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

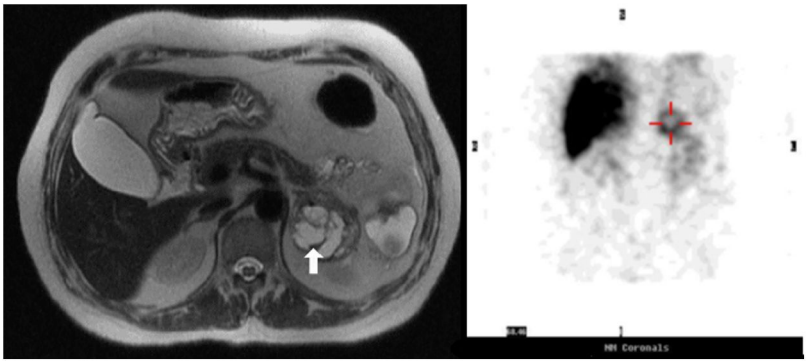

Figure 1 On the left: MRI, on T2, shows a 5.2 cm partially cystic mass (arrow) with a hyperintense solid component on T2. On the right: 123I-metaiodobenzylguanidine (MIBG) scan reveals high uptake of the lesion, that is at the topographical location of the left adrenal gland.

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

Eye symptoms in acromegaly, beyond visual field alteration

La acromegalia es consecuencia de la hipersecreción crónica y excesiva de hormona del crecimiento (GH) que produce aumento de las concentraciones circulantes de IGF-1, una vez cerrados los cartílagos de conjunción. Su desarrollo se produce de forma lenta y los cambios morfológicos clásicos son de instauración paulatina. El exceso de morbimortalidad asociado se debe a la afectación osteoarticular, neurológica y cardiovascular. A nivel ocular, son característicos la afectación del campo visual por compresión de la vía óptica, y con menor frecuencia, cambios en el grosor corneal[1]. Sin embargo, otros síntomas oculares no son frecuentes y no se incluyen dentro del seguimiento habitual de esta patología[2,3].

Presentamos el caso de una mujer de 46 años con antecedentes de hipertensión arterial en tratamiento con irbesartán 150 mg diarios y glucemia basal alterada, que acude a Urgencias por pérdida indolora de visión del ojo derecho (OD) de 48 horas de evolución. Es valorada por Oftalmología y diagnosticada de hemovítreo, que se resuelve sin tratamiento. Se realizó angiografía fluoresceínica que mostró alteración vascular con estrechamiento del calibre venoso y envainamiento en arcada retiniana temporal superior de OD con asas vasculares prominentes en la periferia. No se objetivaron neovasos ni áreas de isquemia vascular (fig. 1 A y C) La presión intraocular (PIO) fue normal y no había alteraciones en el ojo izquierdo.

Durante los siguientes tres meses, la paciente presentó episodios recurrentes de hemovítreo con reabsorción parcial por lo que fue sometida a una vitrectomía posterior y fotocoagulación alrededor de zonas vasculares alteradas. Cuatro días tras la vitrectomía, se produjo un nuevo sangrado, por lo que se amplía el área de fotocoagulación. Se descartaron retinopatía diabética, vasculitis y desgarros retinianos. Incidiendo en el interrogatorio manifiesta aumento de la talla de calzado y engrosamiento de manos, por lo que es remitida a Endocrinología con sospecha de acromegalia.

La paciente refería aumento de partes acras en la última década, dolores óseos múltiples atribuidos a artrosis e incremento de talla del pie del 41 al 43. Sin ciclos menstruales desde los 44 años. Presentaba rasgos físicos compatibles con acromegalia y galactorrea a la presión. La GH basal fue > 40 ng/mL (valor normalidad [VN]: 0,0-5,0 ng/mL) y la IGF-1 basal de 944 ng/mL (VN: 41-209 ng/mL), reconfirmados en una segunda determinación. Se realizó test de sobrecarga oral de glucosa 75 g, con ausencia de supresión de GH siendo todos los puntos > 40 ng/mL. La IGFBP-3 fue de 10,2 mcg/mL (VN 3,4-7,6 mcg/mL). En la RMN presentaba un adenoma hipofisario de 14 x 20 x 14 mm que desplazaba el tallo hipofisario hacia la derecha, comprimía la glándula hipofisaria, abombaba el diafragma selar y se extendía al seno cavernoso izquierdo (grado 2 Knosp-Micko) y sin compromiso del quiasma óptico (fig. 1 E). En la colonoscopia presentó un adenoma tubular con displasia de alto grado, resecado con márgenes libres. La campimetría, ecocardiografía y la ecografía tiroidea fueron normales. Fue remitida a Neurocirugía para exéresis del adenoma que se produjo sin incidencias, la anatomía patológica reveló un adenoma hipofisario con positividad en inmunohistoquímica para GH y ocasional para PRL con Ki-67 bajo.

Tras la cirugía, la paciente ha mejorado su calidad de vida, desapareciendo los dolores óseos junto a disminución de partes acras. La IGF-1 ha ido en descenso, siendo a los 6 meses de la cirugía 278 ng/mL, en espera de reevaluación hormonal demorada en el contexto actual de pandemia, motivo por el cual inicia lanreótida 60 mg cada 28 días, con normalización de IGF-1. La HTA y la elevación de glucemia basal se han resuelto sin precisar tratamiento farmacológico. Desde la cirugía no ha presentado alteración de visión ni datos de hemovítreo. En la angiografía fluoresceínica de control persistían malformaciones vasculares en área temporal superior sin áreas de isquemia ni neovasos en OD (fig. 1 B y D).

La acromegalia de origen hipofisario puede asociarse con alteraciones en el campo visual por compresión del quiasma óptico en el 18-25% de los pacientes[2]. La afectación se inicia en la periferia de los campos temporales superiores y evoluciona a hemianopsia bitemporal, pudiendo incluso causar amaurosis en casos de larga evolución. Los datos sobre otros síntomas oculares son escasos[1–3].

Se han implicado niveles elevados de IGF-1 intravítreos en la fisiopatología de la retinopatía diabética proliferativa[4].También se ha descrito mejoría en retinopatía diabética en pacientes con diabetes que experimentaban una apoplejía hipofisaria o resección del adenoma hipofisario, debido al efecto angiogénico de GH e IGF-1. Por el contrario, los niveles de factor de crecimiento endotelial vascular (VEGF), que están elevados en las patologías proliferativas retinianas son normales en la acromegalia[5]. Fuchtbauer et al.[6]