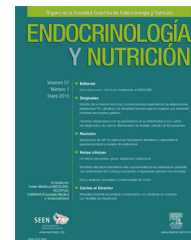




# ENDOCRINOLOGÍA Y NUTRICIÓN

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## SCIENTIFIC LETTER

### Panhypopituitarism and lung neoplasm: A case study

#### Panhipopituitarismo y neoplasia pulmonar: presentación de un caso

Pituitary metastases occur in between 1% and 1.5% of patients with malignant tumors. Metastases was first described in 1857 in the autopsy of a patient with disseminated melanoma. Since then, only 500 other cases have been reported, most frequently found in patients with advanced cancer, particularly breast and lung cancer. Pituitary metastasis usually appear in patients over the age of 60, regardless of their sex. Metastases have a preference for the posterior part of the pituitary gland because, unlike the anterior part, it obtains its blood supply directly from the systemic circulation, diabetes insipidus being the most frequent form of presentation.

A 57 year-old male was admitted to the hospital with a 5 month history of asthenia, anorexia and a 10 kg weight loss. Additional symptoms included increased coughing and 5 l/day polyuria. The patient had stopped smoking 5 years earlier and had a history of type 2 diabetes mellitus with good glycemic control on oral hypoglycemic agents. On arrival at the emergency department the patient also reported several episodes of symptomatic hypoglycemia despite the withdrawal of hypoglycemic agents. A chest X-ray was performed and revealed a mass in the lower lobe of the right lung. Subsequent bronchoscopy confirmed bronchogenic carcinoma, for which the patient was admitted to the oncology department. For staging reasons a body CT scan was performed, showing bone and hepatic metastases.

Consultation with the endocrinology department was requested due to persistent hypoglycemia and polyuria. When questioned, the patient reported a 5 month history of polyuria and polydipsia, along with asthenia, constipation, decreased libido and frequent hypoglycemia. Laboratory results showed: glucose 53 mg/dl (valores normales [VN]: 75–110 mg/dl), creatinine 0.84 mg/dl (VN: 0.6–1.4 mg/dl), plasma sodium 146 mEq/l (VN: 135–145 mEq/l), plasma potassium 4.3 mEq/l (3.5–5 mEq/l), plasma osmolality 307 mOsm/kg (VN: 278–305 mOsm/kg), basal cortisol 1 mcg/dl (VN: 6.2–19.4 mcg/dl). Suspecting diabetes insipidus and adrenal insufficiency, pituitary function tests, ACTH (an adrenocorticotrophic hormone)

stimulation test and water restriction test were requested. Plasma cortisol 30 min after 250  $\mu$ g of ACTH increased to 10.60 mcg/dl and to 11 mcg/dl at 60 min. The ACTH concentrations were 3 pg/ml. All of these data were consistent with secondary adrenal insufficiency. The remainder of the study demonstrated central hypothyroidism and hypogonadotropic hypogonadism: FT4 (free thyroxine) 0.66 ng/dl (VN: 0.9–1.70 ng/dl), FT3 (free triiodothyronine) 1.51 pg/ml (2–4.4 pg/dl), TSH (thyrotropin) 0.2  $\mu$ U/ml (VN: 0.27–4.5  $\mu$ U/ml), total testosterone < 0.025 ng/ml (1.31–8.99 ng/ml), FSH (follicle stimulating hormone) 1.3 mU/ml (VN: 1.5–12 mU/ml), LH (luteinizing hormone) 1.11 mU/ml (VN: 1.7–8.6 mU/ml). No changes were observed in prolactin concentration (13 ng/ml; normal levels 4–15.2) or insulin growth factor (IGF-1) (85.3 ng/ml; NL 81–225 ng/ml). After 8 h of water deprivation, the patient had high plasma osmolality (310 mOsm/kg), high plasma sodium 148 mEq/dl and a urinary osmolality of 126 mOsm/kg (50–1000 mOsm/kg). The patient was given 2  $\mu$ g of desmopressin (DDAVP) and an hour later urine osmolality had risen to 250 mOsm/kg (more than a 50% rise), confirming the diagnosis of central diabetes insipidus.

Suspecting a space-occupying lesion causing panhypopituitarism a pituitary CT scan (computed tomography) was requested; magnetic resonance imaging (MRI) was contraindicated because he had a pacemaker. The CT scan revealed a focal uptake within the pituitary neurohypophysis and infundibulum that extended to adjacent hypothalamic regions.

