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New Molecular, Biological, and Immunological Agents Inducing Hypophysitis

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Abstract
Hypophysitis is a relatively rare disease that exerts a strong autoimmune component encompassing different etiologies. Immunomodulatory drugs, such as interferon-α, are known to rarely induce hypophysitis. In recent years, a large number of new biological and immunomodulatory agents have been introduced into clinical practice. Although immune-suppressing agents used for the treatment of autoimmune disorders only rarely are associated with hypophysitis, it is commonly encountered with immunomodulatory agents used for the treatment of cancer. Hypophysitis related to anti-cytotoxic T-lymphocyte-associated antigen-4 antibodies (anti-CTLA-4 Abs) occurs with a prevalence ranging from 0 to 18% and is considered a distinctive side effect of anti-CTLA-4 Abs treatment. Hypophysitis due to the programmed cell death protein-1 antibodies and their ligand is less common, its frequency ranging from 0 to 0.8%. No cases of hypophysitis have been described with molecular targeted agents. Diagnosis of hypophysitis still remains clinical since anti-pituitary antibodies are not a sensitive marker and thus its true prevalence is probably underestimated. The pathophysiology of hypophysitis induced by anticancer agents is not fully clarified. In most cases, treatment requires dose adjustment of the offending drug and pituitary hormone replacement. This mini-review aims to present currently available information regarding hypophysitis related to new molecular, biological, and immunological agents.

Introduction

Hypophysitis is an inflammatory process of the pituitary gland that can be classified according to the anatomical areas of involvement (adenohypophysitis, infundibuloneurohypophysitis, or panhypophysitis) and/or its etiology (primary and secondary) (Table 1). The primary forms develop from intrinsic pathology of the pituitary gland, whereas the secondary ones are related to systemic diseases, infective processes, and/or pharmacological agents [1]. Histopathologically, primary hypophysitis is divided into 5 types: lymphocytic hypophysitis (LYH), granulomatous, xanthomatous, necrotizing, and IgG4 plasmacytic hypophysitis [2] (Table 1).

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Table 1. Pathological classification of hypophysitis

Types of hypophysitis
Primary
Lymphocytic
Granulomatous
Xanthomatous
IgG4-related
Necrotizing
Mixed forms
Secondary
Inflammatory
Sarcoidosis
Wegener granulomatosis vasculitis
Langerhans cell histiocytosis
Infectious
Tuberculosis
Syphilis
Fungi
Infiltrative
Hemochromatosis
Amyloidosis
Histiocytosis
Immunomodulatory drugs

The prevalence of primary hypophysitis is approximately 0.2–0.88% with an annual incidence of 1/9,000,000 [2]. LYH constitutes 71.8% of all causes of primary hypophysitis [3, 4], and although it was thought to be strongly related to pregnancy [5, 6], it is also encountered in men and women having no relationship to pregnancy [7–9]. The diagnosis is confirmed by histopathology and detection of pituitary antibodies (Abs) in patients with isolated or multiple pituitary hormone deficiencies [4]. However, in most cases diagnosis is usually based on endocrinological and radiological findings in the relevant clinical setting [10, 11].

There has been some evidence in the past that medications affecting the immune system, such as interferon-α and interleukin, could lead to the development of hypophysitis [12, 13]. Recent advances in the understanding of immunology and cancer biology have led to the development of new classes of immunomodulatory agents used for the treatment of autoimmune and malignant diseases. It is increasingly being recognized that new immune checkpoint therapies that inhibit the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and/or the programmed cell death protein-1 (PD-1) or its ligand (PD-L1) can induce hypophysitis [14–17]. Indeed, the National Cancer Institute has recommended a toxicity grading of adverse events including hypophysitis for patients treated with these agents (Table 2).

In this mini-review, we will provide information on currently used biological, molecular, and immunological agents that can lead to the development of hypophysitis in respect to its prevalence, presentation, and natural history, and explore the underlying pathogenic mechanism.

Prevalence of Hypophysitis Related to Immunomodulatory and Anti-Inflammatory Agents Used for the Treatment of Autoimmune Diseases

Adverse effects on endocrine organs have already been reported with the use of older immunomodulatory agents such as interferon-α and interleukins. Although interleukin-2 and interferon-α have well-described effects on thyroid autoimmunity and function [12], only relatively few cases of hypophysitis have been described in patients treated with either interferon alone [12, 13] or in association with ribavirin [12, 13, 18–20]. In the great majority of these cases, the symptoms and/or hormonal deficits of hypophysitis improved after immunotherapy interruption [18–20]. Cases of hypophysitis have also been reported with the more recent immunomodulatory agents used for the treatment of a number of autoimmune disorders, such as the anti-tumor necrosis factor alpha agent infliximab [21] and the monoclonal Ab rituximab [22] (against protein CD20, which is primarily found on the surface of immune system B cells) used for the treatment of a number of autoimmune diseases.

