

The Importance of Nodules in Children and Adolescents Affected with Hashimoto's Thyroiditis

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Abstract

Objectives: To investigate the rates of thyroid nodules and cancer in pediatric cases of Hashimoto's Thyroiditis (HT) in our institution.

Methods: We retrospectively reviewed 89 pediatric and adolescent patients (age, 3–18.0years) with HT who underwent Thyroid Ultrasonography (US) at our institution from February 2006 to July 2016. The diagnosis of HT was based on the presence of thyroid auto antibodies. The presence of any thyroid nodules with US and cytopathologic features was analyzed. The malignancy rate was also determined.

Results: Thyroid nodules were in 20 of the 89 patients (22.4 %). Eight of these 20 patients (40%) had colloid cysts, two (10%) had nodular hyperplasia, one (5%) had follicular adenoma, and Two (10%) had lymphocytic Thyroiditis. Seven of the 89 patients (7.9 %) were confirmed to have a malignancy, all of which were Papillary Thyroid Carcinoma (PTC); of those, five patients had diffuse sclerosing variant PTC, and two had conventional PTC on pathology.

Conclusions: The prevalence of thyroid nodules in children and adolescents with HT was 22.4%. The malignancy rate of children with HT was 7.9%. The malignancy rate among thyroid nodules was 35%, which is higher than the 26% rate generally reported for children with nodules. Therefore, using thyroid US to survey known or suspected thyroid nodules might be helpful in children and adolescents with HT and may provide further useful diagnostic information.

Advances in Knowledge: Thyroid US could help to assess HT patients who have known or suspected thyroid nodules.

Keywords: Thyroid; Nodules; Thyroiditis; Pathology; Imaging; Cancer; STHAN;

5% in adults. Thyroid nodules are rare among children; that said, Gupta, et al. [1] reported a 1.6-fold higher cancer risk of sporadic thyroid nodules in children (22%), compared to adults [1-4].

Hashimoto's Thyroiditis (HT), also called lymphocytic Thyroiditis, and is a goitrous form of Autoimmune Thyroiditis (AIT) and the most common thyroid disorder in children and adolescents, with a prevalence of 1.3% to 9.6% [5]. HT is characterized by diffuse lymphocyte and plasma cell infiltration, fibrous replacement, and eventual atrophy of the parenchyma. According to the American Thyroid Association guidelines for children with thyroid nodules and differentiated thyroid cancer, any patient with AIT and a suspicious thyroid examination (suspected nodule, significant gland asymmetry, or palpable cervical lymph adenopathy) should be evaluated by Ultrasonography (US) with recommendations based on fair evidence [2]. Dailey, et al. [6] first reported 35 cases of malignant thyroid disease among 288 patients with AIT and suggested a positive correlation between Papillary Thyroid Carcinoma (PTC) and HT in adults. Kim, et al. [7] also reported a very strong correlation between PTC and HT in an adult population. Some reports have shown that increased Anti-Thyroid Peroxides Antibody (Anti-TPO-Abs) or High Thyroid-Stimulating Hormone (TSH) levels are associated with an increased incidence of thyroid cancer in patients with HT [8,9]. Subsequent limited adult studies have reported that the prevalence of malignant thyroid disease is 1% to 30% in patients with HT [10]. Only two studies have reported an association between thyroid cancer and children and adolescents with HT. Corrias, et al. [5] reported that the prevalence rates of thyroid nodules and thyroid cancer were 31.5% and 3.0%, respectively, in a pediatric and adolescent juvenile AIT cohort. Of the thyroid nodules, 9.6% were malignant. Keskin, et al. [11] investigated the incidence of nodules in children with HT and reported that the thyroid nodule rate was 13%, and the malignant thyroid cancer rate was 0.67%; 5.12% of thyroid nodules were malignant. However, the prevalence of thyroid cancer among children and adolescents with HT may be different in different areas. The aim of this study was to investigate the rates of thyroid nodules and thyroid cancer in children and adolescents with HT.

Introduction

Sporadic thyroid nodules are less common in children and adolescents, compared to adults, with a prevalence of 0.2% to 1.44% in children, and up to 13% in older adolescents and young adults. However, malignancy rates of thyroid nodules are 22% to 26% in children, which are higher than the rate of approximately

Materials & Methods

Patients and Laboratory Findings

Approval of our institution's ethics committee was obtained for this study, and informed consent was waived due to the retrospective nature of the study. We reviewed 118 patients (range, 3–18.0 years) diagnosed with pediatric or adolescent HT who visited the Pediatric Endocrinology or Head and Neck Surgery department at our institution, with complaints of neck swelling or suspicious thyroid dysfunction (either symptoms of hypo- or hyperthyroidism) from February 2016 to July 2018. Of these, 90 children and adolescents with HT had undergone thyroid US due to neck swelling. One patient was lost to follow-up after the initial US and was excluded. The remaining 89 patients were enrolled in this study. None of the patients had a history of radiation therapy to the head and neck region.

