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SCIENTIFIC LETTER

SHORT syndrome: A good case can break an old acronym

Síndrome SHORT: un buen caso puede estropear un viejo acrónimo

Dear Editor,

A correct diagnosis of the type of diabetes mellitus (DM) is crucial to provide patients with the most appropriate treatment and follow-up.

Here we present the case of a 15-year-old female patient sent to our Diabetes Unit due to DM onset. During an episode of fever, a fasting plasma glucose level of 173 mg/dL was detected, and treatment with diet and physical exercise was started. The first blood test result in our service was: fasting plasma glucose of 137, glycated hemoglobin (HbA1c) of 7.6%, negative pancreatic autoimmunity, and non-stimulated C-peptide of 17.46 ng/mL. Regarding the family history, her grandmother had type 2 DM (DM2). With regards to the patient's history, low birthweight, failure to thrive, and delayed tooth eruption were the most remarkable findings. Her age at menarche was 14 years, and, afterwards, she developed secondary amenorrhea. The physical examination revealed 145 cm of height (below the 3rd percentile), 37.9 kg of weight, and a body mass index of 18 kg/m^2. Additional features were syndromic facies, with a broad forehead and mid-facial hypoplasia and prominent ears. She also had a high-pitched voice, facial and thoracic lipodystrophy, mild acanthosis nigricans on the axillae, complete pubertal development, and no signs of hyperandrogenism. In the complementary examinations due to low height and secondary amenorrhea, a female 46,XX karyotype was confirmed, as well as, negative celiac disease autoimmunity, and normal values of prolactin, estradiol, thyrotropin, follicle-stimulating hormone, luteinizing hormone, testosterone, 17-hydroyprogesterone, dehydroepiandrosterone sulfate, and insulin-like growth factor-1. Moreover, ultrasound detected polycystic ovaries (thus, she met the criteria for polycystic ovary syndrome, given the previously mentioned data). She also displayed a normal bone age (bone/chronological age: 17/16 years). Treatment with metformin 850 mg/12 h was started, with the patient recovering her menstrual cycles after 5 months and maintaining HbA1c < 7%.

The syndromic phenotype led us to conduct a genetic study through next generation sequencing (NGS) for monogenic diabetes, including genes associated with insulin resistance. A heterozygous, de novo (neither the patient's parents nor siblings were affected), pathogenic variant was identified in exon X of *PIK3R1*. This defect is associated with SHORT syndrome, which accounts for less than 60 cases worldwide.[1,2] c.1945C>T is the most frequently described pathogenic variant. *PIK3R1* encodes the regulatory subunit (p85α) of the PI3K holoenzyme. The subunit p85α stabilizes the catalytic subunit (p110α) that regulates the AKT/mTOR pathway. This pathway is critical for proper cell proliferation and growth. When p85α binds to p110α, phosphatidylinositol[3,4] bisphosphate is converted to phosphoinositol[3–5] triphosphate, which recruits AKT and initiates the downstream effectors of cellular growth. In SHORT syndrome, there is a diminished capacity to activate the AKT pathway and downstream targets. Reduced p85α results in p110α not being available for downstream effects.[3] SHORT syndrome is inherited in an autosomal dominant manner, although de novo pathogenic variant cases appear significant. The acronym refers to: Short stature; Hyperextensibility, Ocular depression, Rieger anomaly (a congenital ocular defect caused by anterior segment dysgenesis), and Teething delay. The features most consistently observed are mild intrauterine growth restriction, short stature, partial lipodystrophy, a characteristic facial gestalt (prominent forehead and deep-set eyes, relatively small middle and lower thirds of the face, prominent ears, etc.), insulin resistance and DM. Other frequent features include Axenfeld-Rieger anomaly or related ocular anterior chamber dysgenesis, delayed dentition and other dental issues, and sensorineural hearing loss.[3] These and other manifestations are present with variable frequency in subjects with this syndrome. In addition to the findings already mentioned in the description of our case, she also had mild impaired hearing, with 8000 Hz. As observed in the present case, not all manifestations considered in the syndrome acronym occur always, and others not mentioned may appear. SHORT syndrome is diagnosed in a proband with compatible clinical features (with emphasis on the facial gestalt) and a heterozygous pathogenic variant in *PIK3R1* identified by molecular genetic testing. Management consists of treating the manifestations and monitoring those that may appear.