Prevalence of Hypophysitis with Immune Checkpoint Inhibitors Used for Cancer Therapy

Current immune checkpoint inhibitor therapies are based on stimulation of the negative immunoregulatory receptors on T-cell surface to enhance the host immunity against tumor cells. Immune checkpoint inhibitors are a new and effective class of cancer therapy, with a well-described mechanism of action (Fig. 1, 2).

Anti-Cytotoxic T-Lymphocyte-Associated Antigen-4 Abs

Ipilimumab and tremelimumab are monoclonal IgG1 and IgG2 Abs respectively, directed against CTLA-4, a receptor expressed on T cells that exerts a suppressive effect on the immune response after T-cell/antigen-presenting cell interaction [23, 24]. A number of studies have

Table 2. Common terminology criteria for adverse events (CTCAE) grading system

	Grade 1	Grade 2	Grade 3
Pituitary	Asymptomatic or mild symptoms	Moderate	Severe or medically significant but not immediately life-threatening
Management	Clinical or diagnostic observations only; intervention not indicated	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self

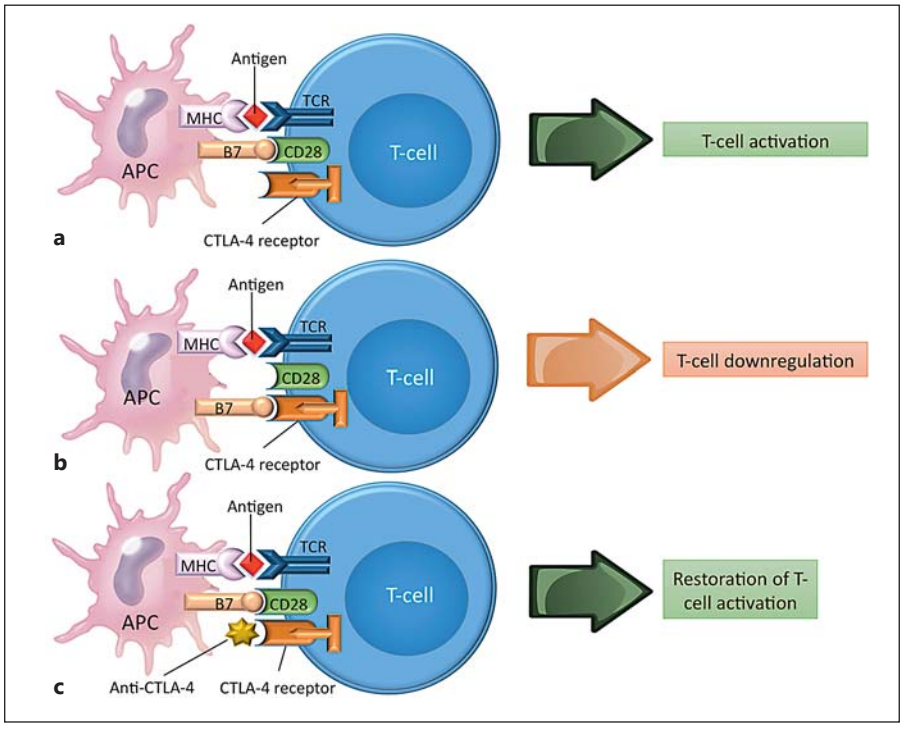

Fig. 1. Immune checkpoint inhibitors, the CTLA-4 pathway. **a** The tumor-associated antigen is presented by the major histocompatibility complex (MHC) on the antigen-presenting cell (APC) and recognized by the T-cell receptor (TCR) of the T cell. Binding B7 on the APC cell with the CD28 receptor on the T cell is the second signal required for the activation of the T-cell and the initiation of the immune response against the tumor cells. **b** CTLA-4 (cytotoxic T-lymphocyte-associated antigen-4) is a homolog of CD28 and limits proliferative response of activated T-cell competing with CD28 for ligand B7. This inhibition occurs in response to binding of B7 on APC with CTLA-4 receptor on the T cell and interrupts the second signal. **c** Anti-CTLA-4 antibodies block CTLA-4 and restore T-cell activation and proliferation.

reported an approximately 1.5–18% prevalence of hypophysitis in patients treated with ipilimumab [25–37] and a 0.4–2% with tremelimumab [38–40]; however, this prevalence varied largely among different studies. This is mainly due to the fact that although in the approved protocol the dose of ipilimumab is 3 mg/kg administered as an i.v. infusion every 3 weeks for a total of 4 doses, in some patients, maintenance therapy may continue with additional infusions at longer time intervals [41]. Additionally, the follow-up of the different studies ranged from few months [41] up to several years [31]. In a recent meta-analysis, it was concluded that hypophysitis due to monotherapy with ipilimumab or tremelimumab is encountered in 2.6% of cases [42].

