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CLINICAL CASE

Arterial hypertension of infrequent cause

A. Rosales-Castillo*, **A. Bustos-Merlo**

Servicio de Medicina Interna, Hospital Universitario Virgen de las Nieves, Granada, Spain

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Abstract Arterial hypertension is generally classified as primary or essential (90%), and secondary (10%). Infrequent causes of the latter include Cushing's syndrome, classified as ACTH-dependent and independent. A small percentage of ACTH-independent cases are due to ectopic ACTH secretion, generally due to neoplasia, and can present as arterial hypertension and hyperglycaemia that are refractory to pharmacological measures, metabolic alkalosis and hypokalaemia that are difficult to control, but which help guide the initial diagnosis.

We present two clinical cases with a diagnosis of ectopic ACTH secretion secondary to small cell lung carcinoma, in which one of the debut manifestations was unknown, difficult to control arterial hypertension.

PALABRAS CLAVE
Hipertensión;
Hipopotasemia;
ACTH;
Neoplasia

Hipertensión arterial secundaria de etiología infrecuente

Resumen La hipertensión arterial generalmente se clasifica en primaria o esencial (90%) y secundaria (10%). Entre las causas infrecuentes de esta última se encuentra el síndrome de Cushing, el cual se clasifica en hormona adrenocorticotropa (ACTH) dependiente e independiente. Un pequeño porcentaje de los casos de ACTH independiente son debidos a la secreción ectópica de ACTH, generalmente por neoplasias, pudiendo tener como manifestaciones, hipertensión arterial e hiperglucemia refractarias a medidas farmacológicas, alcalosis metabólica e hipopotasemia de difícil control, que por otra parte, sirven como orientación diagnóstica inicial. Presentamos dos casos clínicos con diagnóstico de secreción ectópica de ACTH secundaria a carcinoma microcítico de pulmón, en los que una de las manifestaciones principales al debut fue una hipertensión arterial no conocida de difícil control.

* Corresponding author.
E-mail address: anrocas90@hotmail.com (A. Rosales-Castillo).

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Cushing's syndrome encompasses a range of clinical manifestations because of excessive, prolonged, and inappropriate exposure to glucocorticoids. The most frequent cause is exogenous, and there are two main groups of endogenous causes: ACTH-dependent (85%) and ACTH-independent (15%).[1]

We present two cases with debut of arterial hypertension together with hyperglycaemia, metabolic alkalosis, and hypokalaemia secondary to ectopic ACTH secretion by a pulmonary microcytic carcinoma as the aetiology.

Case 1

A 47-year-old male, active smoker with chronic obstructive pulmonary disease GOLD 2 (moderate), presented with asthenia, generalised weakness, unquantified weight loss and oedema of the lower limbs for two months. Physical examination revealed elevated blood pressure (183/100 mmHg), generalised cutaneous and mucosal hyperpigmentation and bilateral oedema with pitting up to pretibial level. Laboratory results showed hyperglycaemia (278 mg/dL), hypernatraemia (147 mEq/L), severe hypokalaemia refractory to treatment (1.9 mEq/L), metabolic alkalosis (pH 7.51, bicarbonate 38.6 mEq/L, pCO2 56.8 mmHg) and significant elevation of LDH (1093 IU/L). The hormonal study showed elevated ACTH (2475 pg/mL), serum cortisol (60 mcg/dL) and 24-h urinary free cortisol (1192 μg/24 h) with suppression of aldosterone (69 pg/mL) and renin (0.7 ng/mL) (Table 1). Tumour markers were normal except for elevated chromogranin A (614 ng/mL) and neuronal specific enolase (124 ng/mL). CT scan showed a 60 × 58 × 65 mm left hilar mass (Fig. 1A) with metastatic involvement at pleural, mediastinal, hepatic (Fig. 1B), and left adrenal levels. Fibrobronchoscopy was performed with sample taking, which was compatible with small cell lung carcinoma. During admission, blood pressure was difficult to control despite treatment with three drugs at maximum doses (amlodipine, enalapril, spironolactone) and a diuretic (furosemide), requiring intermittent perfusion of urapidil. For glycaemic control, repeated adjustments of the bolus-basal regimen and frequent administration of insulin by infusion were required for levels >500 mg/dL, especially in the evening. Hypokalaemia levels of 2.5–3 mEq/L were achieved with maximum doses of spironolactone and intravenous supplementation at a dose of 1 mEq/kg per day, without achieving normal levels. The case was presented to a multidisciplinary committee and treatment with ketoconazole was decided. However, the patient died due to metabolic alterations before chemotherapy was administered.

