CASE REPORT

DOI: 10.4274/jcrpe.galenos.2022.2022-8-20

J Clin Res Pediatr Endocrinol 2024;16(3):340-343

Mitotically Active Follicular Nodule in Early Childhood: A Case Report with a Novel Mutation in the Thyroglobulin Gene

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What is already known on this topic?

Loss-of-function mutations in the thyroglobulin (*TG*) gene are a rare cause of dyshormonogenesis. Cancer development due to TG mutations is rare and mostly occurs in adulthood. Long-term elevated thyroid stimulating hormone causes the growth of thyroid follicular cells. It may play a role in the development of malignant tumors, especially in adulthood.

What this study adds?

A novel compound heterogeneous mutation [c.2149C>T (p.R717*) (P.Arg717Ter)/c.5361_5362delCCinsG(p.H1787Qfs*3) (p.His1787GlnfsTer3)] in the *TG* gene was identified. This patient had a premalignant thyroid lesion in early childhood. A mitotically active follicular nodule, of which pathological features were not previously defined in the literature, is reported.

Abstract

Dyshormonogenesis (DG) is the failure of thyroid hormone production due to a defect in thyroid hormonogenesis. Loss-of-function mutations in the thyroglobulin (*TG*) gene are a cause of DG, leading to gland stimulation by thyroid-stimulating hormone (TSH), resulting in goiter. We report a mitotically active follicular nodule in an 11-year-old female with a novel mutation in the *TG* gene. The patient had been under follow-up for congenital hypothyroidism (CH) since the neonatal period, and she had normal TSH levels on replacement therapy. Genetic test revealed a novel compound heterogeneous mutation [c.2149C>T (p.R717*) (P.Arg717Ter) / c.5361_5362delCCinsG (p.H1787Qfs*3) (p.His1787GlnfsTer3)] in the *TG* gene. She underwent total thyroidectomy for a thyroid nodule that was reported as Bethesda IV on fine needle aspiration biopsy (FNAB) and noted as suspicious for noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Pathological examination revealed a 16 mm, well-demarcated follicular nodule with a solid/insular pattern. Mitotic activity and Ki67 proliferation index were unusually high (10 mitoses/mm^2 and 10%, respectively). Marked cellular pleomorphism and nuclear atypia are well-known diagnostic pitfalls in patients with dyshormonogenetic goiter. However, high mitotic activity is a feature that is less commonly reported in dyshormonogenetic goiter and may raise suspicion of poorly differentiated carcinoma when observed together with a solid pattern. The absence of signs of invasion, history of CH, and awareness of the presence of mutations compatible with dyshormonogenetic goiter can prevent the overinterpretation of such lesions. The risk of cancer development in the dyshormonogenetic thyroid gland is possible in childhood. The close follow-up is life-saving and prevents morbidities and possible mortality.

Keywords: Congenital hypothyroidism, thyroglobulin synthesis defect, thyroglobulin (*TG*)

Cite this article as: Kızılcan Çetin S, Aycan Z, Şıklar Z, Dizbay Sak S, Ceylaner S, Özsu E, Berberoğlu M. Mitotically Active Follicular Nodule in Early Childhood: A Case Report with a Novel Mutation in the Thyroglobulin Gene. J Clin Res Pediatr Endocrinol. 2024;16(3):340-343

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Conflict of interest: None declared
Received: 25.08.2022
Accepted: 08.11.2022

Introduction

Dyshormonogenesis (DG) is the failure of thyroid hormone production in a structurally intact gland due to a defect in thyroid hormonogenesis, leading to congenital hypothyroidism (CH). DG is a rare but significant risk factor associated with developing thyroid cancer (1,2). The thyroglobulin (*TG)* gene is on chromosome 8q24.2-8q24.3. TG is essential for promoting thyroid hormone synthesis, and storage of iodine and inactive thyroid hormones. The incidence of thyroid DG due to *TG* mutations is approximately 1 in 100,000 newborns (3). A TG synthesis defect causes chronic stimulation of the gland by thyroid-stimulating hormone (TSH) (2). Long-standing TSH stimulation often leads to goiter. However, thyroid cancer development is mostly in adulthood (4).