In contrast to conventional LYH that is reported more commonly in females, ipilimumab-related autoimmune hypophysitis is more common in males [16, 28, 29]. Most patients developed hypophysitis after having received a 3 mg/kg dose of ipilimumab and became symptomatic approximately 11 weeks after treatment [43]. Although the risk of other endocrine-related adverts events, such as thyroid diseases, after taking ipilimumab appears to be dose-dependent [31, 32, 44], in the case of hypophysitis, data are less clear. According to recent studies, higher dosages of ipilimumab (10 vs. 3 mg/kg), may increase the risk of hypophysitis [16, 27, 32]. However, in most protocols ipilimumab dosages were escalated rapidly, and hypophysitis typically occurred after several cycles of treatment regardless of the dose administered [32]. Thus, in

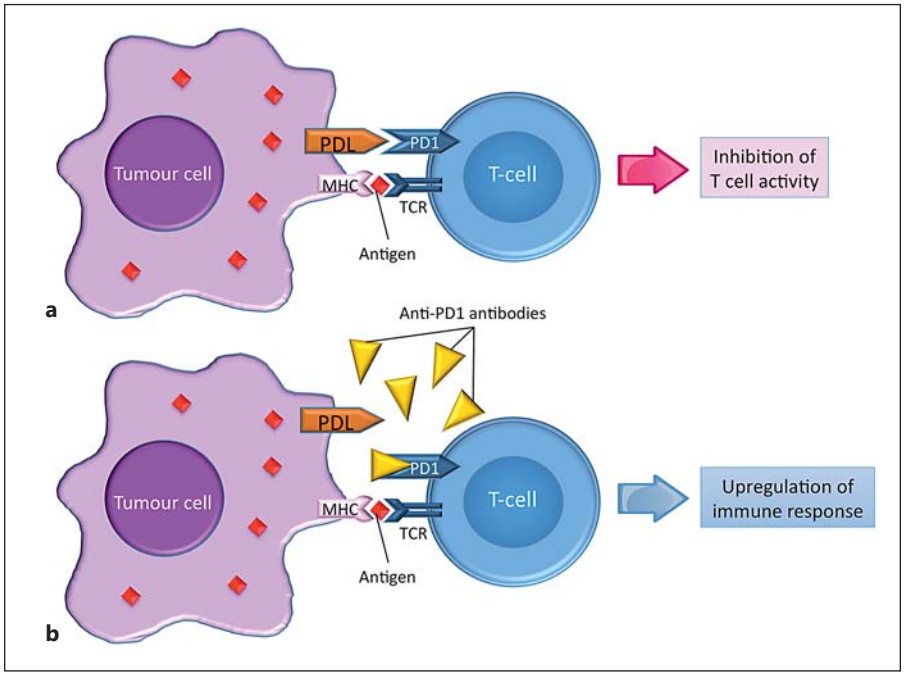

Fig. 2. Immune checkpoint inhibitors, the PD-1 pathway. PD-1 is an immune cell-specific surface receptor, and ligands for PD-1 (PD-L1 and PD-L2) are associated proteins that are found on antigen-presenting cells and cancer cells. When bound to a ligand, PD-1 lowers the threshold for apoptosis, induces anergy via blunted T cell receptor signaling and generally leads to T cell depletion. **a** In certain tumor cells, upregulation of PD-L1 expression has been observed, which leads to increased inhibition of T cell activity in favor of tumor cell survival. **b** A monoclonal antibody against PD-1 can block this pathway and result in upregulation of immune response and inhibition of tumor growth.

contrast to previous analyses and trials showing that anti-CTLA-4-induced hypophysitis may be dose related, a recent meta-analysis found no dose-effect relationship following ipilimumab administration and any of the endocrine-related side effects including hypophysitis [15].

Interestingly, hypophysitis was not reported in patients treated with ipilimumab who had been pre-treated with chemotherapy or radiotherapy, suggesting that the immune cell depletion induced by these treatments may have prevented the development of hypophysitis [16].

Anti-Programmed Cell Death Protein-1 Abs and Their Ligand

Nivolumumab and pembrolizumab are IgG4 Abs against the PD-1 protein that have demonstrated efficacy in patients with advanced melanoma, renal cell carcinoma, and non-small lung cancer [24, 45]. The prevalence of hypophysitis is relatively lower, less than 1%, with these agents compared to anti-cytotoxic T-lymphocyte-associated antigen-4 Abs (anti-CTLA-4 Abs) (Table 3) [45–52]. Two meta-analyses confirmed these results and concluded that the overall prevalence of anti-programmed cell death protein-1 Abs (anti-PD-1 Abs)-induced hypophysitis ranges between 0.2 and 0.8% [14, 53].