Table 1 Comparison of analytical values of the two cases presented.

Analytical parameters	Case 1	Case 2
Glucose (mg/dL)	278	172
Sodium (mEq/L)	147	147
Potassium (mEq/L)	1.9	2.1
LDH (IU/L)	1093	436
pH	7.51	7.48
Bicarbonate (mEq/L)	38.6	45.4
pCO_2 (mmHg)	56.8	60.1
ACTH (pg/mL)	2475	160
Basal cortisol (mcg/dL)	60	56.3
24 h urine cortisol (μg/24 h)	1192	1950
Cortisol/creatinine (μg/g)	2613	2347

LDH: lactate dehydrogenase; pCO2: partial pressure of carbon dioxide; ACTH: adrenocorticotropic hormone.

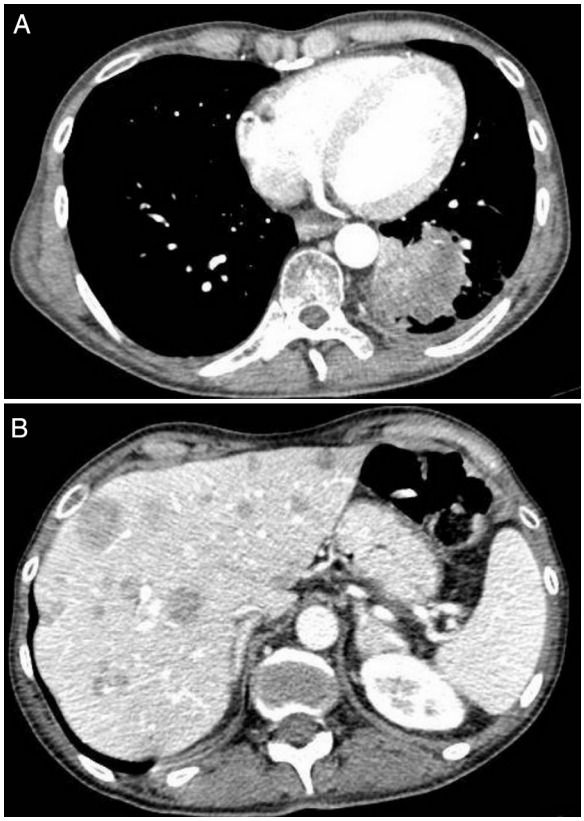

Figure 1 (A) Hilar mass with extension to the left lower lobe. (B) Multiple hypodense lesions in the liver parenchyma, compatible with metastatic lesions.

Case 2

A 59-year-old man with hypercholesterolaemia under treatment and an active smoker consulted due to a 5 kg weight loss, symptoms of insulinopenia (polyuria, polydipsia, and polyphagia) and abdominal pain in the epigastrium and hypochondrium of three months' duration, associated with recent onset of irritable cough. Physical examination revealed elevated blood pressure (170/105 mmHg) and significant hepatomegaly hard on palpation. Biochemistry showed hyperglycaemia (172 mg/dL), abnormal liver function (GOT 39 U/L, GPT 88 U/L, GGT 1335 U/L, AP 178 U/L), elevated LDH (436 U/L), sodium 147 mEq/L and potassium 2.1 mEq/L. Glycosylated haemoglobin was 8%. Venous blood gases showed metabolic alkalosis (pH 7.48, pCO2 60.1, bicarbonate 45.4). CT scan showed a right solid parahilar lesion (Fig. 2A) together with liver metastases (Fig. 2B), and bilateral adrenal thickening. Hormone study confirmed hypercortisolism: ACTH 160 pg/mL, basal cortisol 56.3 g/dL,

