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Case Report

A thyroid adenoma in a pubertal male with thyroxine-binding globulin deficiency

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Highlights

- TBG deficiency may be associated with follicular adenoma.
- TBG deficiency requires careful observation with ultrasonography during the pediatric period, even though biochemical data show a typical deficiency in TBG.

Abstract. Complete deficiency of thyroxin-binding globulin (TBG-CD) is not commonly associated with clinical symptoms, and little is known about thyroid tumors associated with TBG-CD. We present a case report of an asymptomatic follicular adenoma that spontaneously shrank in a patient with TBG-CD. A previously healthy 13-yr-old male presented with a diffusely swollen thyroid gland. Thyroid function tests revealed low total thyroxin and TBG concentrations, indicating a TBG deficiency. Ultrasonography revealed a mildly swollen thyroid gland with a nodule (14 × 12 × 19 mm) in the left lobe. Genetic analysis of peripheral blood revealed a previously reported *SERPINA7* variant, which resulted in complete loss of TBG function. The nodule was identified as a follicular adenoma using fine-needle aspiration. Subsequently, the adenoma shrank without treatment. This pubertal case suggests that careful observation with ultrasonography is warranted for follicular adenoma in patients with TBG deficiency and that treatment may not be required.

Key words: thyroxin-binding globulin, TBG deficiency, thyroid adenoma

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Introduction

Thyroxine (T4) has a long half-life and high serum concentration, as T4 binds to thyroid hormone-binding proteins including T4-binding globulin (TBG), transthyretin (TTR), and albumin (1). The binding affinity of TBG to T4 is 7000 times higher than that of the more abundant albumin. Approximately 70% of thyroid hormones, T4 and triiodothyronine (T3), bind to TBG. TBG is synthesized in hepatic parenchymal cells and functions as the principal transport and storage protein for circulating thyroid hormones. Thus, TBG maintains a large extrathyroidal thyroid hormone pool and a stable free T4 concentration (2).

Despite the high affinity of TBG for thyroid hormones, it may not be essential for hormone distribution (1). TBG is encoded by a single gene, *SERPINA7*, which is located on the long arm of the X chromosome (Xq21-22). A defect in *SERPINA7* causes TBG deficiency with X-linked inheritance, leading to low serum concentrations of T4 and T3 in male patients. In contrast to total thyroid hormones, serum concentrations of the free forms of T4 (FT4) and T3 (FT3) are maintained within the physiological range (3). Therefore, patients with TBG deficiency are usually asymptomatic and do not require treatment. To avoid overtreatment, TBG measurements are recommended for patients with low T4 levels (2).

Inherited TBG defects lead to three phenotypes based on the concentration of TBG in the serum of affected hemizygotes, which include complete deficiency of TBG (TBG-CD), partial deficiency, and TBG excess (2). TBG-CD is defined as the absence of detectable TBG in the serum of affected male hemizygotes (0.03% of the average normal serum concentration) (2). The *SERPINA7* variants that cause TBG-CD to lead to either premature termination of translation or an amino acid substitution inhibiting secretion. The prevalence of TBG-CD is 1 in 15,000 male newborns (2). Most Japanese TBG deficit phenotypes in the literature were TBG-CD; however, no occurrence of thyroid tumors has been reported in TBG-CD (3). Here we present a case of a male with TBG-CD complicated with a thyroid tumor.