The time of onset of nivolumab-induced hypophysitis was 5.5 months (range: 1.6–11 months) and of pembrolizumab 3.3–3.7 months (range: 1 day to 7.2 months) [14, 53]. Up to date, no cases of pituitary dysfunction have been reported in trials evaluating atezolizumab [54], an IgG1 anti-PD-L1 monoclonal Ab in patients treated for cancer, as well as with BMS-936559 another anti-PD-L1 Ab used as antiretroviral treatment in HIV patients [55].

Comparison of Monotherapy with Anti-CTLA-4 versus Anti-PD-1 Abs and of Either Immune Checkpoint Inhibitor with Chemotherapy

A recent study comparing pembrolizumab versus ipilimumab in patients with advanced melanoma showed a higher prevalence of hypophysitis in the ipilimumab-treated patients, whereas the prevalence of other endocrinopathies such as hypothyroidism and hyperthyroidism was higher in the pembrolizumab-treated patients [49]. According to a meta-analysis, monotherapy with anti-PD-1 (nivolumab or pembrolizumab) exhibited an even lower risk for hypophysitis (RR = 0.148 [95% CI: 0.04–0.5]) compared to ipilimumab [14].

In one study, monotherapy with pembrolizumab was associated with hypophysitis in 0.4% of the cases and only in those who received a 10 mg/kg dose, whereas no case was described in the chemotherapy group [46]. In another trial, monotherapy with pembrolizumab at any dose (either with 2 or 10 mg/kg) did not show an increased risk for hypophysitis (<1%) when compared with docetaxel [47]. Monotherapy with tremelimumab was associated with hypophysitis in 1.8% of cases compared to none in the chemotherapy group [39].

Table 3. Prevalence of hypophysitis with immunomodulatory agents anti-CTLA-4 and PD-1

Agents [Ref.]	Type of the study (phase)	Dose of agent	Patients, *n*	Prevalence
Anti-PD-1				
Pembrolizumab vs. chemotherapy[a] [46]	2	2 or 10 mg/kg	540 with ipilimumab-refractory melanoma	0.4% in 10 mg/kg (grade 3, 4)
Pembrolizumab vs. docetaxel [47]	3	2 vs. 10 mg/kg	339 vs. 343 with advanced NSCLC	<1% in both doses
Pembrolizumab [48]	1	2 or 10 mg/kg	173 with ipilimumab-refractory advanced melanoma	0.6% (grade 3, 4) vs. 0%
Pembrolizumab vs. ipilimumab [49]	3	3 vs. 10 mg/kg	555 vs. 256 with advanced melanoma	0.4–0.7% (0.4% grade 3, 4) vs. 2.3% (1.6% grade 3, 4)
Pembrolizumab [50]	3	2 or 10 mg/kg	655 with advanced melanoma ipilimumab refractory or naïve treatment	0.5% (0.15% grade 3, 4)
Pembrolizumab [51]	2	10 mg/kg	41 patients with progressive metastatic carcinoma with or without mismatch-repair deficiency	10% (including also thyroiditis, hypothyroidism)
Nivolumumab [45]	1	0.1–10 mg/kg	296 with advanced melanoma, NSCLC, castration-resistant prostate cancer, or renal-cell or colorectal cancer	<1%
Nivolumumab [52]	1	0.1–1.0 mg/kg	107 with advanced melanoma	1%
Anti-CTLA-4				
Ipilimumab [25]	3	3 mg/kg	131with metastatic melanoma	1.5% (grade 3)
Ipilimumab [26]	Retrospective	3 mg/kg	298 with metastatic melanoma	5.7% (3.3% grade 3,4)
Ipilimumab [27]	3	10 mg/kg	471 with stage III melanoma	18% (5% grade 3,4)
Ipilimumab [28]	Retrospective	3 vs. 10 mg/kg	211 with advanced melanoma	Overall 8% (8 vs. 10%)
Ipilimumab [29]	Retrospective	3 vs. 10 mg/kg	187 with metastatic melanoma	Overall 13.3% (9 vs. 4%)
Ipilimumab [30]	Retrospective	3 vs. 10 mg/kg	154 with metastatic melanoma	Overall 11% (8 vs. 3%)
Ipilimumab [31]	Retrospective	3 vs. 10 mg/kg	131 with advanced melanoma	11.5% (3 vs. 8%)
Ipilimumab [32]	1–2	3–9 mg/kg	46 with metastatic melanoma	Overall 17% (grade 3, 4)
Ipilimumab [33]	2	3 mg/kg	163 with metastatic melanoma and renal cancer	5% (grade 3, 4)
Ipilimumab [34]	2	3 mg/kg	27 with locally advanced or metastatic pancreatic adenocarcinoma	3.7% (grade 3, 4)
Ipilimumab [35]	2	3 mg/kg	61 with metastatic renal cell cancer	3.3% (grade 3, 4)
Ipilimumab [36]	1	3 mg/kg	18 with non-Hodgkin lymphoma	6% (grade 1, 2)
Ipilimumab [37]	2	10 mg/kg	53 with advanced melanoma	4% (grade 2, 3)
Tremelimumab [38]	2	15 mg/kg	251 with advanced refractory or relapsed melanoma	0.4% (0.4% grade 3, 4)
Tremelimumab vs. chemotherapy [39]	3	15 mg/kg	328 with advanced melanoma	2 vs. 0%
Tremelimumab vs. chemotherapy [40]	1	0.01–15 mg/kg	39 with solid tumors	2.5% in 15 mg/kg (grade 2)
Combinations				
Ipilimumab + nivolumumab [44]	1	0.3–10 mg/kg + 1–10 mg/kg	86 with advanced melanoma	Overall: 4% (2% grade 3, 4)
Ipilimumab + nivolumumab [60]	3	3 mg/kg + 3 mg/kg	314 with melanoma	Overall: 7.7% (1.6% grade 3, 4) (nivolumab: 0.6% [0.3% grade 3/4], ipilimumab: 4% [2%, grade 3, 4])