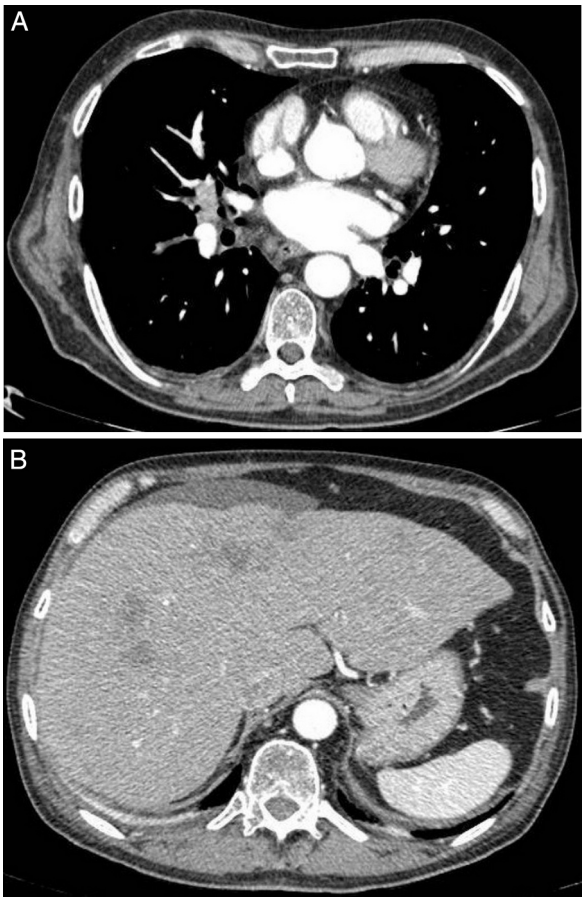

Figure 2 (A) Right solid hilar lesion. (B) Enlarged liver with hypodense lesions in its interior compatible with metastasis.

urine free cortisol 1950 g/dL together with aldosterone and renin suppression (Table 1). Tumour markers were normal except for elevated neuronal specific enolase (36.3 ng/mL). During admission, hyperglycaemia was difficult to control with a basal-bolus regimen and blood pressure readings were high (>160/100 mmHg) despite treatment, together with refractory hypokalaemia despite aldosterone antagonists and oral and intravenous replacement.

A biopsy of the liver lesion was taken, and the pathology was compatible with metastatic small cell lung carcinoma. The case was presented to a committee, and it was decided to start chemotherapy with carboplatin and etoposide. The patient died after starting the first cycle of chemotherapy due to massive haematemesis.

Within the ACTH-dependent group, 10–15% are caused by ectopic ACTH secretion by a non-pituitary tumour, the most frequent being bronchial carcinoid and small cell lung carcinoma,[2] although it has also been described in thymic, medullary thyroid and pancreatic neuroendocrine carcinomas.

The clinical manifestations can be classified into the classic cushingoid phenotype (proximal muscle weakness, peripheral oedema, full-moon facies, buffalo neck, wine-red striae),[3] but it can also manifest at the analytical level with refractory hypokalaemia, metabolic alkalosis or hyperglycaemia that is difficult to control, as in the two cases described. At the clinical level, the onset of refractory arterial hypertension in a patient with the abovementioned abnormalities should alert us to this possibility. In other cases, signs and symptoms may be less florid, proportional to cortisol levels but not to tumour size or exposure time.

There are two main goals in terms of treatment: control of hypercortisolism by steroidogenesis inhibitors or adrenal drugs (ketoconozol, mitotane), with close monitoring due to their interactions and potentially toxic effects; and treatment of the tumour itself, usually with chemotherapy according to histology (e.g., platinum and etoposide-based regimens in small cell lung carcinoma). The prognosis of small cell carcinoma associated with ectopic ACTH production is rather poor (three to six months survival),[4] generally due to advanced stage diagnosis, poor response to chemotherapy and the negative consequences of hypercortisolism, such as infections or episodes of thromboembolism.

To conclude, it is essential that this condition is suspected in the onset of unknown arterial hypertension that is difficult to control pharmacologically, hyperglycaemia or diabetes mellitus onset with high insulin requirements, and analytical alterations such as metabolic alkalosis and hypokalaemia.[5] Recognition of any of these manifestations will enable hypercortisolism to be confirmed and the active search for a possible secretory neoplasm, favouring the prompt administration of targeted treatment that can improve metabolic control and prognosis in these cases.

Conflict of interests

The authors have no conflict of interests to declare.

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