Hypophysitis Induced by Monoclonal Antibodies to Cytotoxic T Lymphocyte Antigen 4: Challenges from a New Cause of a Rare Disease

FRANCESCO TORINO, a AGNESE BARNABEI, c LIANA DE VecCHIS, b ROBERTO SALVATORI, d SALVATORE M. CORSELLO e

aDepartment of Internal Medicine and bDepartment of Neuroscience, University of Rome “Tor Vergata,” Rome, Italy; cEndocrinology Unit, National Institute of Cancer “Regina Elena,” Rome, Italy; dPituitary Center, Division of Endocrinology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; eEndocrinology Unit, Università Cattolica, Rome, Italy

Key Words. Hypophysitis • Ipilimumab • Tremelimumab • Anti–CTLA-4 Monoclonal Antibodies

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify symptoms of hypophysitis as an infrequent immune related side effect of ipilimumab and other anti-CTLA-4 monoclonal antibodies.
2. Select the appropriate diagnostic and therapeutic work-up for patients suspected of having anti-CTLA-4 monoclonal-induced hypophysitis.

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ABSTRACT

Specific human monoclonal antibodies antagonize cytotoxic T-lymphocyte antigen 4 (anti–CTLA-4 mAbs), a negative regulator of the immune system, inducing unrestrained T-cell activation. In patients with advanced or metastatic melanoma, one of these agents, ipilimumab, produced considerable disease control rates and, for the first time, a clear improvement in overall survival outcomes. However, accumulating clinical experience with anti–CTLA-4 mAbs identified a novel syndrome of autoimmune and autoinflammatory side effects, designated as “immune-related adverse events,” including mainly rash, colitis, and hepatitis. Autoimmune hypophysitis has emerged as a distinctive side effect induced by anti–CTLA-4 mAbs. This condition may be life threatening because of adrenal insufficiency if not promptly recognized, but it may easily be diagnosed and treated if clinically suspected. Hypopituitarism caused by these agents is rarely reversible and prolonged or life-long substitutive hormonal treatment is often required. The precise mechanism of injury to the pituitary triggered by anti–CTLA-4 mAbs is yet to be fully elucidated. The Oncologist 2012;17:525–535

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INTRODUCTION
Immunotherapy abrogating immune regulatory molecules represents a new and promising strategy to induce tumor regression and to improve survival in cancer patients. Tremelimumab and ipilimumab are two fully human monoclonal antibodies (mAbs) selectively blocking cytotoxic T-lymphocyte antigen 4 (CTLA-4), hereafter, anti–CTLA-4 mAbs, an immune-inhibitory protein expressed on activated T cells.

Tremelimumab (formerly CP-675,206; Pfizer Inc., New York), a fully human IgG2 mAb, produced response rates of 7%–15% in initial clinical trials in patients affected by various cancers (including melanoma) [1]. Conversely, in a large phase III study in 665 patients affected by advanced or metastatic melanoma (mM) and randomized to receive tremelimumab (15 mg/kg every 12 weeks) or standard chemotherapy (dacarbazine or temozolomide), the overall survival times and response rates were similar in the two arms [2]. Currently, tremelimumab is under study for the treatment of patients with several types of advanced malignancy [1].

Ipilimumab (formerly MDX-010; Bristol-Myers Squibb-Medarex, New York, and Princeton, NJ), a fully human IgG1 mAb, resulted in cancer regression in ∼15% of patients with mM in early clinical trials. In a randomized phase III trial, ipilimumab showed the first-ever overall survival benefit for patients with previously treated mM [3], leading to its approval by the U.S. Food and Drug Administration (FDA). Superior overall survival outcomes and response rate were also seen in previously untreated mM patients who received ipilimumab plus dacarbazine, when compared with those receiving dacarbazine alone [4]. In addition, promising results have been reported from phase II studies in patients with advanced or metastatic renal cell carcinoma (mRCC) and prostate cancer (mPC) [5, 6]. Trials evaluating ipilimumab as neoadjuvant or adjuvant therapy in patients who have undergone radical surgery for melanoma are ongoing [7]. The most common adverse events (AEs), affecting >10% of patients treated with anti–CTLA-4 mAbs, were diarrhea, rash, pruritus, fatigue, nausea, vomiting, and abdominal pain. However, a novel spectrum of autoimmune–inflammatory toxicities, different from those classically encountered with chemotherapy and even other forms of immunotherapy, has emerged following the administration of these agents. The pathogenic mechanism of these new AEs seem to be sustained by the positive modulation induced by anti–CTLA-4 mAbs on the immune system, and they are defined as immune-related AEs (IRAEs) [8–11]. The gastrointestinal tract, liver, skin, and anterior pituitary are more frequently involved with these IRAEs (Table 1). Rarer IRAEs include thyroiditis, primary adrenal insufficiency, polynuropathy, episcleritis or uveitis, polyarthritids or arthralgias, pneumonitis, pancreatitis, asptic meningitis, nephritis, RBC aplasia, myocardiitis, myasthenias gravis, sarcoidosis, and myositis [12]. The frequency and severity of IRAEs seem to be dose dependent [12, 13].

Most AEs and IRAEs induced by anti–CTLA-4 mAbs are mild to moderate, and patients recover following brief medical treatments of symptoms. More severe toxicities, particularly grade 3–4 toxicities, such as diarrhea, colitis, hepatitis, diverticulitis, and hypophysitis (Table 2), have been reported [8–10, 14, 15].

In a pooled analysis of 325 patients who received ipilimumab (10 mg/kg), drug-specific AEs were reported in 84.6% of patients [16]. IRAEs occurred in ~72% of patients. Grade 3–4 IRAEs were reported in ~25% of cases, mainly in the gastrointestinal tract (12%), liver (7%), skin (3%), and endocrine system (E-IRAEs) (3%).