Table 3 (continued)

Agents [Ref.]	Type of the study (phase)	Dose of agent	Patients, *n*	Prevalence
Ipilimumab + nivolumumab [61]	2b	1–3 mg/kg + 3 mg/kg	142 with untreated melanoma	Overall: 12% (2% grade 3, 4)
Ipilimumab + bevacizumab [58]	1	10 mg/kg + 5–7 mg/kg or 15 mg/kg	21 with unresectable stage III or stage IV melanoma	Overall: 14%
Ipilimumab + bevacizumab [59]	1	3 or 10 mg/kg + 7.5 or 15 mg/kg	46 with metastatic melanoma	For all endocrinopathies: 20% (ND for hypophysitis separately)
Ipilimumab + chemotherapy[b] [62]	2b	10 mg/kg + 175 mg/m^2 (paclitaxel) + (AUC 6)	204 with IIIB/IV NSCL	Overall: 0.5% (grade 3, 4)
Ipilimumab + vaccine targeting prostate-specific antigen [56]	1	1–10 mg/kg	31 with prostate cancer	13.3% (grade 2, 3)
Ipilimumab + GVAX [57]	1	0.3 or 1.0 or 3.0 or 5.0 mg/kg + GVAX	32 with metastatic castration-resistant prostate cancer	9% (3 mg/kg), 12.5% (5 mg/kg)
Meta-analysis/systematic reviews				
Anti-CTL-4 or anti-PD-1 monotherapy or association with other agents [16]	Systematic review		705 with melanoma, no Hodgkin lymphoma, renal cancer, pancreatic cancer	Ipilimumab (1–3 mg/kg): 1.8–3.3% (>3 mg/kg): 4.9–17%
Anti-CTLA-4 (ipilimumab or tremelimumab) [42]	Meta-analysis	Ipilimumab: 3 or 5 or 10 mg/kg, tremelimumab: 15 mg/kg	1,265 with melanoma, renal cell, prostate, pancreatic cancer, mesothelioma, colorectal, gastric and esophageal cancer	Overall: 2.6%
Anti-CTL-4 + anti-PD-1 [15]	Meta-analysis		3,728 with melanoma, NSCLC, metastatic castration-resistant prostate cancer	1.8–18.3%
Anti-PD-1 (nivolumab or pembrolizumab) [53]	Meta-analysis		2,330 with metastatic or advanced melanoma, NSCLC, renal cancer	0.47 %
Anti-PD-1 (nivolumab or pembrolizumab) [14]	Meta-analysis		6,578 with melanoma, NSCLC, renal carcinoma	– Overall incidence for nivolumab: 0.5% and for pembrolizumab: 0.4% – Anti-PD-1 vs. ipilimumab alone: RR = 0.148 (95% CI: 0.043–0.5) – Nivolumab + ipilimumab vs. ipilimumab alone: RR = 1.94 (95% CI: 1.7–3.5) – Anti-PD-1 vs. chemotherapy: RR = 2.32 (95% CI: 0.57–9.40)

PD-1, programmed death 1; NSCLC; non-small-cell lung cancer; anti-CTLA-4, anti-cytotoxic T-lymphocyte antigen-4; ND, no data; GVAX, granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells vaccine. [a] Paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine, or oral temozolomide. [b] Paclitaxel and carboplatin.

