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Cowden Syndrome Complicated with Thyroid Lesion: A Pediatric Case Report

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PTEN hamartoma tumor syndrome (PHTS) is a complex disorder caused by germline-inactivating mutations of the PTEN tumor suppressor gene. PTEN hamartoma tumor syndrome is a rare autosomal dominant syndrome with an elevated risk of malignancies, particularly thyroid cancer making its recognition essential to carry out therapeutic strategies.[1] Cowden Syndrome (CS) and Bannayan–Riley–Ruvalcaba syndrome is the most commonly reported variant of PHTS. The difference between the 2 conditions is that CS is usually observed in adults.[2] There are no evidence-based guidelines for the management of these conditions in infancy. Although patients with PHTS are known to have a predisposition for thyroid disease, the exact incidence, the pathophysiology and the best therapeutic management of these patients are still indeterminate. Reports of pediatric patients with CS and thyroid disease are extremely rare in the literature. We present a case report of a child with CS developing a thyroid lesion.

The patient was a full-term boy, with a birth weight of 3200 g (50th-75th centile), a head circumference of 35 cm (90th centile), and a height of 50 cm (75th-90th centile). He was referred to our department at the age of 6 for multiple lipomas of the trunk gradually increasing in number, appearing since the age of 3. On physical examination, we counted 7 renitent masses distributed on the trunk (Figure 1). He had a significant macrocephaly at 58 cm (+ 4.6 Standard Deviation) above the 97th percentile. The height was measured at 117 cm (+ 0.7 SD). Gingival verrucous lesions were identified. Abdominal and thoracic ultrasounds showed multiple subcutaneous and intra-abdominal hypoechoic masses crossed by hyperechoic striations. The biggest one was situated on the para-umbilical right side and measured 50 × 90 mm. Thoracic and abdominal magnetic resonance imaging was performed. They showed all these masses and confirmed the diagnosis of lipomatosis without compression. CS was suspected due to the association of lipomatosis, oral cavity lesions

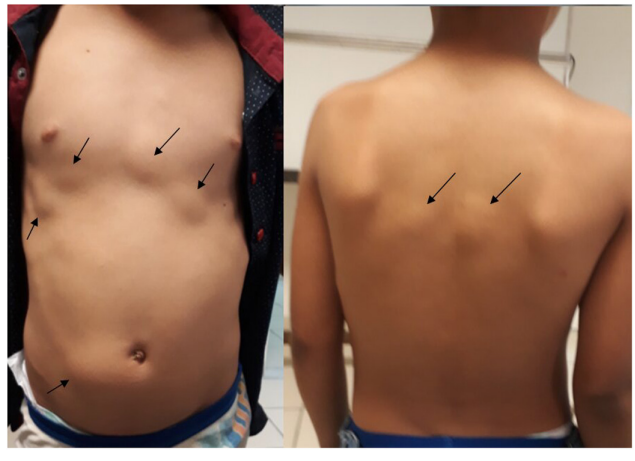

Figure 1. Black arrows: multiple renitent masses distributed on the trunk corresponding to lipomas.

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and macrocephaly. The molecular study showed a deleterious heterozygous mutation in exon 5 of the PTEN gene: c.455C gt;T (p.Gln149*). A multidisciplinary approach was conducted including a pediatrician, geneticist, dermatologist, and pediatric surgeon. Regular control with ultrasound and physical examination was done every 3-6 months. Thyroid function tests were performed with a normally functioning thyroid state. Genetic research on CS in the family was done and did not show any other cases. The US controls at the age of 10 years showed a dominant isoechoic solid nodule of 20 mm in the right thyroid lobe, Thyroid Imaging, Reporting and Data System (TIRADS) 4. Fine needle aspiration cytology result was inconclusive, classified in category I based on The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC, category I). Attending to the risks inherent to CS, the patient has a partial thyroidectomy. Histological examination revealed a benign adenoma.