Similar results were observed in an analysis of safety of six clinical trials involving 786 patients treated with 15 mg/kg tremelimumab [14]. Treatment-related AEs (mainly grade 1 or 2) were reported in 79% of patients; in 23% of cases, AEs were grade ≥3. The most common AEs of any grade included diarrhea (40%), rash (23%), fatigue (23%), pruritus (22%), and nausea (21%). Thyroid abnormalities were reported in 2.4% of patients, whereas hypophysitis or adrenal insufficiency occurred in <1%.

Occasionally (~1%), deaths have occurred as a result of colonic perforation both with tremelimumab and ipilimumab [2, 17, 18].

Different IRAEs seem to manifest at distinct times after starting the drug. Skin IRAEs have an earlier onset (3–4 weeks) than those involving the gastrointestinal tract and liver (6–7 weeks). E-IRAEs become apparent even later (9 weeks) [16]. The times to recovery or improvement after drug withdrawal also differ: a median of 2 weeks for gastrointestinal symptoms, 4 weeks for liver toxicity, 6 weeks for skin toxicity, and longer (median, 20 weeks) for E-IRAEs [13, 16]. Importantly, the treatment of IRAEs with immunosuppressive agents, such as corticosteroids, does not appear to affect the antitumor response [12].

In several large analyses, the presence of grade 3–4 IRAEs correlates with higher rates of clinical response, and among clinical responders IRAEs are more frequent [8, 19–22]. However, high-grade IRAEs are not required for a clinical response, nor is a clinical response always associated with a high-grade IRAE [23]. In addition, these associations are likely biased by the longer period of exposure in patients experiencing a clinical benefit than in patients who worsen or die early [24]. Presently, reliable predictive factors of response and toxicity following treatment with anti–CTLA-4 mAbs are lacking.

HYPOPITUITARISM AND HYPOPYSITIS NOT RELATED TO ANTI–CTLA-4 mAbs
Hytopituitarism is thought to be an infrequent disease, with an incidence of 4.2 cases per 100,000 per year, and it increases with age [25]. Hyopphysitis is among the rarest causes of hypopituitarism [25].

Different classifications of hypophysitis have been proposed based on the anatomical areas damaged in the gland, the etiology, and the histopathological findings (Table 3) [26, 27].