Association of Immune Checkpoint Inhibitors with Adjuvant Therapies

The prevalence of hypophysitis varied significantly depending on the use of adjuvant therapy [16]. In patients receiving ipilimumab with adjuvant therapy, such as prostate-specific antigen vaccine [56], prostatic cancer cell vaccine (GVAX) [57], or the anti-vascular endothelial growth factor bevacizumab [16, 58, 59], the prevalence of hypophysitis ranged between 9 and 14%. In patients receiving the combination of nivolumab with ipilimumab, the prevalence varied between 4 and 12% [45, 60, 61]. Overall, the combination of nivolumab with ipilimumab exhibited an increased risk for hypophysitis compared to ipilimumab alone (RR = 1.94 [95% CI: 1.7–3.5]) [14]. In contrast, the coadministration of ipilimumab with various chemotherapeutic agents, including Taxol, carboplatin, dacarbazine, and fotemustine [58, 59, 62, 63], or other anticancer-targeted agents, such as vemurafenib, and dabrafenib [64], did not increase the prevalence of hypophysitis compared to monotherapy with ipilimumab alone [64]. Overall, a recent meta-analysis revealed that the prevalence of autoimmune hypophysitis due to treatment of ipilimumab at lower doses (1–3 mg/kg) in combination with vaccination was associated with hypophysitis in 9% of cases, whereas higher doses of ipilimumab (5 mg/kg) were associated with hypophysitis in 13.3% of cases.

Potential Pathogenic Mechanisms

The precise mechanisms by which immune checkpoint inhibitors cause hypophysitis remain unclear. An immune-mediated pathogenesis has recently been supported following the detection of anti-thyrotroph, anti-corticotroph, and anti-gonadotroph Abs in patients' serum [65]. Histopathologically, a distinct infiltration with mononuclear cells found in the pituitary gland, but not in other organs, suggests that these mechanisms may be specific to the pituitary gland [65]. The fact that anti-CTLA-4 agents can stimulate de novo pituitary-reactive effector T cells, while anti-PD-1 therapy is not involved in initial T-cell activation could explain the lower occurrence of PD-1-induced hypophysitis (Fig. 1) [66]. The pituitary gland may express CTLA-4, making it a direct target for anti-CTLA-4 Abs [65] leading to the activation of Ab-dependent cell-mediated cytotoxicity by direct binding to pituitary cells [65–68]. In particular, a type 2 hypersensitivity reaction has been proposed as a cause of damage to the pituitary gland. Upon administration of ipilimumab, immune complexes are formed in the pituitary containing CTLA-4 antigen and CTLA-4 Ab inducing an activation of the classical complement cascade [65].

As already mentioned, the difference in the prevalence of hypophysitis induced by the various immunomodulatory agents may be related to their mode of action as anti-CTLA-4 Abs and anti-PD-1 Abs target different pathways (Fig. 1). CTLA-4 is involved in initial T-cell deactivation, whereas PD-1 targets the modulatory phase of the immune response [69]. In an active immune response, CD28 on the T-cell surface binds to the B7 costimulatory ligand on antigen-presenting cells resulting in the T-cell activation that leads to the translocation of CTLA-4 to the plasma membrane. CTLA-4 binds with high affinity to B7 and can compete with CD28 to further inhibit T-cell activity. Thus, the binding of anti-CTLA-4 Abs, such as ipilimumab, to CTLA-4 prevents B7 binding and the upregulation of T-cell activity [70].

PD-1 modulates the immune response in a more peripheral way primarily at the tumor microenvironment. PD-1 is expressed on the surface of activated T- and B-lymphocytes and monocytes and inhibits the immune response of these cells through interaction with its ligand PD-L1 (Fig. 2). PD-1 is upregulated by tumor cells and facilitates the escape of tumors from immune surveillance [71]. Patients treated with PD-1 and/or PD-L1 Abs, which are IgG4 Abs, in contrast to ipilimumab, which is an IgG1 Ab, develop hypophysitis less frequently [72]. This implies that IgG1, which activates the classic complement pathway, might be a possible mechanism of anti-CTLA-4-related hypophysitis [66]. Furthermore, there are differences in the mode of action between PD-1 and PD-L1 Abs. PD-L1 also binds to CD80 in addition to its interaction with PD-1 receptors on activated T cells. This complex setting of ligand-receptor interactions by PD-1 and PD-L1 might account for the differences in incidence of endocrine-related adverse effects [73].

Genetic factors predisposing to immune checkpoint-induced hypophysitis could also be implicated [74]. Polymorphisms in the *CTLA-4* or *PD-1* gene have been shown to be associated with a higher incidence of autoimmune disorders including hypophysitis. As a result, the role of human *CTLA-4* germline mutations in triggering autoimmune disease and the immune checkpoint inhibitor-induced hypophysitis is currently under investigation [74].

