much more common in primary hypophysitis, while the size of the pituitary may appear normal in immune checkpoint inhibitor-induced hypophysitis (in absence of a baseline pituitary MRI) and optic chiasm involvement is rare (5,8).

Table 9. Comparison Between Primary and Immune Checkpoint Inhibitor-Induced Hypophysitis		
Characteristics	**Primary hypophysitis**	**Immune checkpoint inhibitor-induced hypophysitis**
Etiology	Autoimmune.	Immune response reactivation.
Epidemiology	More prevalent in young females (female:male ratio ~3:1), apart from the rare IgG4-related form that is more common in older males. The onset of the lymphocytic subtype is strongly associated with late pregnancy and the post-partum period.	The epidemiology is most likely influenced by the underlying malignancy. 0.5-12% of treated patients develop hypophysitis, depending on the drug used. The female:male ratio is ~1:4 and the mean age at onset is ~60 years (older male patients appear to be the group carrying the higher risk). No prior cancer therapy is associated with higher risk of developing hypophysitis.
Time after the initiating event	Unknown. The median duration of symptoms before clinical presentation is varies according to the anatomic location of the pituitary involvement: • Adenohypophysitis (during pregnancy): 4 months; • Adenohypophysitis (outside of pregnancy): 12 months; • Infundibulo-neurohypophysitis: 3 months; • Panhypophysitis: 4 months.	Ipilimumab: median time to onset 9-11 weeks (range 1-35); * Pembrolizumab: median time to onset 16 weeks (range 1-52); * Nivolumab: median time to onset 21-22 weeks (range 6-48); * Ipilimumab + Nivolumab: median time to onset 11-12 weeks (range 3-32). *
Symptoms at presentation	• Headache: 48% • Adrenal insufficiency: 38% • Polydipsia/polyuria: 34% • Visual disturbances: 32% • Hypogonadism: 21% • Hypothyroidism: 16%	• Adrenal insufficiency: 81% ** • Headache: 45% • Hypothyroidism: 18% • Hypogonadism: 11% • Visual disturbances: 6% • Polydipsia/polyuria: 2%
Pituitary hormone abnormalities	• ADH deficiency: 63%	ACTH deficiency: 96% **

	ACTH deficiency: 60% FSH/LH deficiency: 55% TSH deficiency: 50% GH decreased: 37% Hyperprolactinemia: 39%	TSH deficiency: 63% FSH/LH deficiency: 59% GH decreased: 19% Hyperprolactinemia: 11% ADH deficiency: 4%
Abnormal MRI at presentation	97% of cases	64% of cases ***
Histopathology	Marked infiltration of lymphocytes of the pituitary gland, typically accompanied by scattered plasma cells, eosinophils and fibroblasts, and in later disease stages by fibrosis.	T-cell infiltration and IgG-dependent complement fixation and phagocytosis.
Treatment	Usually good response to glucocorticoids.	Good response to glucocorticoids of the symptoms related to sella compression.
Outcome	Variable: from complete recovery to persistent hypopituitarism.	Pituitary enlargement (if present) eventually resolves. TSH and FSH/LH deficiencies often recover, while central adrenal insufficiency persists almost invariably.

Abbreviations: ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; CTLA-4, cytotoxic T lymphocyte antigen-4; FSH, follicle-stimulating hormone; LH, luteinizing hormone; GH, growth hormone; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone.

* Data from the prescribing information of Ipilimumab, Pembrolizumab and Nivolumab.

** Anti-PD-1/PD1-L1 antibody-induced hypophysitis typically presents with isolated ACTH deficiency, while CTLA-4 antibody-induced hypophysitis more frequently leads to multiple hormone deficiencies (Table 10).

*** MRI abnormalities are transient, can be subtle and precede clinical symptoms in ~50% of cases. Anti-PD-1/PD1-L1 antibody-induced hypophysitis typically lacks MRI changes and causes no mass effect symptoms (Table 10).

The onset of immune checkpoint-induced hypophysitis varies according to the drug used (Table 9); early onset has been reported and it can appear also several months after the initiation of the immunotherapy (122,123). The risk of hypophysitis with Ipilimumab appears to be dose-dependent, with a higher prevalence in those receiving 10 mg/kg vs. 3 mg/kg (124-126). Conversely, patients receiving concomitant cytotoxic chemotherapy or with brain radiotherapy-pretreated metastases might be protected from the risk of developing hypophysitis, presumably through immune cell depletion (95,127).