Hyopphysitis can be classified as adenohypophysitis, infundibuloneurohypophysitis, or panhypophysitis depending on whether it involves the anterior lobe, the posterior lobe and the stalk of the gland, or both [26].
<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Phase</th>
<th>Schedule of anti–CTLA-4 agent</th>
<th>Hypophysitis/ hypopituitarism</th>
<th>Incidence of other E-IRAEs</th>
<th>Incidence of other IRAEs (grade 3–4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribas et al. [10]</td>
<td>Metastatic malignancies (n = 39) (melanoma, n = 34; renal cell, n = 4; colon, n = 1)</td>
<td>I</td>
<td>0.01–15 mg/kg every 90 days</td>
<td>Grade 2 hypopituitarism, n = 1 (5.2%) at 15 mg/kg</td>
<td>Grade 1 hypothyroidism, n = 1 (1.9%) at 15 mg/kg</td>
<td>10 mg/kg: grade 3 asthenia, n = 1 (2.5%); grade 3 diarrhea, n = 1 (2.5%); 15 mg/kg: grade 3 hypothyroidism, n = 1 (2.5%); grade 3 lipase increase, n = 1 (2.5%)</td>
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<tr>
<td>Camacho et al. [79]</td>
<td>Pretreated unresectable stage III or stage IV melanoma; phase I, n = 28; phase II, n = 89</td>
<td>I</td>
<td>3, 6, or 10 mg/kg</td>
<td>0</td>
<td>0</td>
<td>DLTs: hepatitis, n = 2; edema and cellulitis, n = 1; vasculitis, pruritus, skin exfoliation, rash, n = 1; Grade 3 or 4 AEs (diabetes, rash, pruritus, fatigue, and nausea), 13% at 10 mg/kg, 25% at 15 mg/kg</td>
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<td>II</td>
<td>10 mg/kg monthly</td>
<td>0</td>
<td>Thyroiditis– hypothyroidism, n = 1 at 10 mg/kg</td>
<td>SAEs, 9% at 15 mg/kg, 23% at 10 mg/kg; grade 3 diarrhea, 21% at 10 mg/kg, 9% at 15 mg/kg</td>
</tr>
<tr>
<td>Ralph et al. [69]</td>
<td>Pretreated metastatic gastric and esophageal ADC (n = 18)</td>
<td>II</td>
<td>15 mg/kg i.v. every 90 days</td>
<td>No endocrine toxicity reported</td>
<td>Grade 3 diarrhea, perforation, and death, n = 1; grade 3 transaminases, n = 1; only 1 patient received &gt;2 cycles of study drug</td>
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<td>Kirkwood et al. [18]</td>
<td>Refractory or relapsed advanced melanoma (n = 251)</td>
<td>II</td>
<td>15 mg/kg i.v. every 90 days</td>
<td>Grade 3 or 4 hypophysitis, n = 1 (0.4%)</td>
<td>Thyroid disorders, n = 8 (3.2%)</td>
<td>Grade 3 or 4 diarrhea, n = 28 (11%); fatigue, n = 6 (2%); colitis, n = 9 (4%); treatment-related deaths, n = 2 (0.8%)</td>
</tr>
<tr>
<td>Chung et al. [9]</td>
<td>Pretreated chemotherapy-resistant or refractory mCRC (n = 47)</td>
<td>II</td>
<td>15 mg/kg i.v. every 90 days</td>
<td>0</td>
<td>Grade 2 hypothyroidism, n = 1 (2.1%)</td>
<td>Grade 3 or 4 diarrhea, n = 5 (11%); colitis, n = 1 (2.1%); fatigue, n = 1 (2.1%); decreased platelets, n = 1 (2.1%); hypokalemia, n = 1 (2.1%)</td>
</tr>
<tr>
<td>Ribas et al. [2]</td>
<td>Naïve, stage IV or unresectable stage IIc melanoma (n = 635)</td>
<td>III</td>
<td>15 mg/kg i.v. every 90 days with or without chemotherapy</td>
<td>Pituitary or adrenal gland, 5%</td>
<td>Thyroid, 4%</td>
<td>Grade 3 or 4 diarrhea, 14%; treatment-related deaths, n = 3 in tremelimumab arm, 0 in the chemotherapy arm</td>
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<tr>
<td>Attia et al. [8]</td>
<td>Pretreated stage IV melanoma (n = 56)</td>
<td>I-III</td>
<td>3 mg/kg every 3 wks or 3 mg/kg every 3 wks + vaccination with modified HLA-A*0201-restricted peptides from gp100 MAA I–II IPE transfectoma-derived, 2.8 mg/kg every 3 wks</td>
<td>Grade 3 or 4 hypophysitis, n = 1 (1.8%)</td>
<td>0</td>
<td>Grade 3 or 4 colitis, n = 7 (13%); dermatitis, n = 4 (7%); uveitis, n = 1 (1.8%); enterocolitis, n = 1 (1.8%); hypokalemia, n = 1 (1.8%)</td>
</tr>
<tr>
<td>Maker et al. [52]</td>
<td>Naïve metastatic melanoma (n = 36)</td>
<td>I</td>
<td>1.3 mg/kg + IL-2</td>
<td>0</td>
<td>0</td>
<td>Grade 3 or 4 colitis/diarrhea, n = 6 (17%); uveitis, n = 1 (2.8%); arthritis, n = 1 (2.8%)</td>
</tr>
<tr>
<td>Maker et al. [15]</td>
<td>Pretreated stage IV melanoma (n = 46)</td>
<td>I–II</td>
<td>3 mg/kg + peptide vaccinations or intratumor injection of modified peptides (HILA-A*0201 status)</td>
<td>Grade 3 or 4 hypophysitis, n = 8 (17.4%), 5 mg/kg, n = 1, 9 mg/kg, n = 7</td>
<td>0</td>
<td>Grade 3 or 4 colitis/diarrhea, n = 6 (17%); uveitis, n = 1 (2.2%); arthritis, n = 1 (2.2%); dermatitis, n = 1 (2.2%); hypokalemia, n = 1 (2.2%)</td>
</tr>
<tr>
<td>Downey et al. [20]</td>
<td>Pretreated stage IV melanoma (n = 139)</td>
<td>I–II</td>
<td>3 mg/kg + peptide vaccinations or intratumor injection of modified HILA-A*0201-restricted peptides from gp100</td>
<td>Grade 3 or 4 hypophysitis, n = 13 (9%)</td>
<td>0</td>
<td>Grade 3 or 4 enterocolitis, n = 24 (17%); dermatitis, n = 8 (6%); hepatitis, n = 2 (1.5%); colitis, n = 2 (1.5%); arthritis, n = 3 (2.8%); uveitis, n = 3 (2.8%)</td>
</tr>
<tr>
<td>Phan et al. [80]</td>
<td>Pretreated stage IV melanoma (n = 14)</td>
<td>II</td>
<td>3 mg/kg + peptide vaccinations</td>
<td>Grade 3 or 4 hypophysitis, n = 1 (7.1%)</td>
<td>0</td>
<td>Grade 3 or 4 dermatitis, n = 3 (21.4%); enterocolitis/colic, n = 2 (14.3%); hypokalemia, n = 1 (7.1%)</td>
</tr>
<tr>
<td>Blansfield et al. [53]</td>
<td>Pretreated stage IV melanoma (n = 113) and RCC (n = 50)</td>
<td>RS</td>
<td>3 mg/kg every 3 wks</td>
<td>Grade 3 or 4 hypophysitis, n = 8 of 163 (4.9%), n = 6 of 113 mM patients (5%), n = 2 of 54 RCC patients (4%)</td>
<td>NR</td>
<td>NR; report focused on clinical aspects of patients who developed anti–CTLA-4–induced hypophysitis</td>
</tr>
<tr>
<td>Royal et al. [81]</td>
<td>Metastatic pancreatic ADC (n = 27)</td>
<td>II</td>
<td>3 mg/kg every 3 wks × 4 for a maximum of two courses</td>
<td>Grade 2 or 3 hypopituitarism, n = 1 (3.7%)</td>
<td>0</td>
<td>Grade 3 or 4 colitis, n = 1 (3.7%); enterocolitis, n = 1 (3.7%)</td>
</tr>
<tr>
<td>Weber et al. [72]</td>
<td>Stage IIIC or IV melanoma (n = 25)</td>
<td>I</td>
<td>3 mg/kg every 8 wks for 12 months + MART-1/gp100 tyrosinase peptides</td>
<td>Grade 2 or 3 hypopituitarism (DLT), n = 1 (4%)</td>
<td>0</td>
<td>Grade 2 or 3 (DLTs): GI toxicity, n = 2 (8%); skin toxicity, n = 2 (8%)</td>
</tr>
<tr>
<td>Fong et al. [70]</td>
<td>mHRPC (n = 18)</td>
<td>I</td>
<td>Escalating doses (0.5, 1.5, 3 mg/kg) every 3 weeks for 4 cycles + GM-CSF</td>
<td>Grade 3 or 4 hypophysitis, n = 1 (5.6%)</td>
<td>0</td>
<td>Grade 3 skin (DLT)</td>
</tr>
<tr>
<td>Small et al. [71]</td>
<td>mPC (n = 14)</td>
<td>I</td>
<td>3 mg/kg single dose</td>
<td>0</td>
<td>0</td>
<td>Grade 3 or 4 asthenia, n = 1 (7.1%); pain, n = 1 (7.1%); rash, n = 1 (7.1%)</td>
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<tr>
<td>Yang et al. [5]</td>
<td>mRCC (n = 61)</td>
<td>I</td>
<td>≥3 mg/kg or ≥1 mg/kg or all doses at 3 mg/kg every 3 wks</td>
<td>Grade 3 or 4 hypophysitis, n = 2 (3.3%)</td>
<td>Grade 3 or 4 primary adrenal insufficiency, n = 1 (1.6%)</td>
<td>All patients: grade 3 or 4 enterocolitis, n = 17 (28%); skin, n = 1 (1.6%); arthralgia, n = 1 (1.6%); aseptic meningitis, n = 1 (1.6%)</td>
</tr>
<tr>
<td>Weber et al. [21]</td>
<td>Unresectable stage III or IV melanoma (n = 88)</td>
<td>I–II</td>
<td>IPI transfectoma-derived, 2.8 mg/kg for 3 doses, or IPI hybridomas-derived, 3 mg/kg for 3 doses, IPI transfectoma-derived 5 mg/kg for 3 doses</td>
<td>Grade 3 or 4 adrenal insufficiency, n = 1 (1.2%)</td>
<td>0</td>
<td>All patients: grade 3 or 4 colitis, n = 3 (3.4%); diarrhea, n = 4 (45%); GI perforation, n = 1 (1.1%)</td>
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</table>