Hypophysitis attributable to Abs targeting immune mediators, such as tumor necrosis factor alpha or interleukins, used in patients with autoimmune diseases are relatively rare, and only scarce case reports exist. This might be explained by the inherent mechanism of action of these Abs that aim at reducing rather than enhancing the immune activation triggering the disease [17]. In contrast, anti-CTLA-4 Abs, by releasing one of the molecules

involved both in cancer immune escape and autoregulatory activity of the immune response, induce not only tumor response but also autoimmune endocrine-related adverse events [17].

Future Directions on Drug-Induced Hypophysitis

The role of genetic alterations in the pathogenesis of hypophysitis and their usefulness as predictive factors for disease course are under investigation. Tumor mutational load seems to predict efficacy and overall survival in patients receiving ipilimumab. Specifically, de novo somatic mutations of the tumor leading to the production of proteins recognized by the immune system as non-self, may serve as a prognostic marker for treatment efficacy and overall survival in patients receiving ipilimumab, although such an event alone it is not sufficient to induce a clinical benefit [75]. Indeed, there are somatic neoepitopes detected in patients who have experienced a prolonged benefit following treatment with these agents, whereas they are absent in those without such a clinical benefit [75]. Two recent studies identified individuals with germline *CTLA*-4 mutations who developed severe autoimmune diseases such as colitis and autoimmune thyroiditis but no hypophysitis and hypopituitarism [76, 77].

The absence of pituitary abnormalities in these individuals supports the hypothesis that pituitary CTLA-4 expression is a significant factor which mediates hypophysitis. The high expression levels of CTLA-4 in a subset of pituitary adenomas raises the possibility that CTLA-4 may represent a novel direct therapeutic target for the treatment of aggressive pituitary tumors in selected patients [74]. Additionally, a chelated 64Cu-isotope labeled anti-CTLA-4 Abs has recently been developed for use in positron emission tomography [78]. Thus, targeted imaging may be able to predict the risk of hypophysitis in patients treated with ipilimumab or possibly identify candidate patients with aggressive pituitary adenomas for therapeutic treatment with ipilimumab [78].

Clinical Presentation and Natural History

The clinical manifestations of immune checkpoint-induced hypophysitis are related either to structural or to hormonal disturbances [33]. Patients typically present with symptoms of sellar compression, such as headaches and visual field impairment, hypopituitarism, diabetes insipidus, and hyperprolactinemia [79]. Other symptoms that have been reported include confusion, hallucinations, memory loss, erectile dysfunction, dizziness, and insomnia [17, 42].

The role of anti-pituitary Abs in the diagnosis of autoimmune hypophysitis is debated, as positive anti-pituitary auto-Abs have been detected in 6–57% of patients with hypophysitis as well as in patients with other autoimmune diseases such as celiac disease and type 1 diabetes mellitus [80, 81]. Recently, a new autoantigen, rabphilin-3A, has been identified as responsible for the autoimmune response in several patients with lymphocytic infundibuloneurohypophysitis [82].

Anti-CTLA-4 Abs-induced hypophysitis has been associated with pituitary function recovery in approximately 25% of cases only [42]. These data are in line with a recent study that followed patients with anti-CTLA-4-induced hypophysitis for over 2.5 years (median time of follow-up was 33.6 months) and found a long-term hormonal replacement requirement in 86.6% of patients [31]. In the same study, at initial diagnosis 73.3% of ipilimumab-treated patients presented with corticotroph, 86.6% with thyrotroph, and 85.6% with gonadotroph deficiency. Gonadotroph and thyrotroph deficiency persisted in 13% of patents during follow-up, whereas corticotroph deficiency persisted in almost all patients. This presentation is rather atypical compared to classical LYH where patients develop corticotroph deficiency in 32%, 18% present with hyperprolactinemia, and 31% develop diabetes insipidus [4]. According to the authors, such particular features could lead to the hypothesis that ipilimumab-induced hypophysitis is a special entity [31]. However, the assessment of gonadotroph and thyrotroph function is more complicated in patients treated with anticancer agents, as it is difficult to determine whether there is a real improvement in hypophysitis or simple recovery from the underlying illness [28].

Treatment

Treatment of hypophysitis is focused in most cases on symptomatic management. In the acute phase, glucocorticoid replacement is mandatory and in some cases transsphenoidal surgery may be employed in patients with symptoms and/or signs of severe compression to nearby structures [2, 3]. Other immunosuppressive drugs, including azathioprine, methotrexate, cyclosporine A, and recently rituximab [83] and infliximab [21] have also been used successfully in corticosteroid-resistant cases, but data are scanty with these agents [1–3]. In the chronic phase, therapeutic strategy aims at the appropriate replacement therapy in cases of permanent pituitary deficiency.