Patients with immune checkpoint-induced hypophysitis typically present with nonspecific symptoms of adrenal insufficiency like fatigue, headache, myalgia, nausea, vomiting, reduced appetite, light-headedness, and dizziness, whilst

symptoms of other anterior pituitary hormone deficiencies are less common at the time of diagnosis (Table 9) (113,114). Manifestations of adrenal insufficiency often overlap with those of the underlying malignancy but must not be overlooked because of the risk of developing life-threatening adrenal crisis. Visual disturbances are very rare (the pituitary enlargement, if present, is often minor and transient) and central diabetes insipidus is extremely uncommon (95,113,114,128,129). Other less frequent symptoms include confusion, hallucinations, memory loss, labile moods and depression (including suicidal ideation), insomnia, temperature intolerance, and chills (130,131). Importantly, up to 45% of patients can be asymptomatic and are diagnosed only at laboratory evaluation, highlighting the importance of regular monitoring (123,132).

Associated irAEs have been reported in about half of patients with immune checkpoint inhibitor-induced hypophysitis (133). By far, the most common associated irAE was thyroiditis (~30%), followed by colitis (~20%), skin reactions (~15%), pneumonitis (~5%), and hepatitis (~5%) (133).

Patients with anti-CTLA-4 antibody-induced hypophysitis tend to have a more diverse clinical presentation than those with anti-PD-1/PD1-L1 antibody-induced hypophysitis. The latter typically presenting later during treatment, with severe isolated ACTH deficiency (which frequently leads to hyponatremia at the time of diagnosis), and no significant pituitary enlargement both clinically and radiologically. Also, treatment discontinuation is less frequently required in patients with anti-PD-1/PD1-L1 antibody-induced hypophysitis (Table 10) (5,81,114,134-136).

Table 10. Comparison Between Anti-CTLA-4 and Anti-PD1/PD1-L1 Antibody-Induced Hypophysitis

Characteristics	Anti-CTLA-4 antibody-induced hypophysitis	Anti-PD1/PD1-L1 antibody-induced hypophysitis
Number of cases reported	192 (74% males)	69 (72% males)
Mean time to onset (95% CI)	10.5 weeks (9.8-11.2)	*Anti-PD1*: 27.0 weeks (20.9-33.1) *Anti-PD1-L1*: 27.8 weeks (0-58.0)
Mean doses to onset	3.4 doses	10.3 doses
Symptoms at presentation	• Adrenal insufficiency: 75% • Headache: 60% • Hypothyroidism: 21% • Hypogonadism: 16% • Visual disturbances: 8% • Polydipsia/polyuria: <1%	• Adrenal insufficiency: 91% • Hypothyroidism: 7% • Headache: 4% • Polydipsia/polyuria: 3% • Hypogonadism: 0% • Visual disturbances: 0%
Pituitary hormone abnormalities at presentation *	• ACTH deficiency: 95% • TSH deficiency: 85% • FSH/LH deficiency: 75% • GH decreased: 27% • Hyperprolactinemia: 7%	ACTH deficiency: 97% Hyperprolactinemia: 20% FSH/LH deficiency: 13% TSH deficiency: 4% GH decreased: 3%

*

	ADH deficiency: 2%	ADH deficiency: 3%
Prevalence of hyponatremia at presentation **	39% of cases	62% of cases
Abnormal MRI at presentation	81% of cases	18% of cases
Discontinuation of the immune checkpoint inhibitor	No: 56% Yes, temporarily: 3% Yes, permanently: 41%	No: 70% Yes, temporarily: 20% Yes, permanently: 10%
Outcome	Long-term hypopituitarism: 89% Pituitary function recovery after treatment: 5% Spontaneous resolution: 1% Death: 5% Recurrence after treatment: 0%	Long-term hypopituitarism: 90% Pituitary function recovery after treatment: 6% Spontaneous resolution: 0% Death: 4% Recurrence after treatment: 0%

Pituitary hormone deficiencies can be isolated or combined (especially in the case of anti-CTLA-4 antibody-induced hypophysitis). ACTH + TSH deficiency is the most frequent combination observed in these patients.
** Most likely related to cortisol deficiency. It can be a clue to the diagnosis.
Abbreviations: ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; CTLA-4, cytotoxic T lymphocyte antigen-4; FSH, follicle-stimulating hormone; LH, luteinizing hormone; GH, growth hormone; MRI, magnetic resonance imaging; PD1, programmed death 1; PD1-L1, programmed death 1 Ligand 1; TSH, thyroid-stimulating hormone.

According to the degree of symptoms and of the severity of the disease, immune checkpoint-induced hypophysitis is graded 1 to 4 (Table 11) (78). Grade 3 toxicity or worse (including death) has been described in 2-10% of reported hypophysitis cases (137,138).

