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Considerations for total thyroidectomy in an adolescent with *PTEN* mutation

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Abstract: Individuals with PTEN Hamartoma Tumor Syndrome (PHTS) are at greatly increased risk for developing well-differentiated thyroid cancer. Specific circumstances in which total thyroidectomies should be considered have not been defined. A 14-year-old macrocephalic female with history of developmental delay and lipoma over her left flank presented with neck swelling and was found have multinodular goiter and auto-immune thyroiditis. Asymptomatic tracheal narrowing was also detected on her initial diagnostic imaging. Later on, she developed positional dyspnea during sleep. Genetic testing revealed a heterozygous pathogenic variant in the *PTEN* gene (c.463T>A). A total thyroidectomy was performed. In addition to addressing the symptomology in our case, a total thyroidectomy also fortuitously eliminated the thyroid cancer risk. This case spurred us on further to identify specific clinical scenarios where total thyroidectomy may be considered as a true prophylactic measure to manage thyroid cancer risk in PHTS patients.

Keywords: Prophylactic, *PTEN* mutation, thyroid cancer, total thyroidectomy

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Introduction

Individuals with PTEN Hamartoma Tumor Syndrome (PHTS) are at increased risk for well-differentiated thyroid cancer. Thyroid cancers in affected individuals occur at an earlier age (median = 35 years)[1] than in the general population (median = 51 years)[2] and this risk extends to children as young as 7 years.[3–5] Screening is variably implemented due to a number of factors including limited relevant data. Furthermore, this has contributed to a lack of consensus guideline on specific circumstances in which total thyroidectomies should be considered. Fortuitous elimination of thyroid cancer risk in our unusual case with a *PTEN* mutation led us to examine any situations where true prophylactic total thyroidectomy may be considered, given the high incidence of thyroid malignancies in patients with PHTS.

Case presentation

A 14-year-old macrocephalic female with developmental delay and several years history of neck swelling was referred for evaluation of multinodular goiter. The family initially thought that her neck swelling was secondary to her having abnormal weight gain. No neck pain/pressure/discomfort, dyspnea, or dysphagia were reported. She did not have any history of head and neck radiation. She did have a history of a large lipoma (12 cm) over her left flank, which was resected at 5 years of age. She received speech and physical therapy as a toddler, and required to attend after-school programs at older ages due to developmental delay. She reported irregular menses, which later progressed to secondary amenorrhea. Her maternal grandmother had a thyroidectomy for an unknown thyroid problem. Family history of any cancer, including thyroid cancer or cancer predisposing condition, was denied.

She was macrocephalic (head circumference >99th percentile), obese (body mass index 97.5th percentile) and significant thyromegaly was noted bilaterally on physical examination. Laboratory testing was notable for thyroid peroxidase and thyroglobulin antibodies, but normal thyroid-stimulating hormone (TSH) and free T4. A thyroid ultrasound showed multinodular goiter. The

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magnetic resonance imaging of the neck showed diffuse thyroid enlargement (right 11.7 cm × 5.9 cm × 6.3 cm; left 6.8 cm × 2.5 cm × 3.9 cm) with numerous avidly enhancing ill-defined nodules. Additionally, the trachea was severely compressed by the enlarged thyroid at the level of the sternal notch (1.3 × 0.4 cm) when compared with the trachea at the level of subcricoid region (1.3 × 1.4 cm). An I-131 scan showed normal iodine uptake (10% at 4 h and 17% at 24 h), but revealed suspicious hypodense cold nodules. Fine-needle aspiration was not performed.

Gynecologic evaluation was consistent with primary ovarian failure. Her karyotype was abnormal (47, XX, +mar). The constellation of developmental delay, multinodular goiter, history of lipoma, and macrocephaly prompted testing for a germline *PTEN* gene mutation, which revealed heterozygous c.463T>A (p.Y155N) mutation. Parental testing was not performed; however, the mutation was suspected to be *de novo* based on their histories.

During her course, she developed progressive positional dyspnea during sleep. Due to the presence of thyroid enlargement causing symptomatic airway compression, the patient underwent a total thyroidectomy at 15-years old. Histopathology showed multinodular goiter, and lymphocytic thyroiditis without evidence of malignancy. The postoperative recovery was uneventful. Removal of the thyroid gland alleviated the attributable symptoms and mitigated the concerns regarding future malignant disease.

