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Concurrent corticotroph pituitary tumor and granular cell tumor: A very uncommon association☆

Doble tumor hipofisario corticotropo-tumor de células granulares: una asociación muy infrecuente

Dear Editor,

Granular cell tumours (GCTs) belong to the group of posterior pituitary tumours (2017 WHO classification).[1] They are rare tumours, with the common characteristic of having positive immunohistochemistry for thyroid transcription factor 1 (TTF-1), S-100 protein and vimentin. Coexistence with functioning pituitary adenomas is exceptional, with very few cases described to date.[2] We describe the clinical case of a woman with a posterior pituitary GCT associated with Cushing's disease.

The patient was born in 1954 with a history of primary arterial hypertension, type 2 diabetes mellitus and right frontal meningioma. In 2014, she was diagnosed with Cushing's syndrome as a result of changes in the facial phenotype, muscle hypotrophy, increased abdominal girth, spontaneous haematomas and rib fractures. She did not present with stretch marks. Her abdominal girth was 101 cm, weight 60.9 kg, height 154 cm and blood pressure 165/88 mmHg. The biochemical functional study suggested an endogenous hypercortisolism of pituitary origin [urinary free cortisol (UFC) 318 μg/g creatinine (Cr) (normal 10-100 μg/g Cr)]. However, the pituitary magnetic resonance was normal. A petrosal sinus catheterisation confirmed the pituitary origin of the hypercortisolism. It was decided to

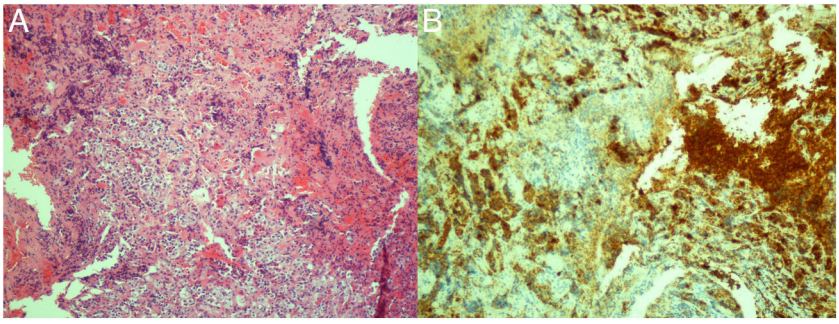

Figure 1 Histological study. A) Haematoxylin and eosin staining. B) Immunohistochemistry for ACTH.

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perform an endonasal endoscopic hemihypophysectomy in May 2016. During the surgical procedure, a normal pituitary was observed, but with a suspicious fibrous posterolateral area, which was resected. The anatomical pathology study reported the presence of a normal pituitary gland in one of the blocks. In the other, the presence of a fibrillar tumour composed of spindle cells, epithelioid cells and granular cells was observed, positive for S-100 protein and TTF-1, and compatible with GCT. Nests of cells positive for synaptophysin and ACTH were observed inside, concordant with a corticotropinoma (Fig. 1).

The surgery was not curative (UFC 311.6 μg/g Cr two months after the intervention), so treatment with fractionated stereotaxic radiotherapy was decided on (accumulated dose of 51 Gy in 28 sessions) and adjuvant ketoconazole was started (800 mg every 24 hours) in July 2016. Despite the high doses of ketoconazole, it was not possible to normalise the concentrations of urinary free cortisol, so the ketoconazole was replaced with pasireotide 20 mg every 28 days. The pasireotide treatment normalised UFC concentrations (87 μg/g Cr) and significantly reduced circulating ACTH and serum cortisol concentrations, but the metabolic control of the patient's prior diabetes was impaired. After three years of treatment with pasireotide and four years after radiotherapy, the patient presented biochemical criteria of controlled disease, with significant clinical improvement. The current dose of pasireotide is 20 mg every six weeks. Diabetes is adequately controlled with sitagliptin 100 mg/day and dapagliflozin 10 mg/day.

The co-existence of functioning pituitary adenomas and posterior pituitary tumours is rare. In a recently published review,[2] 10 cases of posterior pituitary tumours associated with hypercortisolism are described, seven of them with histology of pituicytomas and three with GCT. Updating the data reported by said review, at the time of writing this clinical case, there have been nine pituicytomas associated with Cushing's syndrome and only two GCTs, the one reported by Zhang et al.[3] and the current clinical case, already mentioned previously.[4] The discrepancy in the 2019 review with the aforementioned data is found in the three clinical cases reported by Feng et al.[5], which were in fact two pituicytomas (one associated with hypercortisolism and the other with acromegaly) and only one GCT, associated with acromegaly. The ninth case of pituicytoma associated with Cushing's disease has recently been published.[6] To date, there have been five cases of posterior pituitary tumours associated with acromegaly, two of them with GCT histology.[2] Guerrero et al.[2] theorise that the existence of a posterior pituitary tumour could produce substances (cytokines, growth factors) that stimulate the proliferation of adenohypophysis cells, fostering the emergence of functioning adenohypophyseal tumours.