Table 11. Grading of Immune Checkpoint Inhibitor-Induced Hypophysitis

Grade	Description
Grade 1	Asymptomatic or mild symptoms.
Grade 2	Moderate symptoms, able to perform ADL.
Grade 3	Severe symptoms, medically significant consequences, unable to perform ADL.
Grade 4	Severe symptoms, life-threatening consequences, unable to perform ADL.
Grade 5	Death.

Abbreviations: ADL, activities of daily living.

Diagnosis and Management

An algorithm for diagnosis and management of immune checkpoint-induced hypophysitis in line with the more recent literature is shown in Figure 6. Patients should be regularly monitored with clinical assessment and hormonal tests during treatment with immune checkpoint inhibitors. Almost invariably, patients who develop hypophysitis have ACTH deficiency and cases of fatal acute adrenal insufficiency have been reported (139); this highlights the importance of pituitary function assessment at

baseline and during treatment, also in asymptomatic patients (140). If there is a strong suspicion of adrenal insufficiency on clinical grounds (e.g. G3-G4 symptoms), glucocorticoid replacement should be started without delay (141). TSH deficiency is also very common (>60% of patients). Indeed, a fall in serum TSH and free T4 have been suggested to be early signs of immune checkpoint inhibitor-induced hypophysitis and can be a clue to the diagnosis (141-144). A recent paper has identified antibodies against two autoantigens (anti-GNAL and anti-ITM2B) that may aid in the diagnosis of and predict the risk of developing immune checkpoint-induced hypophysitis (145). Moreover, Kobayashi *et al*. evaluated the usefulness of pituitary antibodies and human leukocyte antigen alleles in predicting immune checkpoint-induced pituitary dysfunction. The authors showed distinct and overlapped patterns of pituitary antibodies and human leukocyte antigen alleles between patients who developed hypophysitis (n=5) or isolated ACTH deficiency (n=17) (117). The usefulness of anti-GNAL and anti-ITM2B antibodies, pituitary antibodies, and human leukocyte antigen alleles as biomarkers in the clinical setting needs to be validated in larger cohorts of patients.

Patients with suspected drug-induce hypophysitis should undergo a pituitary MRI and visual assessment (141,146). The importance of obtaining pituitary imaging was recently highlighted in a retrospective study by Nguyen *et al.*, where 33% of hypophysitis cases would have been missed if no MRI were carried out (143). Also, pituitary MRI is important for the differential diagnosis of other pituitary lesions, in particular metastases (Table 12). Faje *et al.* reported that ~50% of patients with immune checkpoint-induced hypophysitis presented with diffuse pituitary enlargement at MRI before the onset of clinical symptoms (98). ^{18}F-FDG PET performed as part of the staging of the underlying malignancy can show intense radiotracer uptake and may precede clinical symptoms and biochemical abnormalities (147,148); however, its routine use for the diagnosis of hypophysitis is not recommended.

Current guidelines on the management of immune-checkpoint induced hypophysitis suggest clinicians to consider with holding treatment in G1-G2 hypophysitis until the patient is stabilized on hormone replacement (101). We believe that patients with immune checkpoint inhibitor-induced hypophysitis should <u>not</u> stop treatment unless they develop severe and progressive symptoms (G3-G4 hypophysitis). In fact, this type of hypophysitis if often self-limiting and most of patients do not show progression of sella compression. Therefore, the decision whether to withhold a treatment that can have a significant impact on the progression-free survival of the underlying malignancy should be balanced carefully. When G3-G4 hypophysitis is suspected, a course of high-dose corticosteroids given during the acute phase may result in inflammation reversal and ameliorate the compression of sella and parasellar structures. Whether high-dose glucocorticoids have an impact on the anti-tumor effect of immune checkpoint inhibitors is uncertain. Earlier evidence suggested a neutral effect on survival (99,149,150); however, a study from Faje *et al*. questioned this, showing reduced survival among patients with melanoma treated with high-doses glucocorticoids for Ipilimumab-induced hypophysitis (100,126). Nonetheless, <u>treatment should not be delayed in patients with severe symptoms of sella compression</u>.

The resolution of the neuroradiological abnormalities is usually observed within 2 months (128,130). Treatment with high-dose glucocorticoids, however, does not restore ACTH deficiency and most patients will require long-term replacement (Table 10) (5,123). On the other hand, thyroid and gonadal deficiencies often recover and the need for hormone replacement needs to be reassessed in the long term (123,124,143,151,152). In addition, patients developing irAEs can be severely ill and can present with a “euthyroid sick syndrome” and/or a “sick eugonadal syndrome” that can affect the interpretation of the laboratory results (130).

