[a] *Servicio de Endocrinología y Nutrición, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain*
[b] *Grupo de Investigación en Endocrinología, Nutrición, Diabetes y Obesidad, Instituto de Investigación del Principado de Asturias (ISPA), Oviedo, Asturias, Spain*

* Corresponding author.
E-mail address: raulrodriguezescobedo@gmail.com
(R. Rodriguez Escobedo).
◊ Main authors of the article.

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Clinical features of pheochromocytoma masked by VIP co-secretion

Características clínicas del feocromocitoma enmascaradas por la co-secreción de VIP

Vasoactive intestinal peptide-secreting tumors (VIPoma) are rare neuroendocrine tumors (incidence of 0.05–0.2/100,000/yr[1]) first described by Werner and Morrison presenting as a syndrome of watery diarrhea, hypokalemia and achlorhydria.[2] While about 95% of VIPomas arise from the pancreas, some have extra-pancreatic sources.[3,4] VIP-producing pheochromocytomas are extremely rare, with no more than a few cases reported to this date.[5] Due to its several manifestations, management of both conditions can prove to be challenging. We report the case of a woman with a rare VIP-secreting pheochromocytoma presenting as chronic diarrhea and severe hypokalemic metabolic acidosis.

A 63-year-old female was admitted to the Emergency Department for worsening profuse watery diarrhea despite fasting associated with weight loss (14% of total body weight in three months). Upon examination, she was found to be dehydrated and analytical revealed acute kidney injury and hypokalemic metabolic acidosis [*K* 2.8 mEq/L, (reference range (RR) 3.4–5.1); pH 6.9 (RR 7.35–7.45)] requiring intensive intravenous potassium replacement. No increase in inflammatory parameters was found. Mild hypercalcemia (10.9 mg/dL at admission, RR 8.9–10.0) remained after correction of dehydration (10.1 mg/dL), associated with a decreased parathyroid hormone (4.3 pg/mL, RR 15.0–68.3) and normal levels of parathyroid-related protein (<0.5 pmol/L, RR < 1.3). Stool culture and parasitology were negative and endoscopic studies revealed no abnormalities. Abdominal computed tomography (CT) revealed a 6 cm heterogeneous left adrenal mass, and subsequent magnetic resonance imaging (MRI) showed a 5.2 cm partially cystic mass with a hyperintense solid component on T2 (Fig. 1).

She had a history of episodic headaches accompanied by hypertensive crisis (systolic blood pressure > 220 mmHg) three years ago, which resolved after the onset of diarrhea. In the meantime, diabetes mellitus (DM) was diagnosed and initially controlled with metformin 2000 mg and pioglitazone 15 mg daily. Metabolic control has substantially worsened since the onset of diarrhea: HbA1c 9.2% (RR < 6.5) with 40 I.U. of insulin glargine, alogliptin 25 mg and pioglitazone 15 mg daily.

Analysis of the urinary specimen revealed markedly elevated metanephrine (1870 μg/24 h, RR 45–290) and nor-metanephrine (2388 μg/24 h, RR 82–500). VIP plasma levels were elevated, 113 pmol/L (RR < 30), as well as chromogranin A (>700 ng/mL, RR < 100). 123I-metaiodobenzylguanidine (MIBG) scan was performed because it was readily available, revealing high uptake at the topographical location of the left adrenal gland (Fig. 1).

Diarrhea responded poorly to loperamide. The response to treatment with octreotide was impressive, as the patient stopped intravenous fluids, and dehydration and hypokalemia were treated with a dosage of 100 mcg every 8 h. Treatment with octreotide also led to substantial improvements in glycemic control, with a reduction of more than 30% in the total daily insulin dose. Alpha blockade was initiated with phenoxybenzamine, titrated up to 30 mg twice a day, when optimal hemodynamic control was achieved.

Two weeks later, the patient underwent laparoscopic left adrenalectomy without complications. Histological examination revealed a 5.2 cm pheochromocytoma, Ki67 1%, PASS 0. Immunohistochemistry of neoplastic cells showed positivity to chromogranin, synaptophysin, bcl-2 and somatostatin. After surgery, the patient became asymptomatic and plasma VIP and urinary fractionated metanephrine levels normalized (VIP 16.9 pmol/L; metanephrine 59 μg/24 h; and normetanephrine 169 μg/24 h). Two years after surgery, the patient remains disease-free, with no need for antihypertensive therapy and in-target glycemic control with metformin 1700 mg/day (HbA1c 6.8%). The analyzes revealed normal calcium, PTH and vitamin D levels (9.1–9.4 mg/dL, 33.1 pg/mL, and 25 ng/mL, respectively).