The first mutation identified in *TG* was g.IVS3-3C>G in a family with congenital goiter in 1991 (5). Since then, 52 more mutations (11 splice site mutations, 11 nonsense mutations, 23 missense mutations, six deletions, and one single nucleotide insertion) have been identified (4). All patients with mutations in *TG* had a similar phenotype, such as low/absent serum TG, high levels of serum TSH, low levels of thyroid hormones, and enlarged thyroid gland (4).

This paper presents clinical, biochemical, and pathological characteristics and an eleven-year follow-up of a case of primary CH with TG synthesis deficiency. Additionally, the patient had a novel mutation in the *TG* gene, which caused the early development of a mitotically active follicular nodule.

Case Report

An 11-day-old female patient was admitted to our outpatient clinic due to elevated TSH (75.5 µIU/mL), which was detected by a neonatal screening test on the seventh day of life. Her medical history showed that she was born to non-consanguineous parents at 38 weeks of gestation, with a birth weight of 3820 g. A physical examination revealed a weight of 3820 g (68%), a length of 53 cm (85%), and a head circumference of 35.5 cm (51%). The anterior fontanelle was 3x3 cm, and the posterior fontanelle was 1x1 cm. Laboratory tests showed normal hemogram and liver and kidney function and blood glucose. Thyroid function test (TFT) confirmed primary hypothyroidism with a free (f)T4 of 5.58 pmol/L (7-16 pmol/L) and TSH >100 mIU/mL (0.34-5.36 mIU/mL). The urinary iodine level was 159 µg/L (normal value 100-200 µg/L). TG level was <0.1 ng/mL (1.15-50.03 ng/mL). Her thyroid volume was 2.07 mL [4.45 standard deviation (SD) score (SDS)], which excluded thyroid agenesia. Treatment with L-thyroxine (L-T4), 10 µg/kg per day, was initiated on the tenth day of life. One month later, the TSH, fT4, and fT3 levels were normal.

Molecular analysis revealed a novel compound heterogeneous *TG* mutation [c.2149C>T(p.R717*) (P.Arg717Ter) / c.5361_5362delCCinsG (p.H1787Qfs*3) (p.His1787GlnfsTer3)]. The mutation was assessed by Franklin by Genoox. *TG*: c.2149C>T(p.R717*) was pathogenic and *TG*:c.5361_5362delCCinsG likely pathogenic (6).

She was followed up every three months. TSH was carefully managed to remain in the lower part of the normal range (Table 1). She had normal growth and puberty. Neurological evaluation revealed normal language, cognitive, social, and fine motor development.

She underwent periodical ultrasound (US) investigation once a year. At age 10 years, thyroid US revealed a hypoechoic, well-defined nodule of approximately 7x6 mm in size, with high internal hypervascularity in the homogenous parenchyma of the left inferior thyroid lobe, without any sign of calcification. Lymphadenopathy was not observed. She was on L-T4, 2 µg/kg per day. Her TFT at the time was: serum TSH 6 µIU/mL (0.6-4.64 µIU/mL) and fT4 21.8 pmol/L (11-22 pmol/L). Fine-needle aspiration biopsy was performed and interpreted as "suspicious for follicular neoplasm". Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was suggested as a possible diagnosis. The patient underwent a total thyroidectomy six months later when the family agreed to the operation. Histopathological examination revealed a 16 mm, well-demarcated follicular nodule with an insular and solid pattern in the left lobe. Mitotic activity and Ki67 proliferation index were unusually high (10 mitoses/mm^2 and 10%, respectively). No vascular nor capsular invasion was observed in the comprehensive examination of the nodule, and nuclear features were not adequate for a diagnosis of papillary carcinoma. The case was reported with a descriptive diagnosis as a "mitotically active follicular tumor".