Discussion

Mutations in the *PTEN* gene (10q23.31) predispose patients to multiple benign and malignant tumors, including thyroid cancer.[4] The lifetime risk of thyroid cancer has been estimated as 35%.[6]

While thyroid cancer in affected individuals predominates in adults, thyroid nodules and cancer have been reported as early as 5[3] and 7 years of age,[3–5] respectively. Smith and colleagues reported seven patients with *PTEN* mutation, of whom five were diagnosed with thyroid cancer. None of the patients had compressive symptoms due to thyroid enlargement. Thyroid cancer was diagnosed below 13 years of age in four out of five patients, with the youngest being 7 year-old at the time of diagnosis.[4] A retrospective chart review at a tertiary care facility over a 15-year period identified 34 children diagnosed with PHTS *via* genetic testing under 21 years of age.[3] Of those patients, four were diagnosed with thyroid cancer. All four patients were below 14 years of age at the time of diagnosis. The youngest one was diagnosed at 7 years of age, the second one at 11 years and the other two at 13 years. Thyroid nodules were observed in 10 (56%) out of 18 patients with documented thyroid nodule clinical assessment. The earliest age of thyroid nodule diagnosis was 5 years of age. Autism and intellectual disability were consistent findings in this cohort.[3] Thyroid cancer presentation in early childhood has important clinical implications for pediatric surveillance in patients with *PTEN* mutation.

In individuals with *PTEN* mutation, thyroid cancer is the earliest appearing cancer.[1] Although previous screening guidelines recommended starting surveillance with annual thyroid ultrasounds at 18 years of age, recent National Comprehensive Cancer Network (NCCN®) Surveillance Guidelines have recommended initiating thyroid cancer screening from the age of diagnosis.[7]

On the other hand, given the high incidence of significant developmental delay and autism in patients with PHTS, consistently obtaining high-quality imaging studies to enable early detection of concerning lesions may be challenging for some patients. Milas and colleagues[1] reported 32 thyroid cancer cases in a cohort of 225 patients with *PTEN* mutation in a multi-institutional study. Three patients had severe autism to the degree that sedation was required to perform thyroid ultrasonography. This led to a suggestion that prophylactic thyroidectomy be considered in select cases in whom routine monitoring is overly challenging and patients with multiple nodules who comprehend the benefits and risks of undergoing this procedure.[1] The consequence of total thyroidectomy, the need to take lifelong daily hormone replacement therapy, and the risk of a surgical procedure should also be considered in the decision-making process. When indicated, it should be performed at facilities with high-volume thyroid surgery by an expert surgeon to minimize the risk of complications.

Our patient developed airway compression symptoms secondary to mass effect from multinodular goiter. Additional issues were her *PTEN* mutation, which conferred high lifetime thyroid cancer risk, and significant developmental delay. A total

thyroidectomy not only addressed her symptoms, but also fortuitously eliminated her future risk of thyroid malignancy. Compressive symptoms from premalignant thyroid disease are a rare occurrence in individuals with PHTS.[1,4] While this is a clear indication for surgical intervention, we submit that a true prophylactic thyroidectomy may be considered in rare clinical scenarios when surveillance is very challenging, such as developmental delay and severe autism, as previously suggested by Milas and colleagues[1] or respiratory symptoms are deemed likely/imminent because of usual multicentric follicular adenoma presentation, and increased risk of recurrence or progression to thyroid cancer.[1,4,8] However, regular thyroid ultrasound surveillance as recommended by recent expert consensus pediatric oncology guidelines[9] and the NCCN®[7] starting from age 7 or the age of diagnosis, respectively, is of paramount importance.

Conclusion

Patients with germline mutations of *PTEN* (10q23.3) are at risk for multiple benign and malignant tumors, including thyroid cancer. In patients with *PTEN* mutations, thyroid nodule and thyroid cancer can present as early as 5 and 7 years of age, respectively. Given the high incidence and early age of onset of thyroid malignancy in patients with *PTEN* mutation, a prophylactic total thyroidectomy may be considered in rare clinical circumstances based on careful consideration of the risks and benefits.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Disclosure Summary

The authors have nothing to disclose.

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