We report the case of a middle-aged woman with a history of hypertensive crisis, probably caused by catecholamine excess, which resolved when symptoms related to VIP appeared. Its resolution coinciding with the onset of diarrhea might be explained by the increased secretion of VIP, which has vasodilating properties. VIP not only inhibits the absorption of water and electrolytes by the jejunum and the colon but also increases net intestinal secretion, causing secretory diarrhea.[6]

Coincidental diagnosis of DM with hypertensive crisis is justified, in part, by the pheochromocytoma induced hyperglycemia, and its worsening with the onset of VIP-related symptoms raises the question that the increased glycogenolytic activity of the VIP may play an important role, probably due to its structural homology with glucagon.[6] Also, achievement of better glycemic control with somatostatin analog (SSA) treatment supports our hypothesis, since SSAs are associated with hyperglycemia in other contexts.

Although the responsiveness of VIP-secreting pheochromocytomas to SSA has been questioned by Quarles et al.[7] due to a reported scarcity of somatostatin receptors, our patient had an excellent response with a relatively small dose of octreotide, with a drastic reduction in the number of dejections, reaching normokalemia with no acid-base disorders. In addition, control of diabetes was significantly improved. In

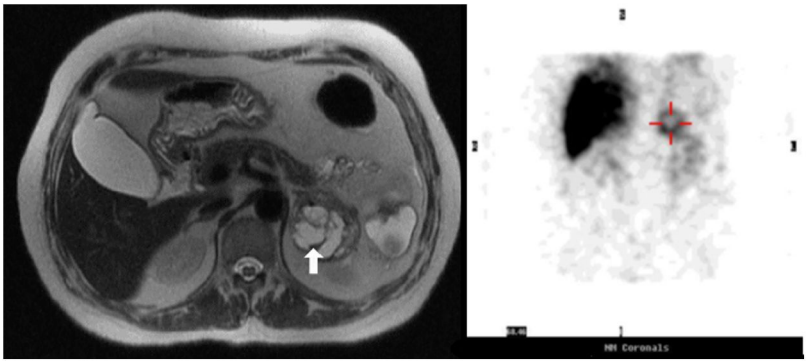

Figure 1 On the left: MRI, on T2, shows a 5.2 cm partially cystic mass (arrow) with a hyperintense solid component on T2. On the right: 123I-metaiodobenzylguanidine (MIBG) scan reveals high uptake of the lesion, that is at the topographical location of the left adrenal gland.

light of our results, a SSA treatment trial might be beneficial as a bridge to surgery for symptom and metabolic control.

Notably, hypercalcemia remained after correction of dehydration, so there may be other pathophysiological mechanisms behind this disorder. In fact, hypercalcemia is present in up to 50% of patients with VIPoma,[8] as a stimulatory effect of VIP on bone resorption has been suggested.[5,9]

Cure was achieved with surgery, and glycemic control was remarkably improved, according to previous reports of up to 90% of patients with pheochromocytoma who achieved ''cure'' of type 2 diabetes after surgery.[10]

Immunohistochemistry for VIP was not performed due to the difficult pathologic technique and a negative result would not rule out the diagnosis. Considering that the diagnosis was supported by typical clinical manifestations, high preoperative plasma VIP levels, clinical improvement with SSA and resolution after surgery, further study is not necessary.

This rare case illustrates the diverse and contrasting manifestations of VIP-secreting pheochromocytomas, since hormones can exert synergistic or antagonizing effects depending on the target site. The complexity and intricacy of these situations require a multidisciplinary team approach, including endocrinologists, internists and endocrine surgeons, in order to provide the best care available to each patient.

Authors' contributions

FSC drafted the manuscript. All authors were involved in critical revision of the manuscript and have approved the final version of the manuscript.

Ethical standards

Written informed consent for publication was obtained.

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Conflicts of interest

The authors declare no conflicts of interest.

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Francisco Simões de Carvalho[a,*], Joana Lima Ferreira[a], Mylene Costa[b], Catarina Tavares[c], Ana Paula Marques[a]

[a] *Department of Endocrinology, Hospital Pedro Hispano, Matosinhos Local Health Unit, Rua Dr. Eduardo Torres, 4464-513 Senhora da Hora, Matosinhos, Portugal*
[b] *Department of Medicine, Hospital Pedro Hispano, Matosinhos Local Health Unit, Rua Dr. Eduardo Torres, 4464-513 Senhora da Hora, Matosinhos, Portugal*
[c] *Department of Radiology, Hospital Pedro Hispano, Matosinhos Local Health Unit, Rua Dr. Eduardo Torres, 4464-513 Senhora da Hora, Matosinhos, Portugal*

* Corresponding author.
E-mail address: franciscosimoesdecarvalho@live.com.pt (F. Simões de Carvalho).