Patient and Methods

A previously healthy 13-yr-old Japanese male was found to have a diffusely swollen thyroid gland during a school medical checkup. His primary physician evaluated thyroid function because the patient did not show any symptoms associated with a goiter. The results showed a lack of TBG, and a diagnosis of TBG deficiency was made. The patient was referred for a more detailed examination. His parents were non-consanguineous, and there was no family history of thyroid disorders for three generations. The patient was born to a healthy mother without a complicated pregnancy. Developmental milestones and growth were normal. No symptoms suggestive of hypothyroidism or hyperthyroidism, such as weight gain or loss, pulsation, sweating, or fatigue, were observed. The patient's height was 156 cm (–0.17 SD) and body mass index was 18.3. The patient's puberty was at Tanner stage 3, and bone age was appropriate for their chronological age. Blood tests revealed low T4 at 1.71 μg/dL (reference range: 6.10–12.4 μg/dL), normal TSH at 1.46 μIU/mL (0.75–4.12 μIU/mL), normal FT4 at 0.90 ng/dL (0.68–1.26 ng/dL), and normal thyroglobulin (Tg) at 10.4 ng/mL (< 32.7 ng/mL). TBG was undetectable (< 3.0 μg/mL; reference range 15.9–35.6 μg/mL). Thyroid ultrasonography revealed a nodule measuring 14 × 12 × 19 mm with clear borders in the left lobe of the thyroid gland accompanied by cystic degeneration and calcification without increased blood flow or surrounding lymphadenopathy (**Fig. 1A**). The left lobe volume was 9.5 mL, and the right was 5.6 mL; both were slightly enlarged for his age (4).

Written informed consent for genetic analysis and publication was obtained from the parents. This study was approved by the Ethics Committee of the National Center for Child Health and Development.

Results

Genetic analysis of the *SERPINA7* by PCR-Sanger sequencing performed on a blood sample demonstrated a previously reported hemizygote *SERPINA7* variant, c.1114delC,p.Leu372Phefs*23 (**Fig. 1B**) (5). The parents were not genetically analyzed.

After five months, repeat ultrasonography demonstrated enlargement of the nodule to 18 × 18 × 22 mm, left lobe volume of 12.3 mL, and right lobe volume of 7.7 mL; however, thyroid hormone concentrations did not change. Considering the enlargement of the nodule and the patient's younger age, fine-needle aspiration cytology (FNAC) was performed to rule out papillary thyroid carcinoma. Pathological examination revealed no evidence of malignancy, and a follicular adenoma was suspected (**Fig. 1C**). On follow-up ultrasonography, the nodule shrank to 5 × 5 × 6 mm without any treatment six months after FNAC (**Fig. 1D**). The size of the thyroid gland spontaneously became normal for their age (left lobe 3.5 mL and right lobe, 6.1 mL) and the nodule continued to shrink. Additional blood tests did not show significant changes in, T4 2.82 ng/mL, TSH 1.54 μIU/mL, FT4 1.06 ng/dL, and Tg 8.69 ng/mL at this follow-up assessment.

Discussion

Here, we present a case of thyroid adenoma in a 13-yr-old male with asymptomatic TBG-CD. Although reports of TBG deficiency and adenoma in adults exists, to our knowledge, this is the first report of a thyroid nodule in a child with TBG deficiency (6). Although thyroid tumor is not typically associated with TBG deficiency in children, we were concerned about the malignancy of our patient's thyroid nodule due to its increased size for his age. Cytological examination revealed benign thyroid follicular cells in this case. Previous ultrasound and postmortem examinations showed that 1%–1.5% of children and up to 13% of older adolescents or younger

