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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

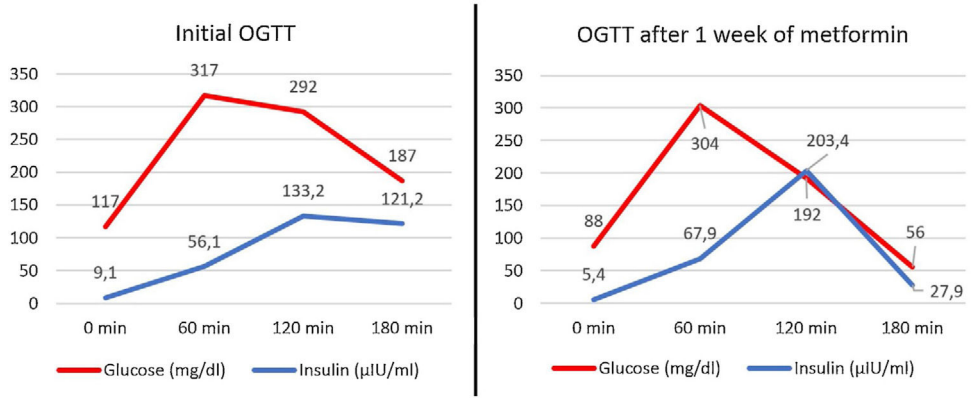

Figure 1 Results of 75 g oral glucose tolerance test (OGTT) before and after 1 week with metformin 850 mg/12 h in a patient with SHORT syndrome.

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.

References

1. Avila M, Dyment DA, Sagen JV, St-Onge J, Moog U, Chung BHY, et al. Clinical reappraisal of SHORT syndrome with PIK3R1 mutations: toward recommendation for molecular testing and management. Clin Genet. 2016;89:501–6.
2. Lee CL, Chuang CK, Chiu HC, Tu RY, Lo YT, Chang YH, et al. The first SHORT syndrome in a Taiwanese boy: a case report and review of the literature. Mol Genet Metab Rep. 2021;27:100768.
3. Innes AM, Dyment DA. SHORT syndrome. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington Seattle; 1993. Available from: http://www.ncbi.nlm.nih.gov/books/NBK201365/ [updated 4.6.20; cited 5.10.22].
4. Lewandowski KC, Dąbrowska K, Brzozowska M, Kawalec J, Lewiński A. Metformin paradoxically worsens insulin resistance in SHORT syndrome. Diabetol Metab Syndr. 2019;11:81.
5. Shashaj B, Luciano R, Contoli B, Morino GS, Spreghini MR, Rustico C, et al. Reference ranges of HOMA-IR in normal-weight and obese young Caucasians. Acta Diabetol. 2016;53:251–60.
6. LaMoia TE, Shulman GI. Cellular and molecular mechanisms of metformin action. Endocr Rev. 2021;42:77–96.

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

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

Anaplastic thyroid cancer (ATC) is an uncommon and extremely aggressive undifferentiated tumour derived from the follicular epithelium. It has an annual incidence of one to two cases per million inhabitants and represents 1%–2% of all thyroid cancers.[1] It generally manifests in a person's fifties and sixties, with a higher incidence in women. The risk factors for the diagnosis of ATC are, on the one hand, low educational level and previous goitre (both factors probably related to iodine deficiency), blood group B and obesity.[2,3]

We present the case of a 76-year-old woman with personal history of interest of a sliding hiatal hernia and gastro-oesophageal reflux, who was admitted to the intensive care unit in June 2020 due to a 15-day history of progressive dyspnoea associated with a non-productive cough and dysphagia for solids. The patient's vital signs at the time of admission were blood pressure 190/120 mmHg, heart rate 135 bpm and basal oxygen saturation 65%, for which she required orotracheal intubation and connection to a mechanical ventilation system. After ruling out SARS-CoV-2 infection, computed tomography angiography was performed, which excluded pulmonary thromboembolism, revealing the presence of a hypodense mass that seemed to be attached to the right thyroid lobe, suggestive of a neoformative process. The study was completed with computed tomography (CT) of the neck, where a solid, hypodense, heterogeneous mass was observed with calcifications measuring 43 × 34 × 44 mm that caused invasion of the tracheal lumen by infiltration of the right posterolateral wall of the trachea without lateral cervical lymphadenopathy of significant size. In view of the clinical suspicion of ATC, it was decided to perform a core needle biopsy (CNB), with tissue fragments composed predominantly of avascular necrosis obtained, with small foci of plasmacytoid-type tumour cells, with abundant cytoplasm and nucleus displaced to the periphery. In the immunohistochemical study, weak nuclear positive expression was observed for PAX-8 and TTF 1 and weak expression for CD56, with absence of expression for thyroglobulin, calcitonin, synaptophysin and chromogranin. The Ki-67 proliferation index score was low, but the interpretation was doubtful due to the presence of intense necrosis in the sample. With these findings, ATC was diagnosed. An ^{18F}-fluorodeoxyglucose positron emission tomography (FDG PET) scan was performed, revealing a right cervical mass with increased metabolic activity with an SUV_{max} of 28.5 and images suggestive of multiple bilateral pulmonary, lymph node (in the right supraclavicular and left axillary area), muscular and right atrium metastases (Fig. 1A).

After the diagnosis of ATC and awaiting the molecular study to detect the $BRAF^{V600}$gene mutation, which was positive, in June 2020 the patient received two cycles of systemic chemotherapy with carboplatin and paclitaxel and two cycles of palliative radiotherapy (RT) on the thyroid lesion, adding a margin of 1 cm for active bleeding from the tracheostomy, with a total dose of 16 Gy. She also received nutritional support with percutaneous endoscopic

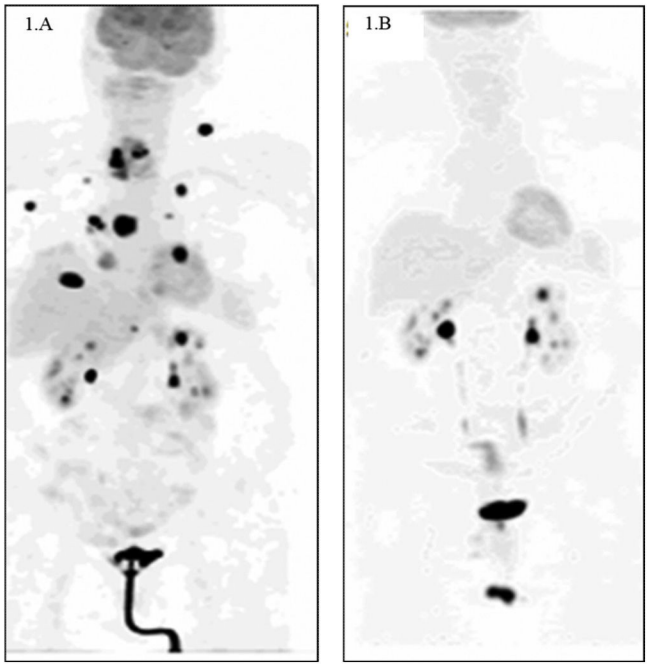

Figure 1 A) ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) on diagnosis. A right cervical mass with increased metabolic activity with an SUV_{max} of 28.5 and images suggestive of multiple bilateral pulmonary, lymph node (in the right supraclavicular and left axillary area), muscular and right atrium metastases. B) FDG PET after 11 months of treatment with BRAF/MEK inhibitors (dabrafenib-trametinib). Morpho-metabolic involution of the right cervical mass with disappearance of the metastatic lesions at all levels is observed.