7. Lane W, Weinrib S, Rappaport J, Hale C. The effect of addition of liraglutide to high-dose intensive insulin therapy: a randomized prospective trial. Diabetes Obes Metab. 2014;16:827–32, http://dx.doi.org/10.1111/dom.12286 [Epub 25.03.14; PMID: 24589127].
8. Morillas C, D'marco L, Puchades MJ, Solá-Izquierdo E, Gorriz-Zambrano C, Bermúdez V, et al. Insulin withdrawal in diabetic kidney disease: what are we waiting for? Int J Environ Res Public Health. 2021;18:5388.
9. Gamble JM, Chibrikov E, Twells LK, Midodzi WK, Young SW, MacDonald D, et al. Association of insulin dosage with mortality or major adverse cardiovascular events: a retrospective cohort study. Lancet Diabetes Endocrinol. 2017;5:43–52, http://dx.doi.org/10.1016/S2213-8587(16)30316-3 [Epub 17.11.16; PMID: 27865756].

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Early thyroid carcinoma in PTEN syndrome. Importance of immediate ultrasound screening

Carcinoma de tiroides precoz en un síndrome PTEN. Importancia del cribado ecográfico inmediato

The PTEN hamartoma tumor syndrome (PHTS) is a rare genetic predisposition disorder to cancer. It is caused by heterozygous germline variants in the tumor suppressor gene PTEN. PHTS is inherited in an autosomal dominant manner with high penetrance. The classic syndromes of Cowden, Bannayan-Riley-Ruvalcaba (BRR), and Proteus-like are currently considered PHTS. All 3 may present multiple mucosal hamartomas and both benign thyroid nodules and differentiated thyroid carcinomas (DTC) from childhood, while in adults, they predispose to breast, endometrial, kidney, and intestinal carcinomas.[1] There is still no consensus on screening for DTC, the only malignant neoplasm in childhood associated with PHTS.

We present a male diagnosed at the age of 5 with BRR syndrome due to a de novo heterozygous variant in the PTEN gene (c.165-2A>C). He had presented with psychomotor delay associated with dysmorphic features (macrocephaly, synophrys, a depressed nasal bridge, anteverted nares, thin upper lip, and diastasis of incisors) and congenital melanotic lesions on the penis. Immediately after the genetic diagnosis, at 5 years of age, an ultrasound revealed the presence of a non-palpable subcentimeter solid hypoechoic nodule in the right thyroid lobe (TI-RADS4). In serial imaging follow-ups, the lesion remained stable until 18 months, when 2 new solid nodules appeared: one in the left lobe—also hypoechoic (TI-RADS4)—and the other one in the right, isochoic but rapidly growing relative to its initial size (TI-RADS3). None exhibited suspicious features for malignancy. Fig. 1 shows the ultrasound image at the 18-month follow-up.

The difficulty of obtaining a satisfactory sample through fine-needle aspiration (FNA) in small nodules, the rapid growth of one of them, and the higher probability of malignancy—primarily of follicular lineage—in the PTEN syndrome led to the decision to perform a total thyroidectomy upfront. The histology of the surgical specimen demonstrated that the nodules were foci of bilateral multicentric follicular variant papillary carcinoma, the largest measuring 14 mm without extrathyroidal, vascular, or lymphatic invasion. The postoperative ultrasound found no residual tissue or lymphadenopathy, and the thyroglobulin levels and anti-thyroglobulin antibodies were undetectable, so no radioiodine was indicated.

PHTS is associated with early thyroid nodular disease, affecting up to half of patients in their third and fourth decades of life1. A total of 17% of nodules are malignant (DTC), with follicular carcinoma being predominant over papillary carcinoma. Those associated with PTEN account for 4% up 12% of total DTCs.[2]

Between 5% and 26% of pediatric patients with PHTS exhibit thyroid disease, with no clear sex predominance.[1,3–5] In children with PHTS, the high proportion of malignant lesions (DTC) is striking, which can reach 47% in some series,[3–5] as well as the predominance of follicular type, which represents 52% of DTCs in this syndrome, vs 10% in sporadic childhood DTCs.[5]

In PHTS, DTCs have been described as early as 4 years of age. In this syndrome, this neoplasm is not more aggressive vs sporadic cases; it is even postulated that it may be less aggressive. However, a higher frequency of multifocality is noted.[5]

Little is known about the natural history of thyroid nodules in this syndrome. In a follow-up study, 80% of nod-