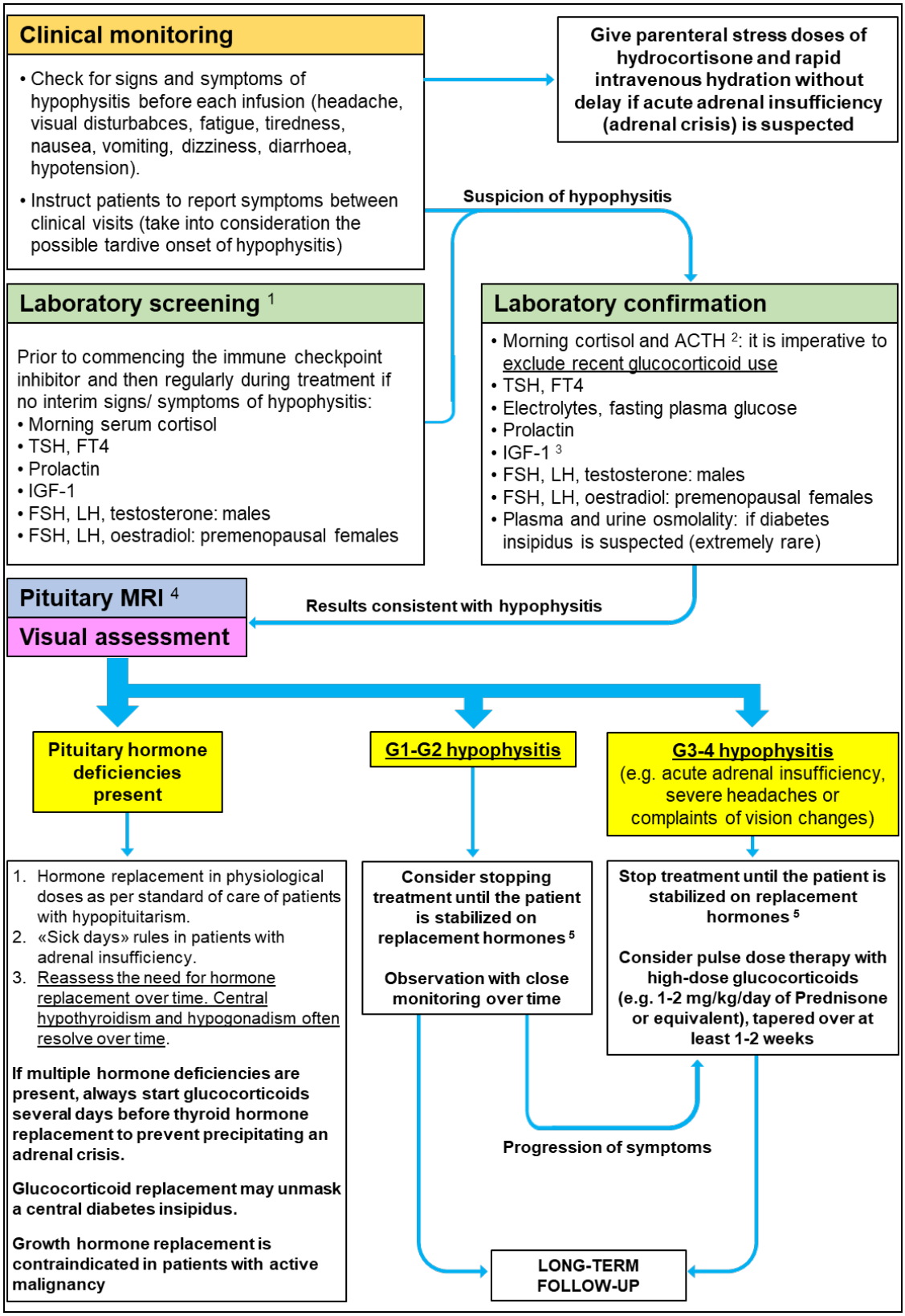
Clinical monitoring
• Check for signs and symptoms of hypophysitis before each infusion (headache, visual disturbabces, fatigue, tiredness, nausea, vomiting, dizziness, diarrhoea, hypotension).
• Instruct patients to report symptoms between clinical visits (take into consideration the possible tardive onset of hypophysitis)
Give parenteral stress doses of hydrocortisone and rapid intravenous hydration without delay if acute adrenal insufficiency (adrenal crisis) is suspected
Suspicion of hypophysitis
Laboratory screening 1
Prior to commencing the immune checkpoint inhibitor and then regularly during treatment if no interim signs/ symptoms of hypophysitis:
• Morning serum cortisol
• TSH, FT4
• Prolactin
• IGF-1
• FSH, LH, testosterone: males
• FSH, LH, oestradiol: premenopausal females
Laboratory confirmation
• Morning cortisol and ACTH 2: it is imperative to exclude recent glucocorticoid use
• TSH, FT4
• Electrolytes, fasting plasma glucose
• Prolactin
• IGF-1 3
• FSH, LH, testosterone: males
• FSH, LH, oestradiol: premenopausal females
• Plasma and urine osmolality: if diabetes insipidus is suspected (extremely rare)
Pituitary MRI 4
Visual assessment
Results consistent with hypophysitis
Pituitary hormone deficiencies present
G1-G2 hypophysitis
G3-4 hypophysitis
(e.g. acute adrenal insufficiency, severe headaches or complaints of vision changes)
1. Hormone replacement in physiological doses as per standard of care of patients with hypopituitarism.
2. «Sick days» rules in patients with adrenal insufficiency.
3. Reassess the need for hormone replacement over time. Central hypothyroidism and hypogonadism often resolve over time.
If multiple hormone deficiencies are present, always start glucocorticoids several days before thyroid hormone replacement to prevent precipitating an adrenal crisis.
Glucocorticoid replacement may unmask a central diabetes insipidus.
Growth hormone replacement is contraindicated in patients with active malignancy
Consider stopping treatment until the patient is stabilized on replacement hormones 5
Observation with close monitoring over time
Stop treatment until the patient is stabilized on replacement hormones 5
Consider pulse dose therapy with high-dose glucocorticoids (e.g. 1-2 mg/kg/day of Prednisone or equivalent), tapered over at least 1-2 weeks
Progression of symptoms
LONG-TERM FOLLOW-UP

