IPILIMUMAB-INDUCED HYPOPHYSITIS IN CANCER PATIENTS

AUTHORS: Christian Lafuente[1], Karina Arcano[1], Fernando Guerrero[2] , Agustina Pia Marengo[2]; Inmaculada Peiró [2], Ainara Soria[3], Juan José Diez[1], Carles Villabona[2] and Pedro Iglesias[1].
AFFILIATIONS: Departments of [1] Endocrinology and [3]Oncology, Hospital Ramón y Cajal, Madrid, Spain and Department of [2]Endocrinology, Hospital Bellvitge, Barcelona, Spain.

CONTEXT: Ipilimumab is a human monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA-4), which enhances stimulation of cytotoxic T lymphocytes resulting in an immune response against the tumor. This drug-induced hyperactivity of the immune system can lead to serious adverse effects including endocrine disorders such as autoimmune hypophysitis, thyroiditis and adrenal insufficiency.

OBJECTIVE: To report our experience on ipilimumab-induced hypophysitis (IIH) in patients with advanced cancer.

RESULTS: Four patients [3 men (75%); aged 67.5 ± 8.7 years (range, 59-75)] with advanced (stage IV) cancer, (3 melanomas and one prostate cancer) were recruited (table 1 and figure 1). The clinical presentation of IIH was similar in all cases regardless of the underlying tumor. IHH developed after 10-20 weeks of starting treatment, usually between 2 and 4 ipilimumab cycles. Main symptoms were fatigue (n=3) and headache (n=2), nausea (n=2) and vomiting (n=2). IIH was associated with partial or total hypopituitarism in 3 cases. Pituitary hormone deficiencies most frequently affected were corticotrophin (ACTH, n=3), thyrotropin (TSH, n=3) and gonadotropins (FSH and LH, n=3). Two patients showed prolactin and growth hormone deficiencies. One patient did not develop any pituitary hormone deficiency although magnetic resonance imaging (MRI) of the pituitary showed morphologic changes of hypophysitis. MRI study showed enlarged pituitary in 3 patients. All patients were treated with high steroid doses (>0.5 mg/kg/day of prednisone or equivalent). After 22.1 ± 13.8 months (range, 3.9-37.6) of follow-up from the first dose of ipilimumab, 3 patients remained with steroid hormone replacement therapy and 2 patients with replacement doses of levothyroxine. One patient recovered thyroid function.

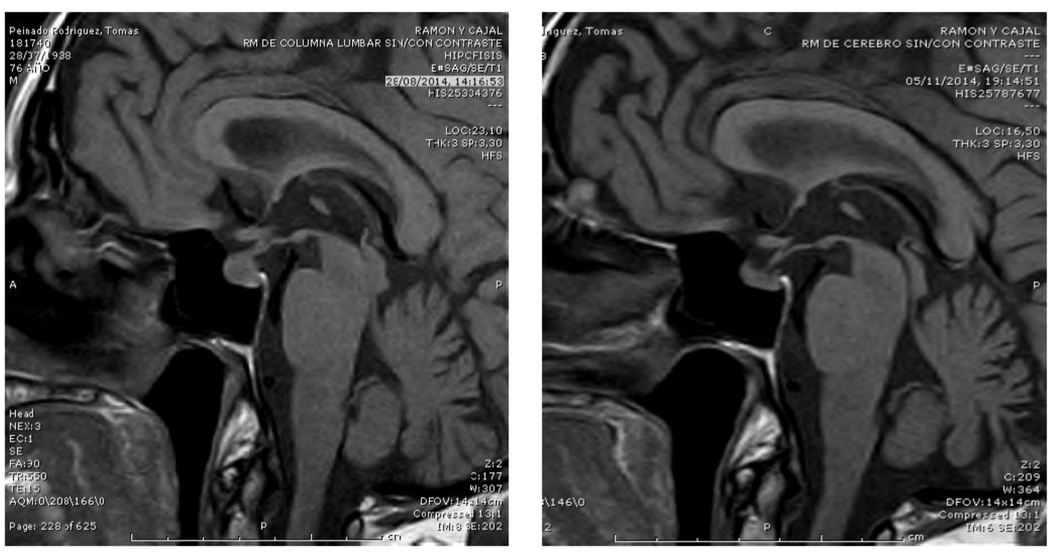

Figure 1. MRI showing enlarged pituitary gland and thickening of the pituitary stalk at IIH diagnosis (left) and three months after starting therapy (right) (patient # 3).

Table 1. Clinical and analytical features of the four patients with ipilimumab-induced hypophysitis.

	Case # 1	Case # 2	Case # 3	Case # 4
Sex	Male	Female	Male	Male
Age (yr)	61	59	75	75
Type of tumor	Uveal melanoma	Uveal melanoma	Acral lentiginous melanoma	Prostate adenocarcinoma
Ipilimumab dose	10 mg/kg	10 mg/kg	3 mg/kg	10 mg/kg
Number of cycles	4	3	3	2
Time to diagnosis (wk.)	10	15	12	19
Hypopituitarism (yes/no)	Yes	No	Yes	Yes
Number of affected axes	4	0	4	5
Corticotropic (ACTH)	Yes	No	Yes	Yes
Thyrotropic (TSH)	Partial	No	Yes	Yes
Gonadotropic (FSH and LH)	Yes	No	Yes	Yes
Somatotropic (GH)	No	No	Yes	Yes
PRL	Yes	No	No	Yes
MR Imaging	Enlarged pituitary gland	Enlarged pituitary gland and pituitary stalk	Enlarged pituitary gland	No abnormalities
IIH therapy	Prednisone 70 mg/day	Dexamethasone 4 mg every 6 hours	Methylprednisolone 60 mg/day	Dexamethasone 4 mg every 6 hours
Time of follow-up (mo.) after starting Ipilimumab therapy	22.9	23.9	3.9	37.6
Pituitary function at the last clinical visit	Partial hipopituitarism: ACTH and gonadotropins deficiencies	Normal	Hipopituitarism: ACTH, TSH, gonadotropins and GH deficiencies	Partial hipopituitarism: ACTH, TSH and GH

Abbreviations: NA, not available; MR, magnetic resonance; IIH, ipilimumab-induced hypophysitis

CONCLUSION: IIH is an immune-related adverse event that can compromise the patient's life because of the possibility of development of adrenal and thyroid insufficiency in a high percentage of patients. Glucocorticoids are the treatment of choice. Hormone replacement therapy is indicated according to hormone deficiencies. Patients receiving immunomodulatory therapies should be closely monitored by baseline and follow-up hormone assessment.

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Christian Lafuente Bernal
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