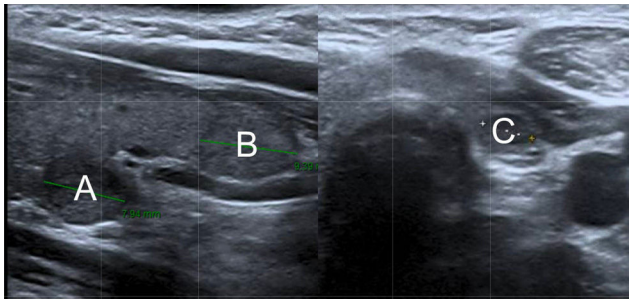

Figure 1 Ultrasound findings at the 18-month follow-up.
Left: Longitudinal section of the right thyroid lobe showing one 6.0 mm × 7.3 mm × 7.9 mm hypoechoic nodule A present since the first ultrasound, and one 14.5 mm × 9.4 mm × 6.2 mm rapidly growing isochoic nodule B.
Right: Transverse section of the left thyroid lobe showing one new-onset 4.3 mm × 3.9 mm × 4.0 mm hypoechoic nodule C.

ules without risk characteristics for malignancy remained unchanged after 3 years. It is speculated that most DTCs are de novo lesions and not a degeneration of previously benign nodules.[6]

Currently, there is no consensus on when, how, and how often to screen for DTC in this syndrome. Guidelines recommend annual screening, but there is significant variation in the age of onset, with some starting in infancy and others at older ages, even some beginning at 18 years.[6] In the Netherlands, for example, they recommend annual thyroid palpation and triennial ultrasound starting at age 10, arguing that only after that age does the risk exceed 5%, a figure that justifies screening for neoplasms.[5] However, in Germany, they advocate performing an ultrasound since syndrome diagnosis and with annual frequency, unless nodules are detected, in which case the ultrasound would be repeated sooner. This is based on the fact that in their series, the mean age of genetic diagnosis is 5.7 years, and even then, some children already show nodules on the first ultrasound.[7]

In conclusion, given the early appearance of DTC in our patient, its multicentricity and bilaterality, the inability to palpate the nodules due to their small size, and the effectiveness of thyroidectomy since the disease was confined to the thyroid, we advocate initiating thyroid pathology screening through ultrasound by an experienced professional as soon as PHTS is diagnosed.

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References

1. Hendricks LAJ, Hoogerbrugge N, Venselaar H, Aretz S, Spier I, Legius E, et al. Genotype-phenotype associations in a large PTEN Hamartoma Tumor Syndrome (PHTS) patient cohort. Eur J Med Genet. 2022;65:104632, http://dx.doi.org/10.1016/j.ejmg.2022.104632.
2. Milani D, Dolci A, Muller I, Pavesi MA, Runza L, Kuhn E, et al. Thyroid findings in pediatric and adult patients with PTEN hamartoma tumor syndrome: a retrospective analysis, and literature review. Endocrine. 2023;81:98–106, http://dx.doi.org/10.1007/s12020-023-03313-x.
3. Smith JR, Liu E, Church AJ, Asch E, Cherella CE, Srivastava S, et al. Natural history of thyroid disease in children with PTEN hamartoma tumor syndrome. J Clin Endocrinol Metab. 2021;106:e1121–30, http://dx.doi.org/10.1210/clinem/dgaa944.
4. Tuli G, Munarin J, Mussa A, Carli D, Gastaldi R, Borgia P, et al. Thyroid nodular disease and PTEN mutation in a multicentre series of children with PTEN hamartoma tumor syndrome (PHTS). Endocrine. 2021;74:632–7, http://dx.doi.org/10.1007/s12020-021-02805-y.
5. Jonker LA, Lebbink CA, Jongmans MCJ, Nievelstein RAJ, Merks JHM, Nieveen van Dijkum EJM, et al. Recommendations on surveillance for differentiated thyroid carcinoma in children with PTEN hamartoma tumor syndrome. Eur Thyroid J. 2020;9:234–42, http://dx.doi.org/10.1159/000508872.
6. Plitt G, Brewer T, Yehia L, Jin J, Shin J, Eng G. Development and progression of thyroid disease in PTEN Hamartoma Tumor Syndrome: refined surveillance recommendations. Thyroid. 2022;32:1094–100, http://dx.doi.org/10.1089/thy.2022.0181.
7. Plamper M, Schreiner F, Gohlke B, Kionke J, Korsch E, Kirkpatrick J, et al. Thyroid disease in children and adolescents with PTEN hamartoma tumor syndrome (PHTS). Eur J Pediatr. 2018;177:429–35, http://dx.doi.org/10.1007/s00431-017-3067-9.

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