(continued)
The etiological classification identifies primary and secondary forms. Primary hypophysitis, the most common form, has an autoimmune pathogenesis with no obvious causative agent [26]. It may occur as an isolated disease or as part of a multiorgan syndrome (i.e., polyglandular autoimmune syndromes and IgG-related systemic disease) [27]. Secondary hypophysitis includes local and systemic disease, with a clearly identified etiological agent. For local disorders, inflammation of the pituitary appears as a reaction to a sellar disease (i.e., Rathke’s cleft cyst, craniopharyngioma, germinoma, and pituitary adenoma). For systemic diseases, hypophysitis stems from the involvement of different organs by infectious or inflammatory disorders (e.g., Wegener’s granulomatosis, sarcoidosis, tuberculosis, or syphilis).

On pathology, two common forms of hypophysitis (lymphocytic and granulomatous) and three rarer variants (xanthomatous, necrotizing, and plasma cell rich) are recognized (Table 3) [27]. Lymphocytic hypophysitis (LYH), often referred to as autoimmune hypophysitis (AH), is the most common. The clinical features of ~500 patients with primary hypophysitis have been reported so far [28]. The exact incidence is unknown and likely underestimated [29]. LYH/AH is mostly seen in striking temporal association with pregnancy or postpartum, but it may also occur in women irrespective of pregnancy, in males, and in children [26, 27].

LYH/AH is characterized by dense diffuse lymphocytic infiltration of the pituitary that may be organized in lymphoid follicles. Plasma cells are also common, whereas eosinophils, macrophages, and neutrophils are rare. In a small percentage of patients in whom a biopsy specimen was obtained, hypophysitis, a rare variant, was observed (4%) with lymphocytic infiltration of the pituitary, which may be organized in lymphoid follicles. A rare variant, dysimmune hypophysitis (DYH), is characterized by dense lymphocytic infiltration of the pituitary. Another rare variant, lymphomatous hypophysitis, is characterized by lymphoid follicles containing a variety of lymphocytes, including B cells, T cells, plasma cells, and histiocytes. The third rare variant, granulomatous hypophysitis, is characterized by the presence of epithelioid cells, multinucleated giant cells, and Langhans’ giant cells. A mixed form of hypophysitis, characterized by the presence of lymphocytes, histiocytes, and multinucleated giant cells, is also observed.