The clinical findings of neurohypophyseal tumours are indistinguishable from non-functioning pituitary macroadenomas, their presentation more frequently being visual disturbances (64%) or headache (33%).[1] Usually, a space-occupying lesion is observed on imaging tests, and the definitive diagnosis is obtained with the result of the pathological anatomy study. Histological findings are comparable to those described in the clinical case, but as a differential characteristic compared to pituicytomas and fusiform cell oncocytomas, GCTs are positive in periodic acid Schiff (PAS) staining.[1]

It is agreed that the treatment for this type of tumour should be surgical, preferably via the transsphenoidal route. Prognosis is dependent on complete resection.[4] Due to their anatomical location and greater tendency to bleed (they are more vascularised structures), the surgery is more complex than that performed for pituitary adenomas.[4,7]

The present case describes a GCT with an infiltration of corticotropic cells, responsible for the hyperproduction of ACTH, without evidence of a sellar mass. Coincidentally, in the other case described of Cushing's syndrome and GCT[3] a tumour mass wasn't visualised on magnetic resonance either. However, biochemical control was achieved after the intervention. In the present case, use of radiotherapy was necessary as an adjuvant treatment to control hypercortisolism in the long term. Ketoconazole was used as medical treatment, without response, so it was decided to switch to pasireotide.

Pasireotide is the first agent with a direct effect on pituitary hormone secretion approved in the SmPC for the treatment of Cushing's disease. It has a high affinity for the somatostatin receptor type 5 (SSTR5), which is strongly expressed in corticotropinomas, having shown normalisation and reduction of hypercortisolism in its pivotal studies.[8] In 'real life'[9] a 68% biochemical normalisation of hypercortisolism is described in resistant or recurrent Cushing's disease (previously treated with surgery, radiotherapy or medical treatment). This suggests that there must be one or more differential characteristics in the pasireotide-responsive tumour subgroup, perhaps a higher expression of SSTR5. It is possible that the suggested pathogenesis for the association of two contiguous but different gland tumours may explain the excellent response of ACTH hypersecretion to treatment with pasireotide seen in the case described. Obviously it would take a much larger series to reach a conclusion. Unfortunately, we do not have molecular data available on the expression of somatostatin receptors in this tumour, so it is not possible to establish a relationship with the response to pasireotide.

We present the case of a patient with GCT with corticotropic cell nests in its interior responsible for Cushing's disease with excellent response to treatment with pasireotide.

Ethical considerations

Informed consent is obtained from all patients operated on for pituitary disease at our centre, whereby they agree to the inclusion of their samples in the biobank and the use of their anonymised clinical data in scientific dissemination.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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COVID was not to blame☆

No toda la culpa fue de la COVID

We present a case of severe hyponatraemia in a 67-year-old male patient, admitted to a tertiary hospital with a diagnosis of SARS-CoV-2 coronavirus respiratory infection confirmed by PCR. The patient had a medical-surgical history of ischaemic heart disease with revascularised acute myocardial infarction (AMI) in 2009, congenital right hemiparesis, mild intellectual disability, hydrocephalus and pharmacologically well-controlled epilepsy.

At 20 days following admission, he developed symptoms compatible with facial myoclonus, temporary disorientation and dysarthria lasting four minutes, with complete recovery. On examination he was conscious and oriented, with a blood pressure of 169/89 mmHg, afebrile, with capillary blood glucose of 180 mg/dl and arrhythmic tachycardia at 130 beats per minute, with known atrial fibrillation confirmed by ECG at admission.

Previously, the patient did not have fluid therapy. Treatment with 300 mg of amiodarone was then started and urgent blood tests were requested, highlighting hyponatraemia of 108 mEq/l (results in Table 1, 2nd column, with previous tests in 1 st column). The patient was re-evaluated and still did not present any neurological abnormalities, so admission to the ICU was ruled out and an infusion was started of 250 ml of 3% hypertonic saline in four hours. At that time, thyroid dysfunction (TSH: 1.62 mU/l) and adrenal insufficiency (ACTH: 24.2 pg/ml and basal cortisol: 15 mcg/dl) were also ruled out. The lab test results after four hours are reflected in Table 1 (3rd column).

It was decided to leave an infusion of 500 ml 3% hypertonic saline to be administered in eight hours. After that, lab tests were performed again, including the N-terminal fraction of brain natriuretic peptide (NT-proBNP): 5350 pg/ml (previously 6830 pg/ml) (rest of the parameters in Table 1, 4th column). On examination, he presented with arterial hypertension (172/100 mmHg) and controlled heart rate, was afebrile and maintained a baseline oxygen saturation of 98%. There were no data on decompensated heart failure. When questioned in a targeted manner, he reported a daily intake of more than four litres of water, with preserved diuresis (he wore adult absorbent briefs at that time) and an increase of up to five bowel movements in 24 h. He had a good level of consciousness and in the rest of the examination only palpation of a non-painful infraumbilical mass stood out which was first assessed as possibly being a bladder overdistension, but that was ruled out due to good daily diuresis. At that time, abdominal CT was requested to rule out underlying neoplasia. The patient had undergone a pulmonary CT five days beforehand, which ruled out the presence of pulmonary thromboembolism, as well as neoplastic pathology, reporting the presence of lesions consistent with the underlying infectious process.

The treatment with omeprazole was suspended, as well as the daily furosemide tablet (the diuretic had been previously decreased, with decreasing NT-proBNP figures) and a fluid restriction of one litre of water was indicated, initiating an infusion of one litre of isotonic saline with two 10 ml ampoules of 20% hypertonic saline after calculating

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