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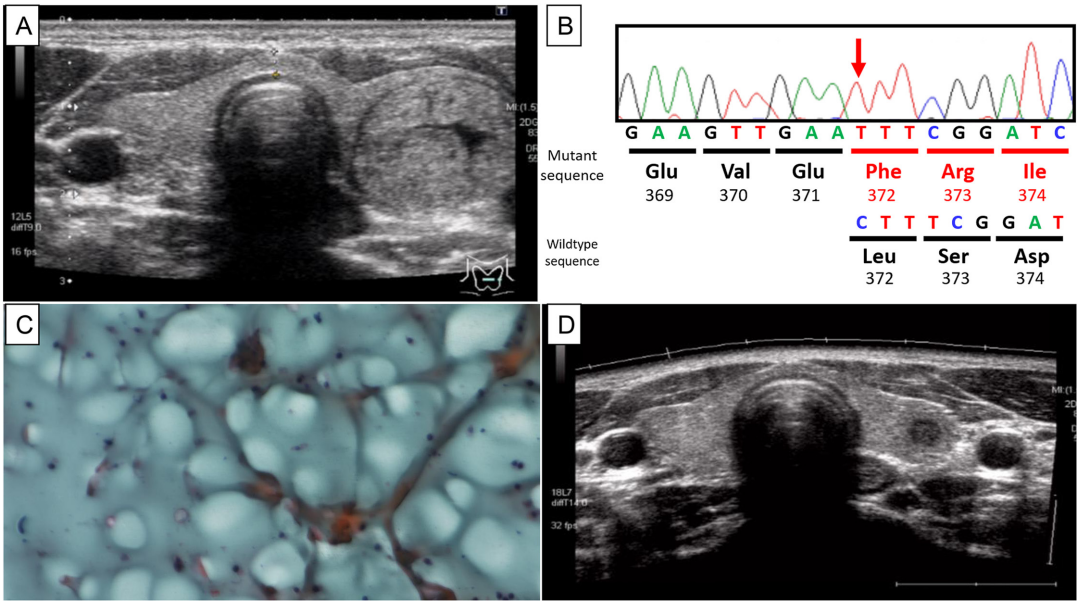

Fig. 1. A) Initial ultrasonography shows a nodule in the left lobe of the thyroid gland and cystic degeneration with some calcification inside. B) The first base deletion of the 372nd codon (missing the 1114th base C) by PCR-Sanger sequencing, resulting in a frameshift mutation. C) Papanicolaou stain shows numerous round, small, and concentrated nucleated cells without findings suggestive of malignancy. D) Shrunken nodule six months after the initial study.

adults have thyroid nodules (7). The percentage of 13-yr-old males with nodules that had a maximum diameter of 19 mm, such as our patient, was very low (0.06%) in a study conducted in Fukushima (8). This previous report showed that the frequency of malignancy increased with size and age (8).

Rapid growth during adolescence increases the demand for thyroid hormones and increased thyroid volume as supported by recent studies (3, 9). In the absence of TBG, there is rapid depletion of extrathyroidal T4. This shortened half-life of thyroid hormones due to TBG deficiency may promote increased thyroid hormone production, particularly during puberty (2). A previous report described a case of partial TBG deficiency in a patient with delayed puberty (10). This report suggested that adolescents are more likely to develop TBG deficiency due to relative hypothyroidism. The increased demand for thyroid hormones in cases of TBG deficiency may cause continuous TSH production (10). In contrast, we report normal serum TSH concentration, which is likely because the thyroid response to TSH is not disturbed in TBG-CD. In contrast, transient hypothyroidism in infancy may indicate subnormal thyroid function and presents with mildly elevated serum TSH concentration caused by increased thyroid hormone requirements during puberty.

A single-nucleotide deletion in the coding sequence is associated with a frameshift that can largely change the structure of a protein. In the case of TBG, this altered structure in affected individuals may not have a direct effect on tumorigenesis in the thyroid because TBG is produced in the liver; however, this structural alteration affects TBG function (5). In our case, both goiter and thyroid nodules were transient and normalized without treatment. A previous study reported that continuous chemical stimulation of thyroid hormone secretion caused thyroid tumors in mice (6). Previous studies have shown that molecular deformation of TBG leads to decreased thyroid hormones, forcing the thyroid gland to secrete high amounts of hormones. This may result in thyroid gland enlargement and support existing tumor growth (6, 11). Once the peak growth period during puberty has passed, thyroid hormone requirements may become reduced, resulting in spontaneous shrinkage of such a tumor. Follow-up studies of follicular adenomas in children showed that the adenomas regressed spontaneously (12, 13); this corresponds with the spontaneous tumor shrinkage observed in this case. Thus, the reduced production of thyroid hormones likely led to both the thyroid gland and tumor shrinking.

Conclusion

Thyroid adenoma due to TBG deficiency may not require therapeutic intervention. This case suggests that thyroid adenoma in cases of TBG deficiency requires careful observation with ultrasonography, especially during the pubertal period.

Conflict of interests: The authors declare no conflicts of interest.

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