Figure 6. Diagnosis and Management of Immune Checkpoint Inhibitor-Induced Hypophysitis. [1] Some authors suggest laboratory evaluation before the first infusion, then at 8 weeks for patients receiving Ipilimumab (i.e., prior to cycle 3) and then at week 16 if there are no interim signs/symptoms suggestive of hypophysitis. Other authors recommend laboratory evaluation for hypophysitis prior to each infusion of immune checkpoint inhibitors in the first 12-16 weeks of treatment, in order to pick up early or late onset of the disease. [2] Check random ACTH and cortisol if acute adrenal insufficiency is suspected. Exclude recent glucocorticoid use and concomitant treatment that may alter serum cortisol measurement (e.g., oral estrogens). As a guide, in patients that are unwell serum cortisol >450 nmol/L makes the diagnosis of adrenal insufficiency unlikely. Adrenal insufficiency is possible if morning cortisol 200-450 nmol/L or random cortisol 100-450 nmol/L; consider confirmatory testing with Synacthen, although this can give false-positive results in the early stages of central adrenal insufficiency. Adrenal insufficiency is likely if morning cortisol <200 nmol/L or random cortisol <100 nmol/L and patients should be started on hormone replacement. These cut-offs should be seen only as a guide and need to be adapted to local laboratory assays and reference ranges. Patients receiving immune checkpoint inhibitors can also develop adrenalitis and primary adrenal insufficiency. These patients have high ACTH and renin/aldosterone should be measured to investigate mineralocorticoid deficiency. [3] IGF-1 is valuable to confirm changes from baseline that may suggest new-onset hypophysitis. However, further tests to prove GH deficiency are not required because these patients would not be treated (active malignancy). [4] Pituitary MRI is normal in ~20% and ~80% of hypophysitis cases associated with anti-CTLA-4 and anti-PD1/PD1-L1 antibodies, respectively. Therefore, normal imaging does not exclude hypophysitis. MRI changes can be very subtle (Table 11). [5] We believe that patients with immune checkpoint inhibitor-induced hypophysitis should not stop treatment unless they develop severe and progressive symptoms (G3-G4 hypophysitis). Once the acute symptoms of hypophysitis have resolved, restarting treatment with immune checkpoint inhibitors is not contraindicated. Adequately treated, long-term hypopituitarism is not a contraindication to restarting immune checkpoint inhibitors.

An important differential diagnosis in patients with suspected drug-induced hypophysitis and a sella mass are pituitary metastases (Table 12) (95,141,153-155). The early studies on immune checkpoint inhibitors mainly assessed their efficacy in patients with advanced melanoma. Pituitary metastases are rare in melanoma (~2.5% of pituitary metastasis cases reported in the literature); however, these drugs are increasingly used for other malignancies including lung cancer, which accounts for ~25% of pituitary metastases (153). Central diabetes insipidus in immune checkpoint inhibitor-induced hypophysitis is extremely rare; therefore, a sella mass associated with diabetes insipidus is strongly suggestive of a metastasis.