The patient is now 11 years of age and on 100 µg of L-T4 daily (2.3 µg/kg/day). She weighs 42.7 kg (0.55 SD) and her height is 154.3 cm (1.24 SDS). BMI is 17.9 kg/m^2 (-0.05 SDS). Her growth, pubertal and mental development are normal. Her TFT is now: serum TSH 2.64 µIU/mL (0.6-4.64 µIU/mL) and fT4 22 pmol/L (11-22 pmol/L), anti-TPO antibody (Ab): 2.3 IU/mL (0-34 IU/mL), anti-TG Abs 10 IU/mL (0-115 IU/mL). She is under close follow-up by physical examination every three monthly, with periodic neck US. No lymphadenopathy or metastases were observed.

Table 1. Eleven year follow-up of the patient

Age at screening	TSH (0.6-4.64 µIU/mL)	free T4 (11-22 pmol/L)	free T3 (3.8-6 pmol/L)	LT4 dose (µg/kg)	Thyroid volume (SDS) on US*
11 days	74.3	5.58	6.27	10	2.07 mL (4.45 SD)
1 month	5.28	14.9	5.3	10	-
1 year	1.3	18.35	6.2	3.5	2 mL (2.14 SD)
2 years	2.9	18.5	6.8	3.2	-
3 years	2.3	18	7	3	5.53 mL (2.9 SD)
4 years	5.4	17.04	-	2.8	-
5 years	2.8	19	-	2.5	6.1 mL (3.5 SD)
6 years	1.3	21.8	-	2.4	-
7 years	5.3	18	-	2.3	7.5 mL (2.6 SD)
8 years	5.2	16.6	6.8	2.4	7.1 mL (2.4 SD)
9 years	6.8	18	7.3	2.2	9.7 mL (4.1 SD)
10 years	6	21.8	7.2	2.2	10.2 mL (4.4 SD)**
11 years	2.64	22	6.3	2.3	Total thyroidectomy

*Thyroid SD measurements were calculated using age and gender for the Turkish population and an online calculator then available online at Turkish Society for Pediatric Endocrinology and Diabetes online (10,11).
**A nodule of 7x6 mm in size, hypoechoic, well-defined with high internal hypervascularity on the homogenous parenchyma of the left inferior thyroid lobe.
SDS: standard deviation (SD) score US: ultrasound, TSH: thyroid-stimulating hormone

Discussion

We describe a case with a novel, compound heterogeneous mutation in the *TG* gene. Her histopathological findings were unusual. We observed a mitotically active follicular nodule in the context of a dyshormonogenetic goiter. To the best of our knowledge, these pathological features were not previously reported in the literature. Mitotic activity and Ki67 proliferation index were unusually high in the present case. High mitotic activity is a feature that is less well-known in DG and may be more alarming for the pathologist, raising suspicion of poorly differentiated carcinoma, especially when observed together with a solid insular trabecular (STI) pattern. In the recent World Health Organization classification of thyroid tumors, two types of high-grade follicular-derived carcinomas are described. Differentiated high-grade thyroid carcinoma is a papillary or follicular carcinoma with increased mitotic counts (≥5 mitosis/mm^2) or tumor necrosis. The second category is poorly differentiated thyroid carcinoma (PDTC), and it is defined as a malignant tumor of follicular cells with a STI pattern, without typical papillary carcinoma nuclei, and with the presence of convoluted nuclei or necrosis or high levels of mitosis (≥3 mitosis/mm^2) (7). Although the present nodule shows a much higher mitotic activity and a STI pattern, it did not exhibit any clear-cut histopathological features of malignancy. Although high mitotic activity is a worrisome histopathologic feature in a STI patterned follicular nodule, according to our clinical experience the diagnosis of PDTC should not be made, especially in a pediatric patient, based solely on the presence of a STI pattern and high mitotic activity in a completely well-circumscribed nodule without capsular or vascular invasion. The absence of signs of invasion, history of CH, and awareness of the presence of mutations compatible with DG may prevent the overinterpretation of such lesions. Although it is not possible to diagnose such a nodule as a malignant tumor in the presented case, the definitive nature of the present tumor remains to be characterized by follow-up of similar cases. Since thyroidectomy was performed in this case, it is not possible to comment on whether this particular nodule would have developed an invasive character. The high mitotic activity and high Ki67 index observed in the present case may be related to the novel TG mutation. We believe that radio-iodine ablation or lymph node dissection was unnecessary. However, since follow-up information on similar cases has not been reported to date, it will be safer to keep the patient under close follow-up, for early detection of a recurrence, albeit with a low probability.