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Eye symptoms in acromegaly, beyond visual field alteration☆

Síntomas oculares en la acromegalia, más allá de la alteración del campo visual

Acromegaly results from chronic growth hormone (GH) hypersecretion which causes an increase in circulating insulin-like growth factor 1 (IGF-1) levels, once the articular cartilage is closed. It develops slowly, with its classic morphological changes having a gradual onset. The excess morbidity and mortality associated with this disease are due to osteoarticular, neurological and cardiovascular impairment. In the eyes, visual field impairment (due to compression of the optic pathway) and, less often, changes in corneal thickness are characteristic.[1] However, other eye symptoms are not common and therefore not included in the usual follow-up of this disease.[2,3]

We report the case of a 46-year-old woman with a history of hypertension being treated with irbesartan 150 mg daily and abnormal baseline blood glucose who visited the accident and emergency department due to painless vision loss in her right eye (RE) for the past 48 hours. She was assessed by ophthalmology and diagnosed with vitreous haemorrhage, which resolved without treatment. Fluorescein angiography showed vascular abnormality with venous stenosis and sheathing in the superior temporal retinal arcade of the RE with prominent vascular loops on the periphery. No neovessels or areas of vascular ischaemia were seen (Fig. 1A and C). Intraocular pressure (IOP) was normal, and there were no abnormalities in the left eye.

In the three months that followed, the patient had recurring episodes of vitreous haemorrhage with partial reabsorption. She was therefore referred for posterior vitrectomy and photocoagulation around the areas of vascular abnormality. Four days after vitrectomy, she presented rebleeding, whereupon the photocoagulation area was enlarged. Diabetic retinopathy, vasculitis and retinal tears were ruled out. Upon enquiry, she stated that her shoe size had increased and that her hands had thickened. As a result, acromegaly was suspected and she was referred to endocrinology.

The patient reported acral enlargement in the last decade, multiple bone pain attributed to osteoarthritis, and an increase in shoe size from 41 to 43. She no longer had menstrual cycles as of age 44. She had physical features consistent with acromegaly and galactorrhoea upon application of pressure. Baseline GH was >40 ng/mL (reference range [RR]: 0.0-5.0 ng/ml), and baseline IGF-1 was 944 ng/mL (RR: 41-209 ng/mL); these findings were confirmed in repeat testing. A 75-g oral glucose tolerance test revealed no GH suppression, with all points >40 ng/mL. IGF binding protein 3 (IGFBP-3) was 10.2 mcg/mL (RR: 3.4-7.6 mcg/mL). Magnetic resonance imaging (MRI) showed a pituitary adenoma measuring 14 mm x 20 mm x 14 mm that displaced the pituitary stalk to the right, compressed the pituitary gland, caused bulging of the diaphragma sellae and extended to the left cavernous sinus (Knosp grade 2) with no compromise of the optic chiasm (Fig. 1E). Colonoscopy revealed a tubular adenoma with high-grade dysplasia, resected with clear margins. Campimetry, echocardiography and thyroid ultrasound were normal. She was referred to neurosurgery for removal of the adenoma, which proceeded without incident. Pathology reported a pituitary adenoma with positivity in immunohistochemistry for GH and incidental positivity for prolactin with a low Ki-67 index.

Following surgery, the patient's quality of life improved; her bone pain resolved and her acral enlargement subsided. Her IGF-1 levels dropped; six month after surgery, they were 278 ng/mL. While awaiting hormonal re-evaluation, which was delayed by the COVID-19 pandemic, she started lanreotide 60 mg every 28 days, with normalisation of her IGF-1 levels. Her hypertension and elevated baseline blood glucose resolved without any need for drug treatment. Since her operation, she has not presented any visual abnormalities or evidence of vitreous haemorrhage. Follow-up fluorescein angiography showed persistent vascular malformations in the superior temporal area with no areas of ischaemia or neovessels in the RE (Fig. 1B and D).

Acromegaly of pituitary origin may be associated with visual field abnormalities due to compression of the optic chiasm in 18%-25% of patients.[2] Impairment starts at the periphery of the superior temporal fields and progresses to bitemporal hemianopia; in long-standing cases, it may even cause amaurosis. Evidence of other eye symptoms is limited.[1–3]

Elevated intravitreous IGF-1 levels have been implicated in the pathophysiology of proliferative diabetic retinopathy.[4] In addition, improvement in diabetic retinopathy has been reported in patients with diabetes who experienced pituitary apoplexy or underwent pituitary ade-

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