Table 12. Differential Diagnosis of Immune Checkpoint Inhibitor-Induced Hypophysitis and Pituitary Metastases		
Characteristics	**Immune checkpoint inhibitor-induced hypophysitis**	**Pituitary Metastases**
Clinical presentation	Central diabetes insipidus is extremely rare; Anterior pituitary insufficiency is very common (chiefly ACTH, FSH/LH and TSH deficiency). Headache is a frequent presenting symptom.	Central diabetes insipidus is the most common hormonal abnormality (~45%); Cranial nerve deficits due to involvement of the chiasm and the cavernous sinus are common (22-28%); Anterior pituitary insufficiency has been described in ~24% of patients; Headache and retro-orbital pain have been reported in ~16% of patients;
Imaging	MRI: Mild-to-moderate diffuse enlargement of the pituitary (up to 60-100% of the baseline size). Pituitary height typically does not exceed 2 cm. Pituitary enlargement resolves in most cases over the course of weeks/months. Empty sella can develop in the long term. Extension into the cavernous sinus or above the sellar diaphragm is uncommon. Homogeneous (more frequent) or heterogeneous enhancement (less frequent) post-gadolinium; Suprasellar extension with compression and displacement of chiasm is uncommon; The pituitary stalk may be thickened but not deviated; The posterior pituitary is preserved in most of cases.	MRI: Sella or suprasellar mass; Isointense or hypointense mass on T1WI, with a usually high-intensity sign on T2WI; Homogeneous enhancement post-gadolinium, although hemorrhage, necrosis and areas of cystic degeneration can be observed; Thickened and enhancing pituitary stalk is possible, but it is typically less common than immune checkpoint inhibitor-induced hypophysitis; Presence of other brain metastases (~15%); Invasion of the cavernous sinus, chiasm, or hypothalamus (~14%) Loss of bright spot of the neurohypophysis (~13%); Dumbbell-shaped mass (~11%); Sphenoid sinus invasion (~9%); CT: may show bony destruction.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; T1WI, T1 weighted images; T2WI, T2 weighted images.

DRUG-INDUCED HYPOPHYSITIS: OTHER DRUGS

Reversible or irreversible hypopituitarism may be a rare side effect following treatment with interferon-α, and interferon-α/ribavirin combination therapy has been associated with cases of granulomatous hypophysitis with anterior pituitary dysfunction (156-160). The anti-interleukin-12 and -23 monoclonal antibody ustekinumab (used in the treatment of psoriasis) has been associated with a case of hypophysitis with panhypopituitarism (161).

HYPOPHYSITIS SECONDARY TO SELLA AND PARASELLAR DISEASE

Pituitary inflammation can be triggered by sella and parasellar disease. The infiltrate is mainly lymphocytic or xanthogranulomatous and focuses around the lesion rather than diffusing to the entire gland (4).

Germinoma

Germinomas are rare brain tumors predominantly affecting prepubertal children. They are highly immunogenic tumors and can induce a strong immune response that can involve the pituitary leading to secondary hypophysitis (162-169). Histologically, lymphocytic or granulomatous hypophysitis is seen in ~80% and ~20% of cases linked to germinomas, respectively (169).

Germinomas arising in the sella and parasellar region are difficult to differentiate from hypophysitis in children because of similar clinical features (diabetes insipidus + GH deficiency + visual disturbances). This differentiation, nevertheless, is critical for patient care due to different treatments of the two diseases. Biopsy-proven cases of primary hypophysitis are extremely rare in children and adolescents (41); therefore, in children below 10 years a germinoma should be considered the most likely diagnosis.

Tumor markers such as α-fetoprotein, β-human chorionic gonadotropin, or placental alkaline phosphatase in the cerebrospinal fluid may be useful for diagnosing germinoma. However, a pituitary biopsy is the gold standard for differentiating the two conditions, although germinomas can have a marked lymphocytic infiltrate that can outnumber the neoplastic cells making differential diagnosis difficult (168). If germinoma is part of the histologic differential diagnosis, markers for germinomas such as Oct3/4, PLAP and NANOG may be useful.

Finally, it should be noted that the hypopituitarism caused by sella germinomas can precede for years a visible pituitary mass, so that prolonged symptomatic periods prior to diagnosis are common (168).

Rathke's Cleft Cyst

The rupture of Rathke's cleft cyst can cause hypophysitis associated with visual disturbances, headache and hypopituitarism including – very frequently – central diabetes insipidus (170-175). Histopathology can show lymphocytic, granulomatous, xanthomatous or mixed forms of hypophysitis (174). Some authors have suggested that many cases of xanthomatous hypophysitis may actually be related to rupture of Rathke's cleft cysts (12,13).

Other Sella and Parasellar Masses

Cases of secondary hypophysitis have been described in association with craniopharyngiomas (176), pituitary adenomas (177-182) and primary pituitary lymphomas (177,183).