Lewandowski KC et al. reported the case of an individual with an identical pathogenic variant who, after four days of treatment with metformin, showed worse glycemia levels and an increase in insulin resistance, identified through a 75 g oral glucose tolerance test (OGTT).[4] Our patient underwent the same test before starting treatment and after one week on 850 mg/12 h of metformin, which showed a good response to metformin (Fig. 1) and an improvement in homeostasis model assessment (HOMA) of insulin resistance, which changed from 2.6 (score associated with

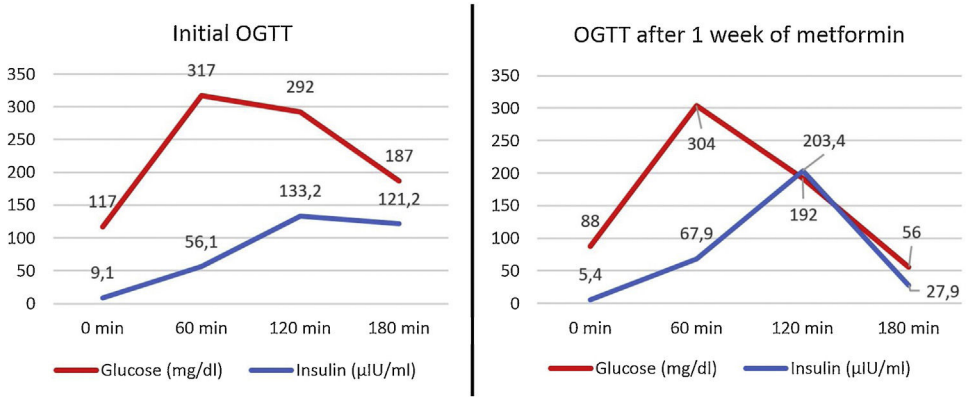

Figure 1 Results of 75 g oral glucose tolerance test (OGTT) before and after 1 week with metformin 850 mg/12 h in a patient with SHORT syndrome.

suspected insulin resistance) to 1.08 (no insulin resistance),[5] and in HOMA β cell function, which changed from 60.86 to 78.26. In Lewandowski KC et al. case, it was hypothesized that the worsening found after starting metformin could be since the drug partially inhibited the PI3K signaling pathway, a pathway that affects very immediate post-receptor steps of insulin signaling and that is mutated in SHORT syndrome. Nevertheless, the main mechanism by which metformin lowers blood glucose is the inhibition of hepatic gluconeogenesis. Hypoglycemic effects by action on muscle or intestine are considered less important.[6] Therefore, the possible affectation of the PI3K signaling pathway by metformin would not influence the main hypoglycemic mechanism of the drug, and the decrease in pancreatic glucotoxicity could explain the improvement in the insulin response to the OGTT.

This case demonstrates the relevance of achieving an accurate DM diagnosis. Indeed, the syndrome was diagnosed due to the assessment of the type of DM. NGS can be useful in patients with DM and a characteristic phenotype or several, apparently non-related, defects. *PIK3R1* gene should be incorporated into the genetic panels for the study of monogenic diabetes.

Authorship

All authors had access to the data and a role in writing this manuscript.

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Conflict of interest

The authors have no conflicts of interest to declare for this work.

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Carcinoma anaplásico de tiroides con supervivencia prolongada. A propósito de un caso

Anaplastic thyroid cancer with prolonged survival. Report of a clinical case

El carcinoma anaplásico de tiroides (CAT) es un tumor indiferenciado que deriva del epitelio folicular, infrecuente y extremadamente agresivo. Presenta una incidencia anual de uno a dos casos por cada millón de habitantes y representa 1-2% de todos los cánceres de tiroides[1]. Se manifiesta generalmente entre la sexta y séptima década de la vida, con una mayor incidencia en mujeres. Los factores de riesgo para el diagnóstico de CAT son, por un lado, el bajo nivel educativo y la presencia de bocio previo (ambos factores probablemente relacionados con el déficit de yodo), el grupo sanguíneo B y la obesidad[2,3].