Thyroid US and TG levels are some of the considerabletools to determine the etiology of CH, since all published patients with DG due to *TG* variants present with low/absent serum TG, high levels of serum TSH, low levels of thyroid hormones, and enlarged thyroid gland. Few patients develop a fetal goiter, diagnosed by antenatal US, and need intrauterine hormone replacement. However, others present with goiter at a later age (4). In the present case, we showed a mitotically active follicular nodule at an early age, which may have been related to the novel mutation.

Dyshormonogenetic goiter is a rare risk factor for developing thyroid cancer. In a study, 56 cases of dyshormonogenetic goiters with ages ranging from newborn to 52 yr were evaluated (8). Ten cases (18%) were diagnosed with thyroid cancer. Follicular type thyroid cancer was mainly seen, and almost all ten patients were diagnosed with thyroid cancer in adulthood. None of them had TG synthesis defects. Long-term elevated TSH causes the growth of thyroid follicular cells, and it might have a role in developing malignant tumors. However, cancer occurs after a long time under TSH stimulation, especially in adulthood (9). The most exciting aspect of the present case, from our point of view, was that her TSH level was normal from the beginning of her life with the exception of the last three years before presentation with the nodule. However, it was never markedly elevated under treatment (Table 1). This observation is significant in considering the genotype effect on tumorigenesis. Defining underlying genetic mechanisms will be more helpful in understanding the progression of the disease.

Conclusion

It can be speculated that we may have detected the nodule before the development of an aggressive tumor in adulthood. We want to emphasize two points about the present case. Firstly, an annual thyroid US examination was significant and potentially lifesaving. We believe that serial thyroid US examination was to our advantage for the early diagnosis of this nodule. Secondly, in the last three years of the follow-up, we realized that this patient had elevated TSH levels, although fT4 was in the normal range (Table 1). TSH stimulation might have initiated tumor development.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Authorship Contributions

Surgical and Medical Practices: Sirmen Kızılcan Çetin, Zehra Aycan, Zeynep Şıklar, Serpil Dizbay Sak, Serdar Ceylaner, Elif Özsu, Merih Berberoğlu, Concept: Sirmen Kızılcan Çetin, Zehra Aycan, Merih Berberoğlu, Design: Sirmen Kızılcan Çetin, Zeynep Şıklar, Serdar Ceylaner, Merih Berberoğlu, Data Collection or Processing: Sirmen Kızılcan Çetin, Serpil Dizbay Sak, Serdar Ceylaner, Elif Özsu, Merih Berberoğlu, Analysis or Interpretation: Sirmen Kızılcan Çetin, Serpil Dizbay Sak, Serdar Ceylaner, Literature Search: Sirmen Kızılcan Çetin, Zehra Aycan, Serpil Dizbay Sak, Serdar Ceylaner, Elif Özsu, Writing: Sirmen Kızılcan Çetin, Zehra Aycan, Zeynep Şıklar, Merih Berberoğlu.

Financial Disclosure: The authors declared that this study received no financial support.

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