The patient was started on levothyroxine 50 mcg/day, desmopressin 0.2 mg/day and hydrocortisone 20 mg/day. He also received pituitary radiotherapy and 6 cycles of chemotherapy. Three months after having started the treatment, thyroid function tests (FT4 0.98 ng/dl, TSH 0.40  $\mu$ U/ml, FT3 2.25 pg/ml), osmolality and plasma sodium were within normal range. Clinically, he had not had any more episodes of symptomatic hypoglycemia and diuresis had decreased to 1.5–2 l/day. However, imaging testing performed on completion of chemotherapy and radiotherapy revealed prominent tumor progression affecting bone, liver and causing vasogenic brain edema, which led to his death 2 months later.

In autopsy series, latent metastases to the pituitary gland are revealed in 5% of patients with known malignancy.<sup>1</sup> Breast cancer is the most common tumor to metastasize to the pituitary gland. Its frequency is followed by that of lung

cancer. Prostate, renal cell and gastrointestinal cancers, as well as lymphoma, leukemia, thyroid carcinoma and plasmocytoma, have also been reported to spread to the pituitary gland. Pituitary metastases from lung cancer is a rare clinical situation and less than 20 cases have been reported in the last 5 years.<sup>2,3</sup>

Metastatic deposits can reach the sella via several routes: direct hematogenous spread to the pituitary parenchyma or diaphragma sellae; spread from a hypothalamo-hypophyseal or infundibulum metastasis through the portal vessels; extension from juxtaseilar and skull base metastasis; and meningeal spread through the suprasellar cistern.

Metastases have a preference for the posterior part of the pituitary gland because, unlike the anterior part, it obtains its blood supply directly from the systemic circulation. The involvement of the pituitary infundibulum, like the one that affected our patient, is even less frequent.<sup>4</sup> McCormick et al., reviewing the location of pituitary metastasis in 201 cases, found an involvement of the posterior lobe, either alone or in combination with the anterior lobe, in 84.6% of the cases; whereas the anterior lobe was affected in 15.4% of the cases.<sup>1</sup>

Panhypopituitarism is a rare initial clinical presentation of metastatic disease. Although metastatic spread of neoplasms to the pituitary gland is a relatively common finding in autopsy series of cancer patients, less than 10% of these are symptomatic. The majority of patients are asymptomatic or succumb without identification of pituitary metastasis because of overwhelming systemic complications of malignancy, including fatigue, weight loss, or central nervous system involvement, which may mask symptoms of hypopituitarism. Accordingly, there may be a significant number of patients with primary cancers whose pituitary insufficiency is not appropriately diagnosed. The most common symptom seems to be diabetes insipidus reflecting a dominance of metastasis to the posterior lobe.<sup>5</sup> McCormick et al.,<sup>6</sup> in their review of 40 symptomatic cases noted diabetes insipidus in 70% of the cases, whereas only 15% of the cases had one or more anterior pituitary deficiencies. In the series by Morita et al.,<sup>7</sup> hypothyroidism and hypoadrenalism were the most frequent types of symptomatic hypopituitarism, followed by hypogonadism. In exceptional cases, metastasis may present with pituitary hyperfunctional syndrome. Cushing's syndrome and acromegaly have been reported in cases of metastasis to a preexisting corticotroph or somatotroph cell adenoma, as well as in exceptional cases of metastasis originating from primary tumors with ectopic ACTH or GH (growth hormone) secretion.<sup>8</sup>

Effective treatment for patients with pituitary metastasis is limited because when pituitary metastases are diagnosed the cancer is usually in an advanced stage. Surgery, chemotherapy and radiotherapy are the main treatment alternatives.<sup>1</sup> When our patient was diagnosed he was already at stage IV which made him ineligible for surgery. Thus, he only received chemotherapy and radiotherapy. Pituitary hormone substitution therapy is beneficial in ameliorating quality of life.

The prognosis of patients with metastasis to the pituitary gland is poor because of the aggressiveness of the

primary neoplasia. Mean survival length in clinical series is 6–7 months. In our patient's case it was 8 months. In a review of 72 cases it was found that only 10% of patients survived more than 1 year after diagnosis.<sup>9</sup>

To conclude we would like to point out that diabetes insipidus may be the first presentation of a hidden primary tumor and should always raise the suspicion of pituitary metastasis, since it is only present in 3% of the cases of adenoma. Differentiation between a benign lesion and metastasis is essential for determining the therapeutic plan and the prognosis.<sup>10</sup>

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