HYPOPHYSITIS SECONDARY TO SYSTEMIC DISEASE

Sarcoidosis

Sarcoidosis is a multisystem inflammatory disease of unknown origin characterized by the formation of non-caseating granulomas that can involve all organ systems. The central nervous system can be affected in 5-15% of patients (neurosarcoidosis) and may be the presenting feature of the disease (184). Granulomas can involve the pituitary, hypothalamus and the stalk in ~0.5% of patients with sarcoidosis, resulting in varying grade of hypopituitarism (185,186). ~60% of the cases reported in the literature are males presenting in the 3rd and 4th decade. Central diabetes insipidus, FSH/LH deficiency and hyperprolactinemia are among the most frequent hormone abnormalities (187). Patients with sarcoidosis and hypothalamic-pituitary involvement tend to have more frequent multi-

organ involvement, as well as neurosarcoidosis and sinonasal involvement (187).

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (previously known as Wegener's Granulomatosis) is an antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis of unknown etiology with multisystem involvement and formation of necrotizing granulomas and vasculitis in small- and medium-sized blood vessels. Pituitary involvement is a rare and usually late manifestation of the disease (186,188,189), but it can also be the presenting complaint (190,191). Secondary hypogonadism and central diabetes insipidus are the most common endocrine abnormalities; diabetes insipidus can recover after adequate treatment of the underlying vasculitis, while anterior pituitary dysfunction is permanent in the majority of patients (192).

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis is a rare disease mainly occurring in childhood, involving clonal proliferation of myeloid Langerhans cells that can infiltrate multiple organs (bones, skin, lymph nodes, lungs, thymus, liver, spleen, bone marrow, and central nervous system including the pituitary). Patients often carry the *BRAF* V600E mutation in the clonal myeloid cells (193).

The most common endocrine abnormality in patients with Langerhans cell histiocytosis is hypothalamic-pituitary infiltration causing central diabetes insipidus. These patients usually have multi-organ and cranio-facial involvement, although localized disease of the hypothalamic-pituitary region has been reported (194,195). Up to 40% of patients develop symptoms consistent with diabetes insipidus within the first four years, particularly if there is multisystem involvement and proptosis (196-198). Anterior pituitary hormone deficiency is also possible at diagnosis and during follow up (194,199).

Langerhans cell histiocytosis and germinoma are the most common cause of central diabetes insipidus in children and adolescents; therefore, germinoma should always been considered in the differential diagnosis (200).

The definitive diagnosis of Langerhans cell histiocytosis is the biopsy-proven infiltration of the pituitary with Langerhans cells with eosinophils, neutrophils, small lymphocytes, and histiocytes. However, pituitary biopsy is invasive and the diagnosis can be suggested by the presence of the characteristic histopathologic features in other tissues when a multisystem disease is present. For patients with suspected disease isolated to the pituitary, identification of *BRAF-V600E* in the peripheral blood or cerebrospinal fluid can support the diagnosis and rule out germinoma, although it does not distinguish Langerhans cell histiocytosis from Erdheim-Chester disease (see below) (201).

When hypophysitis secondary to Langerhans cell histiocytosis is suspected but pituitary biopsy is not available, it is reasonable to initiate therapy empirically with a plan to follow disease response with MRI. Treatment options include prednisone, alone or in combination with vinblastine, cladribine and vemurafenib, alongside desmopressin and other pituitary hormone replacements to treat hypopituitarism.

Erdheim-Chester Disease

Erdheim-Chester's disease is a rare multisystem histiocytic disorder, most often seen in adults, which may be confused with Langerhans cell histiocytosis. Histiocytic infiltration leads to xanthogranulomatous infiltrates of multiple tissues (bones, skin, lungs, facial, orbital and retro-orbital tissue, retroperitoneum, cardiovascular system and cerebral nervous system including the pituitary). Long bone pain and symmetric osteosclerotic lesions suggest this diagnosis, which is confirmed by tissue biopsies showing histiocytes with

non-Langerhans features. Patients often carry the *BRAF* V600E mutation in the clonal myeloid progenitor cells (193).

Pituitary involvement may manifest as central diabetes insipidus and anterior hypopituitarism, which typically persist even with radiographic regression of the disease. As for Langerhans cell histiocytosis, the definitive diagnosis of Erdheim-Chester's disease is the finding of the typical histologic features at pituitary biopsy, which can be supported by the finding of the *BRAF* V600E mutation. Treatment options include vemurafenib, interferon-α, dabrafenib, trametinib, cobimetinib, cladribine, cyclophosphamide and glucocorticoids.

Rosai-Dorfman Disease

Pituitary involvement has been described in Rosai-Dorfman disease, a rare histiocytic disorder. Patients may have both anterior pituitary dysfunction, central diabetes insipidus and visual disturbances (202,203).