Table 1. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Phase</th>
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<th>Incidence of other E-IRAEs</th>
<th>Incidence of other IRAEs (grade 3–4)</th>
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<tbody>
<tr>
<td>Gerritsen et al. [73]</td>
<td>Chemotherapy-naive mHRPC patients (n = 28)</td>
<td>I</td>
<td>Monthly escalating dose (0.3, 1.3, or 5 mg/kg) + GVAX immunotherapy</td>
<td>Grade 2 or 3 hypophysitis, n = 5 (18%) in combination arm, n = 0 in ipilimumab arm</td>
<td>Grade 3 adrenal insufficiency, n = 1 (3.6%)</td>
<td>Grade 3 anorexia, n = 1 (3.6%); fatigue, n = 1 (3.6%)</td>
</tr>
<tr>
<td>Ansell et al. [74]</td>
<td>Relapsed or refractory B-cell NHL (n = 18)</td>
<td>I</td>
<td>3 mg/kg → monthly 1 mg/kg × 3 mos (dose level 1), → escalation to 3 mg/kg monthly × 4 mos (dose level 2)</td>
<td>Grade 1 or 2 hypophysitis, n = 1 (6%)</td>
<td>Grade 3 fever, n = 5 (28%); fatigue, n = 1 (6%); neutropenia, n = 1 (6%)</td>
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<tr>
<td>Hodi et al. [3]</td>
<td>Pretreated unresectable stage III or IV melanoma (n = 676)</td>
<td>III</td>
<td>3 mg/kg every 4 weeks for 4 doses with or without ipilimumab versus gp100 alone</td>
<td>Grade 3 hypophysitis, n = 0 (0%); hypopituitarism, n = 1 (1.5%)</td>
<td>Grade 2 hypophysitis, n = 1 (1.5%); hypopituitarism, n = 1 (1.5%)</td>
<td>Grade 3 or 4 diarrhea, 30.3%–27.5%; nausea, 39.9%–35.1%; vomiting, 19.7%–23.7%; abdominal pain, 17.6%–15.3%; colitis, 5.3%–7.2%; constipation, 21.3%–20.6%; parathyroiditis, 17.8%–24.4%; hepatitis, 2.1%–3.8%; fatigue, 36.1%–42%; pyrexia, 20.5%–12.2%; headache, 17.1%–14.9%</td>
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<tr>
<td>Hersh et al. [75]</td>
<td>Chemotherapy-naive patients with unresectable stage III or IV melanoma (n = 72)</td>
<td>II</td>
<td>3 mg/kg every 4 weeks for 4 doses with or without ipilimumab (up to 6 cycles; 250 mg/m² per day × 5 days)</td>
<td>Grade 2 adrenal insufficiency, n = 1 (1.4%) in ipilimumab + DTIC arm</td>
<td>Grade 4 diarrhea, n = 3 (2.8%); vomiting, n = 1 (1.4%); rash, n = 1 (1.4%); fatigue, n = 1 (2.8%)</td>
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<tr>
<td>Wolchok et al. [76]</td>
<td>Pretreated unresectable stage III or IV melanoma (n = 217)</td>
<td>II</td>
<td>0.3, 3, or 10 mg/kg every 4 weeks for 4 cycles with induction (ipilimumab 10 mg/kg every 3 mos, maintenance)</td>
<td>Endocrine IRAEs are globally reported: grade 1, 0/4; grade 2, 1 (3%); grade 3, 0/4; grade 4, 0/4</td>
<td>Grade 4 hypophysitis, n = 0/4 (0%); hypopituitarism, n = 0/4 (0%); adrenal, n = 0/4 (0%); thyroid, n = 0/4 (0%); hypothyroidism, n = 0/4 (0%); hypogonadism, n = 0/4 (0%); hypogonadism, n = 0/4 (0%); hypogonadism, n = 0/4 (0%); hypogonadism, n = 0/4 (0%)</td>
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<tr>
<td>Hodi et al. [77]</td>
<td>Unresectable stage III or IV melanoma (may or may not be pretreated, n = 21)</td>
<td>I</td>
<td>10 mg/kg every 3 weeks × 4 → every 3 mos → bevacizumab 7.5 mg/kg (sofort 1) or 15 mg/kg (colibri 2) every 3 weeks</td>
<td>Hypophysitis (grade not specified), n = 5 (24%)</td>
<td>Thyroiditis (grade not specified), n = 0 (0%)</td>
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<tr>
<td>O’Day et al. [78]</td>
<td>Pretreated, unresectable stage III or IV melanoma (n = 155)</td>
<td>II</td>
<td>10 mg/kg every 4 weeks for 4 cycles (induction) every 3 mos (maintenance)</td>
<td>Endocrine IRAEs are globally reported: grade 1, 0/4 (0%); grade 2, 1 (3%); grade 3, 0/4; grade 4, 0/4</td>
<td>Grade 3 or 4 skin, n = 5 (32.9%); GI, n = 13 (8.8%); liver, n = 11 (7.1%); others, n = 4 (2.5%)</td>
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<tr>
<td>Ku et al. [22]</td>
<td>Refractory melanoma (compassionate use, n = 53)</td>
<td>II</td>
<td>10 mg/kg every 4 weeks for 4 cycles → every 12 weeks</td>
<td>Grade 2 or 3 hypophysitis with adrenal insufficiency, n = 2 (2%)</td>
<td>Grade 2 hypothyroidism, n = 1 (2%)</td>
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<tr>
<td>Dy Giacomo et al. [55]</td>
<td>Pretreated unresectable stage III or IV melanoma (expanded access program, n = 27)</td>
<td>I</td>
<td>10 mg/kg every 3 weeks for 4 doses → every 12 weeks in cases of CB</td>
<td>Grade 1 or 2 hypophysitis, n = 2 (7.4%)</td>
<td>Grade 3 diarrhea, n = 2 (7.4%); transaminis, n = 1 (3.7%); grade 4 pancytopenia, n = 1 (3.7%)</td>
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Abbreviations: ADC, adenocarcinoma; ANA, antinuclear Ab; anti–CTLA-4, anti–cytotoxic T lymphocyte antigen 4; CB, clinical benefit; DLT, dose-limiting toxicity; DTIC, dacarbazine; GI, gastrointestinal; GVAX, granulocyte-macrophage colony-stimulating factor (GM-CSF) gene-transfected tumor cell vaccine; HLA, human leukocyte antigen; IL-2, interleukin 2; IPI, ipilimumab; IRAE, immune-related adverse event; MAA, melanoma-associated antigen; MART-1, melanoma antigen recognized by T-cells-1; mHRPC, metastatic hormone-refractory prostate cancer; mM, metastatic melanoma; mRCC, metastatic renal cell carcinoma; NHL, non–Hodgkin’s lymphoma; NR, not reported; RS, retrospective study; SAE, serious adverse event.
sent different stages of the same disease, rather than a granulomatous form of hypophysitis [26]. In some studies, the predominant lymphocytic subpopulation is represented by cytotoxic T lymphocyte (CD8\(^+\)) cells, suggesting that T cell–mediated cytotoxicity is critical in the pathogenesis of the disorder [30]. Several other aspects appear to indicate that this condition results from an autoimmune process. Almost 30% of LYH/AH patients have a coexisting autoimmune disease, such as Hashimoto’s thyroiditis, Addison’s disease, type 1 diabetes, or pernicious anemia [26, 31–34]. LYH/AH is considered a condition results from an autoimmune process. Almost 30% of LYH/AH patients have a coexisting autoimmune disease, such as Hashimoto’s thyroiditis, Addison’s disease, type 1 diabetes, or pernicious anemia [26, 31–34]. LYH/AH is considered a model of LYH [40]. Permanent partial hypopituitarism or panhypopituitarism may be the clinical consequence, depending upon the extent of damage to the different components of the pituitary gland [26].

Usually, LYH/AH is confined to the anterior pituitary, with symptoms such as headache (53%) and impaired vision (43%). Hypopituitarism is present in 44% of patients and, in contrast to other forms of hypopituitarism, is more commonly associated with a deficit of adrenocorticotropic hormone (ACTH) (56%), followed by a deficit of thyroid-stimulating hormone (TSH) (49%), gonadotropins (52%), and growth hormone (GH) (39%) [26]. Hypproactinemia (23%) or hyperproactinemia (11%) may be seen, depending on whether the damage involves prolactin-producing cells or stalk, respectively [34]. Diabetes insipidus (DI) is less common (1%) and is related to involvement of the posterior pituitary [26, 31–35]. Occasionally, hypophysitis may primarily involve the infundibulum and posterior pituitary, causing intracranial mass-effect symptoms, DI, and hyperproactinemia. In these cases, anterior pituitary function is usually preserved [26, 29, 31–35, 41].