Treatment of hypophysitis is influenced by the severity of symptoms and hormonal deficits in relation to the underlying malignancy. Concerning mild forms (grade 1) of

immune checkpoint-related hypophysitis, continuation of immunotherapy and close observation are recommended [84]. For all other toxicity grades, it is recommended that ipilimumab be withheld and not resumed until the resolution of adverse events to grade 1 [83]. However, this recommendation has recently been debated following a large study suggesting continuation of immunotherapy with concomitant hormonal replacement [31]. The majority of experts agree that the clinical benefits of an anti-CTLA-4 treatment, such as ipilimumab in patients with potentially fatal malignancy, outweigh the risks of continuing therapy using an appropriate hormonal replacement therapy, although in an adjuvant setting the decision regarding treatment should be made after the patient has been fully informed of the risk of hypophysitis and corticotrophin deficiency that usually persists [31, 85].

For severe hypophysitis (grade 3 or 4), most authors use high-dose systemic steroids (prednisolone 1 mg/kg/day or equivalent) with sequential tapering to a physiological replacement dose of hydrocortisone or prednisolone [30, 43, 83]. However, the use of high-dose steroids did not alter the recovery of the pituitary function [31].

Prevalence of Hypophysitis Related to Molecular Targeted Therapies

Regarding molecular targeted agents such as everolimus and tyrosine kinase inhibitors (TKIs), data are scarce. Up to now, no cases of hypophysitis related to everolimus have been described [14, 86, 87], and data on the effect of TKIs on pituitary function are under investigation. In particular, there are ongoing phase 3 (CheckMate 214) (ClinicalTrials.gov: NCT02231749) and phase 2 (ClinicalTrials.gov: NCT03075423) trials investigating the combination of nivolumab with ipilimumab versus sunitinib in subjects with metastatic renal cell carcinoma. A further phase 1 study (BMS-936558; MDX-1106) evaluates the combination of nivolumab with sunitinib, pazopanib, or ipilimumab in metastatic renal cell carcinoma (ClinicalTrials.gov: NCT01472081).

Prevalence of Drug-Induced Hypophysitis and New Agents

Currently, several ongoing clinical trials (ClinicalTrials.gov) are investigating new anti-CTLA-4 Abs or anti-PD-1 Abs for malignant and nonmalignant diseases increasing the interest in the prevention of drug-induced hypophysitis. Abatacept is a CTLA-4-Ig (BMS-188667) that is already used in a phase 2 study for prevention of type 1 diabetes in relatives of patients with type 1 diabetes (NCT01773707) as well as in other phase 1 and 2 studies including patients with systemic psoriasis (NCT00306878 and NCT00287547), granulomatosis with polyangiitis (Wegener's) (NCT02108860), and Takayashu arteritis, and in a phase 4 study including patients with primary biliary cirrhosis (NCT02078882). Another CTLA-4-Ig, belatacept, is included in trials for rheumatoid arthritis (NCT00279760). There are also combination protocols such as the association of tremelimumab with another anti-PD-L1 agent (MEDI4736) in colorectal cancer. Durvalumab is another new anti-PD-L1 agent currently tested in breast cancer patients in association with tremelimumab (NCT03132467). CX-072 is a Probody agent directed against PD-L1 also tested in subjects with advanced or recurrent solid tumors or lymphomas (NCT03013491).

Conclusions

Better understanding of cancer biology has led to the development and wide use of novel immunomodulatory agents. Hypophysitis has emerged as a new specific side effect of treatment with anti-CTLA-4 Abs and particularly ipilimumab but is encountered less frequently with anti-PD-1 Abs. The pathophysiology of hypophysitis induced by these anticancer agents is not fully clarified, and the prevalence among the different studies varies widely. This is due to the heterogeneity of the studies regarding the design (phase 1, 2, 3), dose, follow-up (ranging between months to years), and treatment administered. Diagnosis of hypophysitis remains clinical since anti-pituitary Abs are not a sensitive marker, and thus its true prevalence is probably underestimated. Corticotroph, thyrotroph, and gonadotroph function seems to be the most affected, with thyrotroph and gonadotroph functions usually recovering during follow-up. However, particular attention needs to be paid to corticotroph function, which has a possible delayed onset and may not recover. The development of a method to evaluate tissue CTLA-4 expression prior to CTLA-4-targeted therapy is expected to allow treatment administration in line with evidence-based data, leading to cost-efficient medical care and avoidance of potential adverse effects. Therefore, as the use of these immunomodulatory agents is increasing, it is important for treating oncologists and endocrinologists to be aware of this association, allowing early identification and appropriate treatment of this side effect.

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