Inflammatory Pseudotumor

The inflammatory pseudotumor is a rare inflammatory disorder commonly involving the lung and orbit. It can be isolated or associated with the IgG4-related disease (204). Pituitary infiltration is a rare manifestation and patients can present with anterior and posterior hypopituitarism. The inflammatory pseudotumor can also spread to the sphenoid sinus, the cavernous sinus and the optic chiasm (205-207).

Tolosa-Hunt Syndrome

Tolosa-Hunt syndrome is a painful ophthalmoplegia caused by idiopathic retro-orbital inflammation involving the cavernous sinus or the superior orbital fissure. Histology shows nonspecific granulomatous or nongranulomatous inflammation. Patients with pituitary involvement present with anterior and posterior hypopituitarism, diplopia and retro-orbital pain (often unilateral) (208-212).

Other Systemic Diseases

Cases of secondary hypophysitis have been described in association with Takayasu's arteritis (granulomatous hypophysitis) (213), Cogan's syndrome (214) and Crohn's disease (215,216). A case of isolated ACTH deficiency in a patient with Crohn's disease has also been published (217).

OTHER CAUSES OF SECONDARY HYPOPHYSITIS

Thymoma and Other Malignancies (Anti-Pit-1 Antibody Syndrome)

Pit-1 is essential for the differentiation, proliferation, and maintenance of somatotrophs, lactotrophs, and thyrotrophs in the pituitary (218). Yamamoto *et al*. described three cases of acquired combined TSH, GH, and PRL deficiency, with circulating anti-Pit-1 antibodies (219). Cytotoxic T-cells that react against Pit-1 are likely the cause of anti-Pit-1 antibody syndrome (220-222). All these patients later developed thymomas that express Pit-1. Removal of the thymoma resulted in a decline in antibody titer, suggesting that aberrant expression of Pit-1 in the thymoma plays a causal role in the development of this syndrome (223). A handful of cases of anti-Pit-1 antibody syndrome not associated with thymoma have since been published. The malignancies causing this paraneoplastic syndrome included diffuse large B-cell lymphoma of the bladder and a metastatic cancer of unknown origin (222,224). Based on these cases, Yamamoto *et al*. have proposed diagnostic criteria for anti-PIT-1 hypophysitis (Table 13).

Table 13. Diagnostic Criteria for Anti-PIT-1 Hypophysitis			
Criteria		**Probable diagnosis**	**Established diagnosis**
Criterion 1	Acquired specific GH, PRL, and TSH deficiency. *	**CRITERION 1**	**CRITERION 1** and **CRITERION 2**
Criterion 2	Presence of anti-PIT-1 antibody or PIT-1-reactive T cells in the circulation.		
Criterion 3	Coexistence of thymoma or malignant neoplasm. **		

* The secretion of other pituitary hormones is not impaired. The MRI of the pituitary is typically normal, but a slight atrophy of the anterior pituitary can be observed.

** Criterion 3 may help the diagnosis and clarify pathogenesis but may not be necessarily obvious at the time of diagnosis.

Infections

Infections of the pituitary are a rare cause of hypophysitis and hypopituitarism (225). They can affect either exclusively the pituitary area or as a part of disseminated infections. Risk factors are diabetes mellitus, organ transplantation, human immunodeficiency virus infection, non-Hodgkin lymphoma, chemotherapy, and Cushing's syndrome. They can occur by (186):

- Hematogenous spread in immuno-compromised hosts;
- Contiguous extension from adjacent anatomical sites (meninges, sphenoid sinus, cavernous sinus and skull base);
- Previous infectious diseases of the CNS of different etiologies;
- Iatrogenic inoculation during trans-sphenoidal surgery.

However, in the majority of cases of pituitary abscess an obvious cause cannot be identified.

Tuberculosis can cause granulomatous involvement of the hypothalamus, the pituitary or the stalk. Tubercular meningitis and hypothalamic-pituitary involvement seem to affect mostly anterior pituitary function (226).

Several viruses can cause meningitis, meningoencephalitis and encephalitis that can involve the hypothalamic-pituitary region. Partial or complete hypopituitarism may develop as a result (186). A study by Leow *et al*. has shown that ~40% of patients with severe acute respiratory syndrome (SARS)-associated with *Coronavirus* infection can develop reversible central adrenal insufficiency, suggesting a possible inflammation of the pituitary in these patients (227). *Hantavirus* can also cause viral hypophysitis with pituitary ischemia and hemorrhage as part of the hemorrhagic fever with renal syndrome (HFRS), leading to partial or complete hypopituitarism, including diabetes insipidus (186,228,229).

Mycoses with hypothalamic-pituitary involvement are extremely rare. Patients frequently present with central diabetes insipidus and anterior pituitary dysfunction (mainly FSH/LH deficiency and hyperprolactinemia) (186).

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