As a result of the enlargement of the gland, headache together with visual field impairment are usually recognized as “sentinel symptoms” at disease onset, followed by hormone function disorders. ACTH deficiency is considered the earliest functional alteration in LYH/AH and is the most frequent “isolated” pituitary hormone deficiency [42]. These aspects appear to suggest that antigen(s) targeted by the immune system to trigger autoimmune reactions reside within the corticotroph cells. However, isolated ACTH deficiency may also be observed in the absence of LYH/AH, and isolated deficiencies of other anterior pituitary hormones have been described in LYH/AH patients [43–45]. The greater frequency of ACTH deficiency may simply represent an ascertainment bias, because these patients may come to medical attention more than those with other adenohypophyseal hormone deficiencies because of the more evident symptomatology [26].

Similarly to symptoms, the imaging features of LYH/AH are not specific [34, 46]. Computed tomography and magnetic resonance imaging (MRI) typically reveal a diffuse enlargement of the pituitary gland with loss of normal signal intensity of the posterior pituitary on precontrast images and variable enlargement of the infundibulum. Enhancement is usually uniform, may also be heterogeneous, and may be delayed or even absent in the posterior pituitary area [46, 47].

Currently, the diagnosis of LYH/AH requires pathological analysis. However, a presumptive clinical diagnosis can be based on the history of gestational or postpartum hypopituitarism, a contrast-enhancing sellar mass, a pattern of pituitary hormone deficiency with early loss of ACTH and TSH, relatively rapid development of hypopituitarism, and a degree of pituitary failure inconsistent with the size of the mass [26, 48]. Approximately 30% of patients with clinically suspected LYH/AH are diagnosed by combining symptoms and laboratory and radiological findings [28]. Current immunological tests for LYH/AH, particularly immunoaffluorescence for antipituitary antibodies, offer good sensitivity but lack adequate specificity, and therefore are of limited value in the diagnosis.
and management of LYH/AH patients [28, 31]. However, recent advances in this field open promising perspectives [49]. The natural history of LYH/AH is variable [26 –28]. Most patients show improvement in symptoms after mass-reducing treatment (pituitary surgery or high-dose glucocorticoids), but the majority (72%) require some form of long-term hormone replacement. Approximately 4% may improve spontaneously without treatment. When an MRI follow-up was available, reduction or complete disappearance of the initial pituitary mass was demonstrated in 88% of cases, no significant change was seen in 12% of patients, and 10% of these patients developed an “empty sella.” Unfortunately, it is estimated that 7% of patients affected by LYH/AH die presumably as a result of irreversible and unrecognized adrenal insufficiency [26–28].

**Clinical Features of Hypophysitis Induced by Anti–CTLA-4 mAbs**
The incidence of hypophysitis induced by anti–CTLA-4 mAbs (hereafter, anti–CTLA-4–IH) varies considerably (Table 1), reported in 0%–17% of treated melanoma patients [50]. However, accumulating clinical experience demonstrates that this side effect also occurs in patients with solid tumors of various types, including kidney and prostate cancer [51]. In a trial on 46 patients with mM treated with various doses of ipilimumab, eight patients (17%) experienced hypophysitis, with the majority of cases in patients on the higher drug dose regimen (9 mg/kg) [15]. In a previous study with lower doses of the drug (1–3 mg/kg), a lower incidence of hypophysitis (1.8%) was reported [52]. In another study on 163 patients with mM or mRCC treated with ipilimumab (3–9 mg/kg every 3 weeks), alone or in combination with another type of immunotherapy, hypophysitis was diagnosed in eight patients (4.9%) [53]. Recently, two

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<th>Table 3. Pathological classification of hypophysitis</th>
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<td><strong>Type of hypophysitis</strong></td>
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<td>IgG4-related/plasma cell rich hypophysitis</td>
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Abbreviations: anti–CTLA-4 mAb, anti–cytotoxic T lymphocyte antigen 4 monoclonal antibody; F, female; M, male.
cases of hypopituitarism, presumably resulting from hypophy-
sitis, were described in patients submitted to experimental
treatment with ipilimumab for mPC [50].

In the large phase III trial that led to the FDA approval of
ipilimumab, in which 676 pretreated patients affected by un-
resectable stage III or IV melanoma received the drug as a sin-
gle agent or in combination with gp100 versus gp100 alone,
grade 3 hypophysitis was reported in both groups receiving ip-
ilimumab. The incidences of hypophysitis were 1.5% in the
combination group (two of 380 patients) and 0.5% in the sin-
gle-agent arm (two of 131 patients), with no cases in the gp100
arm [3]. Conversely, no cases of hypophysitis were reported in
a phase III trial evaluating dacarbazine with and without ipil-
imumab in treatment-naive patients with mM, in a phase II trial
evaluating chemotherapy with and without ipilimumab in pa-
ients with non-small cell lung cancer, and in one of two ex-
panded access programs to ipilimumab administered at con-
ventional dosages in patients with mM, both in the induc-
tion and maintenance phases, with the incidence of this AE be-
ing 4% in the other trial (Table 1) [4, 22, 54, 55].

Tremelimumab (15 mg/kg) has been reported to induce hy-
pophysitis in 0.4%–2.5% of patients (Table 1) [2, 10, 14, 18].

