Anti-CTLA-4 therapy-related autoimmune hypophysitis in a melanoma patient
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Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is an immunoregulatory molecule expressed by activated T cells and resting CD4\textsuperscript{+}CD25\textsuperscript{+} T cells. In patients with advanced melanoma, anti-CTLA-4 antibody therapy achieves cancer regression in 15% of patients. Treatment may be associated with grade III/IV autoimmune manifestations that included dermatitis, enterocolitis, hepatitis, uveitis, and rarely hypophysitis. Many of these toxicities require and respond to brief courses of high-dose corticosteroids. We report on a case of autoimmune hypophysitis with severe clinical symptoms that resolved rapidly after treatment with steroids. It is important to consider both autoimmune hypophysitis and brain metastasis in the differential diagnosis of melanoma patients receiving CTLA-4 blockade who present this constellation of symptoms. "Melanoma Res 00:000–000 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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A 60-year-old man with stage IV M1c melanoma (adrenal gland lesion of 10 cm in diameter and abdominal lymph node metastases up to 1.9 cm) without evidence of brain metastases following magnetic resonance imaging (MRI) was treated with ipilimumab, monoclonal antibody to cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), as second-line therapy in the context of a clinical trial. Earlier he had received first-line treatment with dacarbazine (800 mg/m\textsuperscript{2}) every 28 days combined with interferon-\textalpha 2b (3 Mio subcutaneously three times a week) for 2 months. He received ipilimumab 10 mg/kg once every 3 weeks for a total of four cycles (four doses in total) and tolerated this well without any side effects. The treatment was continued because of stabilized disease. After the seventh dose of this therapy, he presented with a severe frontal headache, emesis, ataxia, visual disorders (diplopia, vertical nystagmus), and vertigo. MRI of the brain showed a solitary brain lesion of 2 mm diameter and enlargement of the pituitary gland and stalk (Fig. 1). Laboratory tests showed low levels of serum cortisol, thyroid-stimulating hormone (TSH), and testosterone (cortisol 2.1 \textmu g/dl, normal range 6–23; TSH 0.07\textmu IU/ml, normal range 0.27–4.2; fT\textsubscript{4} 0.88 ng/dl, normal range 0.9–1.7; fT\textsubscript{3} 1.6 pg/ml, normal range 2.0–4.4; testosterone < 0.2 ng/ml, normal range 1.5–5.6).

The differential diagnosis included CTLA-4 antibody-induced autoimmune hypophysitis and metastatic disease to the pituitary gland (Fig. 2). The suspicion of a CTLA-4 antibody-induced autoimmune hypophysitis was confirmed. The small brain metastasis was treated with stereotactic surgery. Thyroxine replacement has since been discontinued because of recovery of TSH production. The patient continued to receive hydrocortisone 25 mg replacement until his death because of progressive disease in July 2008. The last MRI of the brain confirmed the absence of brain metastases in April 2008.

CTLA-4 is an immunoregulatory molecule expressed by activated T cells and resting CD4\textsuperscript{+}CD25\textsuperscript{+} T cells. Signals from the T-cell receptor binding with major histocompatibility complex alone are not sufficient for a
strong immune response and a second costimulatory
signal is required to overcome a threshold. This is
provided primarily by CD28 on the T cell that is triggered
by the binding to the molecule B7 expressed on the
antigen-presenting cells. However, once activated, T cells
express a second receptor, CTLA-4 that can also bind
the same B7 molecules. Unlike CD28, CTLA-4 inhibits
the T cell, blocking the ongoing immune response. Two
monoclonal antibodies that inhibit CTLA-4 are currently
in clinical development in a number of different tumor
types. The most relevant toxicities associated with this
are immune events related to stimulation of the immune
system [1,2]. The most frequently reported immune
events are diarrhea caused by an autoimmune colitis and
dermatitis. Rarely autoimmune hepatitis, uveitis, and
hypophysitis have been reported [3]. There is some
evidence that patients developing immune breakthrough
events have a better outcome [3]. These events are
sometimes serious or potentially fatal, and may require
treatment with high-dose corticosteroids and other
immunosuppressant therapies.

For patients with autoimmune hypophysitis, radiological
changes appear to predate the development of clinical
symptoms [4]. Histological examination of the pituitary
gland shows typically an infiltration by lymphocytes,
plasma cells, and macrophages. The pituitary gland seems
to be a target for autoimmunity although the pathogen-
esis remains unclear. Hypophysitis may cause impairment
of pituitary function, with low levels of adrenocortico-
tropic hormone, TSH, and gonadotrophins, resulting in
low levels of T4, cortisol, and testosterone [3]. Although
the symptoms of pituitary failure may be nonspecific,
the enlargement of the hypophysis may cause headache
and visual impairment [3]. In rare cases, autoimmune
hypophysitis also involves the neurohypophysis with
clinical signs of diabetes insipidus.

In contrast to other autoimmune events, where short
courses of high-dose steroids lead to a complete
resolution of symptoms, permanent hormone substitution
with physiological doses of steroids may be necessary
for patients with an autoimmune hypophysitis. Careful
consideration of pituitary function should precede the
discontinuation of hydrocortisone. There is no clear
evidence that the use of low-dose steroid therapy
adversely impacts on CTLA-4 treatment efficacy [2,3].

The presenting symptoms of immune-mediated hypo-
physitis may be subtle and clinicians need a high index
of suspicion. Early imaging with an MRI scan can
detect pituitary enlargement before the onset of com-
plete pituitary failure, ensuring timely treatment of this
potentially serious complication.

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