Patients with PHTS should be especially concerned with regard to thyroid disease.[2-4] Thyroid cancer can be often the most serious complication observed in the evolution of CS.[4-6]

Reports of pediatric patients with PHTS and thyroid disease are extremely uncommon. Table 1 presents the different pediatric cases of PHTS with the appearance of thyroid lesions reported in the literature.[5-11] Starting at the age of 18, the National Comprehensive Cancer Network's clinical guidelines advised that patients with CS should get a yearly physical examination.[9] Our patient was 6 years old at the time of the diagnosis, and

Table 1. Reported Pediatric Cases in Literature of PHTS with Thyroid Lesions

Series	Mean Age (Years)	Macrocephaly	Additional Clinical Features	Mutations	Thyroid Abnormalities	Mean Age of Development of Thyroid Lesions (Years)
Tuli et al[5] (n = 12)	7.33	+(3.9) SD	Facial, sacral and foot angiomas, lipomas	c.959 dup, alias c.956_957 insT exon 8, Exon 1 deletion, c.635-1 G > C Intron 6, deletion exon 6	- Thyroid adenomatous nodules -Thyroid follicular adenoma	9.36
Martin et al[6] (n = 4)	7	+ 2 SD	Genital lentiginosis, keratotic papules of the hands, gingival papules, lipomas	c.1019delA c.987_990delTAAA c.984_987delinsTA	-Papillary carcinoma - Multinodular goiter - Cystic thyroid	13.25
Patraquim et al[7] (n = 1)	17	+2 SD	Facial trichilemmomas, abdominal keratosis, lipomas	Mutation in exon 5 of PTEN gene: c.405 406 insA	Lymphocytic thyroiditis	15
Plamper et al[8] (n = 16)	5.7	+ 2SD	Multiple GI polyps, hemangioma, lipomas	c.49C>T;p.Gln17* (exon 1), c.389G>A;p.Arg13c.737C > T;p.Pro246Leu (exon7)0Gln (exon 5)	-Papillary microcarcinoma -Autoimmune thyroid disease -Follicular carcinoma - Nodular goiter	9.8
Hansen-Kiss et al[9] (n = 47) (Pediatric cases = 6)	11.3	+5.6 SD	Penile freckling and GI hamartomatous polyps	c.697C>T (exon 7) c.518G>A (exon 6) c.388C>T (exon 5) c.386G>A (exon 5) c.607_608delAT (exon 6) c.1003C>T (exon 8)	- Goiter and/or nodules - Cystic structures	None reported
Smith et al[10] (n = 64) (Pediatric cases = 20)	6	+ 4 SD	Vascular malformations, neurologic findings	None reported	- Papillary microcarcinoma - Follicular carcinoma	13
Smith et al[11] (n = 7)	9	None reported	Lipomas, penile freckling, inflammatory polyps, mucosal neuromas	c.968dupA (exon 8) IVS8-1G>A (intron 8) c.609_611delTCC insATAAAT(exon 6) c.491delA (exon 5) c.512–513insA (exon 6) c.604_610delACTATTC (exon 6)	- Follicular thyroid carcinoma - Follicular adenoma - Papillary carcinoma	11
Our patient	6	+ 4,6 SD	Gingival lesions, lipomas	Mutation in exon 5 of PTEN gene: c.455C gt;T (p.Gln149*).	Thyroid adenoma	10

PHTS, PTEN hamartoma tumor syndrome.

regular monitoring made it possible to detect a thyroid lesion 4 years later. The authors determined 10 years as the age of occurrence of thyroid cancer. Given that the risk of thyroid cancer begins early in childhood and since ultrasonography is a safe screening method, some authors advise that all patients with CS receive baseline thyroid ultrasound at the age of diagnosis, with follow-up on an annual basis.[5-8]

Management of PHTS is based on surveillance to detect malignant tumors. Although about two-thirds of patients with CS develop a thyroid lesion, the treatment of this pathology remains controversial.[5,6,7,8] In the present case, it was decided to perform a partial right thyroidectomy given the young age of the patient and the presence of a single nodule located in the right hemi lobe of the thyroid.

In order to begin the proper cancer screening and avoid any potential consequences linked to PHTS, it is crucial to identify patients with this syndrome as early as possible. The most important complication is thyroid benign and malignant lesions. These patients should have multidisciplinary surveillance. The search for this syndrome in the family is also required.

Informed Consent: Written informed consent was obtained from the patient's parents who agreed to take part in the study.

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