In contrast to other forms of LYH/AH, patients who expe-
rience anti–CTLA-4–IH are mostly male. These patients usu-
ally present with nonspecific symptoms such as headache,
visual impairment, fatigue, weakness, confusion, memory
loss, erectile dysfunction and loss of libido, anorexia, labile
moods, insomnia, temperature intolerance, subjective sensa-
tion of fever, and chills [5, 13, 20, 50]. The onset of symptoms
usually occurs after 2–6 months of treatment. Contrast-en-
Hanced MRI shows marked enlargement of the pituitary gland,
often with thickening of the hypophyseal stalk. In some cases,
the pituitary gland enhances homogeneously, whereas in other
cases there is heterogeneous enhancement. Levels of ACTH,
cortisol, TSH and/or free T4, GH, prolactin, insulin-like
growth factor I, follicle-stimulating hormone, luteinizing hor-
mones, and testosterone are variably altered, indicating differ-
ent degrees of hypopituitarism [52]. Very rarely DI has been
reported.

Similar to classic primary LYH/AH, the treatment used for
anti–CTLA-4–IH is high-dose corticosteroids, slowly tapered
as symptoms and hormone tests improve (Fig. 1). Almost all
patients who developed anti–CTLA-4–IH experience clinical
resolution of acute symptoms in a few days following with-
drawal of the study drug and starting of corticosteroids [53].
The efficacy of corticosteroids is confirmed by the rapid
shrinkage of the pituitary gland on MRI. However, pituitary
function may be impaired for a longer period of time. More-
over, the duration of replacement therapy with physiological
glucocorticoid dosages (mean, 20 weeks) may be considerably
longer or even be life long [13, 16, 51]. Hypopituitarism is the
only potentially irreversible IRAE induced by anti–CTLA-4
mAbs [56]. In particular, the hypothalamic–pituitary–gonadal
and hypothalamic–pituitary–thyroidal axes frequently re-
cover, but only a few patients can discontinue glucocorticoid
replacement [50, 51]. At the onset of anti–CTLA-4–IH, it is
impossible to predict which patients will develop persistent
hypopituitarism.

The protective role of corticosteroids in reducing the inci-
dence and severity of anti–CTLA-4–IH remains to be ex-
plored. In anti–CTLA-4 mAb–induced colitis, preventive
administration of budesonide was not found to reduce the in-
cidence of this IRAE. Surprisingly, hypopituitarism was ap-
parently more frequent in the group receiving budesonide
(6.9% versus 3.5%) [57]. High-dose corticosteroid treatment
(and replacement therapy) does not appear to decrease the an-
titumor effects of CTLA-4 blockade [12]. When indicated, re-
treatment with ipilimumab after suspension because of
hypophysitis seems to be safe [12].

**DISCUSSION**

LYH/AH is emerging as a not so uncommon IRAE of anti–
CTLA-4 mAbs. Selective deficit of pituitary hormones may be
induced by various anticancer treatments [58, 59]. Usually, the
clinical onset of these endocrine AEs (E-AEs) is not acute and
they progress subclinically [58, 59]. The spectrum of E-AEs
experienced by patients treated with anti–CTLA-4 mAbs in-
cludes hypopituitarism, primary thyroid disease, and primary
adrenal insufficiency. These side effects have been occasion-
ally found in the same individual. The pathogenic mechanism
of these E-AEs seems to be related to autoimmunity [5, 8, 15,
17, 21]. The prevalence of this autoimmune hypophysitis is
variable among different studies (0%–17%) [50]. Autoim-
mmune hypophysitis has never been reported to be a conse-
quence of exposure to other classes of anticancer drug.
However, reversible or irreversible hypopituitarism may be a
side effect following treatment with other immunomodulatory
drugs, such as interferon-α [60–62]. A case of granulomatous
adrenohypophysitis occurring after treatment with interferon-
α2b and ribavirin for hepatitis C was reported [63]. Another
patient affected by hepatitis C experienced central hypothy-
roidism during treatment with pegylated interferon-α and riba-
virin and a clinical diagnosis of hypophysitis was made [64].

The clinical presentation of LYH/AH (or other forms of
hypophysitis) is similar to that of any expanding sellar mass. In
healthy individuals, LYH/AH is suspected if symptoms appear
in temporal relationship with pregnancy and postpartum. Simi-
larly, the diagnosis should be considered when symptoms oc-
cur in cancer patients under treatment with anti–CTLA-4
mAbs. Simple clinical guidelines for diagnosis and treatment
can be routinely adopted (Fig. 1).

Patients who need to receive anti–CTLA-4 mAbs should
be carefully educated on the importance of their vigilance in
early detection and prompt reporting of symptoms potentially
related to IRAEs, and that these symptoms may occur weeks to
months after the start of treatment. In these patients, TSH, free
T4, serum electrolytes, serum glucose, and blood cell counts
should be assessed before initiating treatment and before each
cycle. If the patient develops symptoms such as headache, nau-
sea, vomiting, lethargy, or constipation, the drug should be
withheld and tests, including morning cortisol, should be re-
done. In addition, when anti–CTLA-4–IH is suspected, refer-
ral to an endocrinologist or even admission to a hospital, if
clinically indicated, is advisable. In these cases, a pituitary protocol MRI scan should be performed to evaluate for hypophysitis and complete pituitary function should be assessed (Fig. 1).

High-dose glucocorticoid therapy is the most widely used treatment for anti–CTLA-4–IH. If high-dose glucocorticoids are initiated, a suggested regimen is 4 mg dexamethasone every 6 hours for 7 days, followed by a gradual tapering to 0.5 mg daily and then a change to prednisone or hydrocortisone at replacement doses under the guidance of an endocrinologist [65]. A brief interruption of anti–CTLA-4 therapy may be warranted during the acute stage of hypophysitis. However, once hypophysitis resolves with appropriate treatment and adequate hormone replacement has been tailored, rechallenge with the anticancer treatment should be considered, providing that the anti–CTLA-4 therapy may prolong survival in a patient with an otherwise fatal malignancy. Clearly, this decision should be made on an individual case basis. If the agent is restarted, close monitoring of pituitary function should be done [65].