Presentamos el caso de una mujer de 76 años con hernia de hiato por deslizamiento y reflujo gastroesofágico como antecedentes personales de interés, que ingresa en junio del año 2020 en la Unidad de Cuidados Intensivos por cuadro de disnea progresiva de 15 días de evolución asociada a tos no productiva y disfagia para sólidos. Las constantes vitales en el momento del ingreso eran tensión arterial 190/120 mmHg, frecuencia cardiaca 135 lpm y saturación de oxígeno basal 65%, por lo que precisó intubación orotraqueal y conexión a sistema de ventilación mecánica. Tras descartar infección por SARS-CoV-2, se realizó angiotomografía computarizada excluyendo tromboembolismo pulmonar, evidenciándose la presencia de una masa hipodensa que parecía depender del lóbulo tiroideo derecho sugerente de proceso neoformativo. Se completó el estudio con tomografía computarizada (TC) de cuello observándose una masa sólida, hipodensa, heterogénea, con calcificaciones de 43 x 34 x 44 mm que provocaba invasión de la luz traqueal por infiltración de la pared posterolateral derecha de la tráquea sin adenopatías laterocervicales de tamaño significativo. Ante la sospecha clínica de CAT, se decidió realizar biopsia con aguja gruesa (BAG), obteniéndose fragmentos de tejido compuesto predominantemente por necrosis avascular, con pequeños focos de células tumorales de hábito plasmocitoide, con abundante citoplasma y núcleo desplazado a la periferia. En el estudio inmunohistoquímico se observó expresión positiva nuclear débil para PAX-8 y TTF 1 y expresión débil para CD56, con ausencia de expresión para tiroglobulina, calcitonina, sinaptofisina y cromogranina. El índice de proliferación Ki-67 era bajo, pero la interpretación resultó dudosa por la presencia de intensa necrosis en la muestra. Con estos hallazgos se emitió el diagnóstico de CAT. Se realizó tomografía por emisión de positrones con ^{18}F-fluorodesoxiglucosa (PET/FDG) en el que se observaba masa cervical derecha con incremento de la actividad metabólica con una $SUV_{máx}$ de 28,5 e imágenes sugestivas de metástasis pulmonares bilaterales múltiples, ganglionares (en zona supraclavicular derecha y axilar izquierda), musculares y en aurícula derecha (fig. 1A).

Tras el diagnóstico de CAT y en espera del estudio molecular para detectar la presencia de la mutación del gen $BRAF^{V600}$, que resultó positiva, en junio de 2020 la paciente recibió dos ciclos de quimioterapia sistémica con carboplatino y paclitaxel y dos ciclos de radioterapia (RT) paliativa sobre la lesión tiroidea añadiendo un margen de 1 cm por sangrado activo por la traqueostomía, con una dosis total de 16 Gy. Asimismo, recibió soporte nutricional por

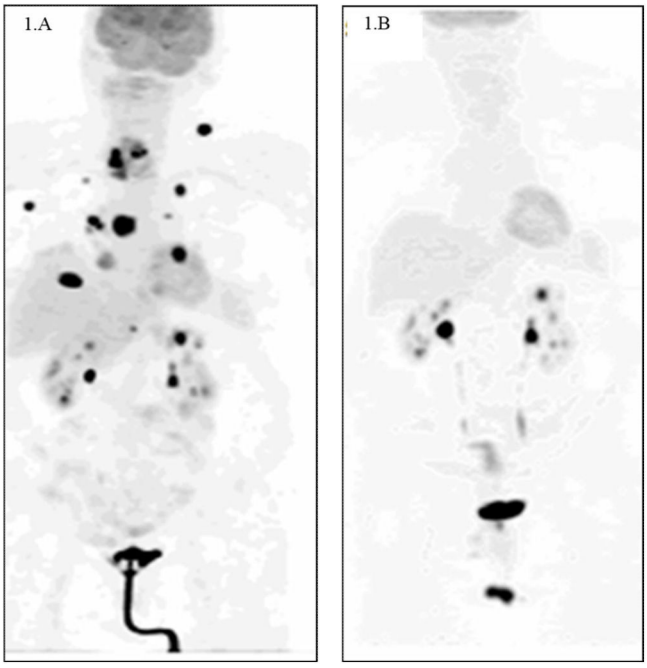

Figura 1 A) Tomografía por emisión de positrones con ^{18}F-fluorodesoxiglucosa (PET/FDG) al diagnóstico. Se observa masa cervical derecha con incremento de la actividad metabólica con una $SUV_{máx}$ de 28,5 e imágenes sugestivas de metástasis pulmonares bilaterales múltiples, ganglionares (en zona supraclavicular derecha y axilar izquierda), musculares y en aurícula derecha. B) PET/FDG tras 11 meses de tratamiento con inhibidores de BRAF/MEK (drabefenib-trametinib). Se observa involución morfometabólica de la masa cervical derecha, con desaparición de las lesiones metastásicas a todos los niveles.