Several issues concerning anti–CTLA-4–IH remain to be fully elucidated. The exact incidence of this and other E-IRAEs, the reason for the unusually high prevalence in males, and the role of CTLA-4 gene polymorphisms, which are known to correlate with the development of autoimmunity, need to be better clarified in larger studies. Also, the lower incidence of anti–CTLA-4–IH in patients exposed to tremelimumab than in those exposed to ipilimumab remains to be confirmed. In addition, although tumor regression has been frequently associated with IRAEs, correlation between tumor response and the incidence and severity of IRAEs needs to be defined using an appropriate analytical approach [24].

Of major importance, the exact immunologic mechanisms responsible for both anti–CTLA-4–induced tumor regression and IRAEs have not been clearly explained. It was initially suggested that anti–CTLA-4 mAbs may act by depleting T-regulatory cells (T-regs) [19]. In another study, the antitumor and autoimmune effects were a result of the direct activation of CD4+CD8+ effector cells [15]. Although CD8+ cytotoxic T lymphocytes are likely to play a major role, the exact tumor and tissues antigen(s) involved in the tumor response and toxicity are unknown. It is still unclear whether the effects are a result of T cells specifically acting against antigens shared by tumor and normal cells or a result of concomitant activation of multiple populations with separate antihost and antitumor activities [8, 19, 20, 66]. Melan-A, an antigen shared by melano-
noma cells and normal melanocytes, has been associated both with tumor regression and with immune-related skin reactions [66]. In a patient affected by mM and treated with ipilimumab, marked melan-A–specific T-cell reactivity in tumor and skin tissue was found, with CD8 T cells localized to nevi and a simultaneous increase in melan-A–specific CD8 T cells in the peripheral blood [66].

It has been hypothesized that anti–CTLA-4–IH may be induced by antibodies directed against the pituitary gland [53], but the presence of antipituitary antibodies in patients who receive anti–CTLA-4 mAbs remains to be demonstrated.

To the best of our knowledge, the diagnosis of anti–CTLA-4–IH has always been made by clinical, laboratory, and radiological data. No patient has undergone a pituitary biopsy. Indeed, biopsy of the pituitary gland in cancer patients suspected of having developed anti–CTLA-4–IH raises a series of ethical issues, and it is not necessary either for diagnosis or for treatment. Nonetheless, this remains the only way to obtain essential information to improve our knowledge on the pathophysiology of this IRAE. Pituitary autoimmunity is a complex and incompletely defined spectrum of clinical conditions [26], ranging from histologically proven forms of LYH/AH to the presence of pituitary antibodies in apparently healthy individuals [28]. Interestingly, Mirocha et al. [67] observed two distinct entities of primary LYH that can be distinguished on the basis of the prevalence of T-reg or T-17 helper lymphocytes (THL-17). One of these entities, in agreement with the classical description of LYH/AH, demonstrates an autoimmune process with THL-17 dominance and lack of T-reg. The other one appears as a process in which T-reg control the immune response, which may not be self-targeted but foreign targeted (infective agents?). Hypophysitis triggered by an immune homeostatic process should not be treated with immunosuppression, whereas autoimmune-sustained hypophysitis may benefit from it [67]. Patients with anti–CTLA-4–IH usually benefit from corticosteroids and this ex juvantibus criterion, together with other clinical aspects, may indirectly confirm its autoimmune pathogenesis. The potential of the precautionary use of steroids in reducing the long-term sequelae of this E-IARE, especially in preventing prolonged substitutive treatment, still remains to be evaluated.

Because the hurdles in defining the histological characteristics of anti–CTLA-4–IH persist, anti–CTLA-4–IH offers a unique opportunity to assess the fluctuation of the available pituitary antigens and relative antibodies, with the aim to improve their reliability as diagnostic and predictive tools. Pituitary antigens and antibodies could be monitored in a homogeneous cohort of patients with a specific disease and known pituitary-damaging agents, such as anti–CTLA-4 mAbs, at baseline, before each cycle of treatment, and during follow-up. Such a study would offer the possibility of defining a series of important clinical, laboratory, and radiological correlations, including refinement of the diagnosis and the real incidence of anti–CTLA-4–IH, the potential existence of a subclinical form of anti–CTLA-4–IH, the impact (if any) of this syndrome on the quality of life of patients, and the possible predisposition of a subgroup of these patients to develop anti–CTLA-4–IH and other E-AEs. This approach appears even more logical in light of recent data regarding the predictive role of antibodies to thyroglobulin and thyroperoxidase and the TSH receptor in the development of thyroid autoimmune disease [68]. Similarly, in a population of patients with autoimmune polyendocrine syndrome, measurement of antipituitary antibodies allows the identification of patients at higher risk for developing pituitary autoimmune dysfunction [49].

CONCLUSIONS

Hypophysitis is an infrequent IRAE triggered by anti–CTLA-4 mAbs. Because the clinical suspicion of anti–CTLA-4–IH can only be based on symptoms, it should be considered when hypopituitarism or sellar mass-effect symptoms appear in cancer patients under treatment with this class of drugs. This IRAE, if promptly suspected, may be presumptively diagnosed and treated, thus avoiding life-threatening complications, namely, acute adrenal insufficiency. Appropriate correlative studies on anti–CTLA-4–IH may contribute to improving our knowledge regarding the pathophysiology of pituitary autoimmunity.

AUTHOR CONTRIBUTIONS

Conception/Design: Francesco Torino, Agnese Barnabei, Salvatore M. Corsello
Collection and/or assembly of data: Francesco Torino, Agnese Barnabei, Salvatore M. Corsello
Data analysis and interpretation: Salvatore M. Corsello, Francesco Torino, Agnese Barnabei, Roberto Salvatori, Liana De Vecchis
Manuscript writing: Francesco Torino, Agnese Barnabei, Salvatore M. Corsello, Roberto Salvatori, Liana De Vecchis
Final approval of manuscript: Francesco Torino, Agnese Barnabei, Liana De Vecchis, Roberto Salvatori, Salvatore M. Corsello

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