The diagnosis of HT was based on a combination of clinical features (classic signs of hypothyroidism), and the presence of anti-TPO-Abs and Thyroglobulin antibodies (Tg-Ab). Thyroid function was evaluated at the time of diagnosis as hyperthyroid, euthyroid, or hypothyroid. Laboratory data, including the serum levels of free triiodothyronine (T3, normal range 0.85–2.02 mU/L), free Thyroxine (T4, normal range 0.93–1.71 mU/L), TSH (normal range, 0.27–4.2 mU/L), anti-TPO-Abs (normal range, 0–0.3 U/mL), and Tg-Ab (normal range, 0–0.3 U/mL), were retrospectively evaluated using the clinical records. Radioimmunoassay was used for laboratory examinations and was performed on the day closest to the day of the US imaging study.

Analysis of US Images and Pathology

US and color Doppler examinations were performed using a 5- to 12-MHz Linear Array Transducer (LAT) (HITACHI ALOKA PROSOUND A-7; Andover, MA, USA), a 5- to 12-MHz LAT (PROSOUND ALOKA A-7 Japan), or a 6- to 15-MHz LAT (LOGIQ-E9; GE Healthcare, Milwaukee, WI, USA). Patients were evaluated by thyroid US and Fine Needle Aspiration Biopsy (FNAB) by one of two experienced faculty radiologists with 6 and 26 years of experience in thyroid imaging. The presence of any thyroid nodule was recorded. The following US features of all thyroid nodules were analyzed:

- i) **Size;**
- ii) **Number: single or multiple (≥2);**
- iii) **Location: left or right;**
- iv) **Echogenicity: anechoic, hypo echoic, isochoic, or hyper echoic; and**
- v) **Composition: cystic, mixed, or solid. In addition to the nodule analysis, the thyroid parenchyma was analyzed for US findings of HT, including size, echogenicity, vascularity, and the presence of micro nodules or septations.**

Since the size criterion for a thyroid nodule is problematic in children because thyroid volume changes with age, the indication for FNAB was based on the presence of suspicious features. The following suspicious US features have been suggested by Kim et al.,

Moon et al. and the American Thyroid Association guidelines for children with thyroid nodules and differentiated thyroid cancer: marked hypoechogenicity, irregular or microlobulated margins, increased intraocular blood flow, presence of micro calcifications, taller than wide shape [2,12,13]. A thyroid nodule with at least one suspicious US finding was classified as a suspicious nodule and FNAB was performed for suspicious thyroid nodules. Three patients who had thyroid nodules without suspicious features underwent FNAB at the parents' request. FNAB specimens were categorized according to the Bethesda Thyroid Cytopathology Reporting system [14]. Surgical resection was recommended for patients with Bethesda categories III–VI. Patients were classified as malignant and benign on the basis of cytological and histopathological results. Patients with colloid cysts and benign cytological results were followed up for at least 21 months.

Statistical Analysis

Means and standard deviations were used to summarize continuous variables, while frequencies and percentages were used to summarize categorical variables. To compare clinical characteristics between groups, the chi-square test or Fisher's exact test was conducted for categorical variables. In the case of continuous variables, Student's t-test for age and the Mann-Whitney U-test or the Kruskal-Wallis test were used to compare levels of auto antibodies, serum TSH, and hormonal status after normality and equivalent variance testing. A two-tailed P-value < .05 was considered significant. All statistical analyses were performed using R (ver. 3.3.2, The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients and Laboratory Findings

Subjects included 13 (14.6%) males and 76 (85.4%) females with ages ranging from 3 to 18. years (mean 11.1 ± 3.7 years). Thyroid nodules were found in 20 (22.4 %) of the 89 children and adolescents with HT. Among 20 patients, 18 (90%) showed nodules concomitant with the diagnosis of HT. Two patients developed thyroid nodules at 18 and 27 months after the HT diagnosis. The median Follow up period was 48 months (range 17-72 months) for patients without newly developing thyroid nodules. The mean volume of all thyroid nodules was 5.54±7.59 cm³ (benign 2.53 ± 5.6 cm³, malignant 13.0 ± 7.59 cm³, P = 0.006). Thirteen patients (14.6%) had benign nodules and seven had Malignant nodules (7.9%). Patients without thyroid nodules tended to be younger (P = .06) with higher TSH levels than patients with nodules alone (P = .06) although statistical significance was not attained. The evaluation of thyroid function at the time of diagnosis in cases with benign nodules revealed that five were euthyroid, six were subclinical hypothyroid, and Two were overt hypothyroid. Among the seven patients with PTC, two were hyperthyroid, two were euthyroid, and three were sub clinically hypothyroid.

Analysis of US Images and Pathology

Both lobes of the thyroid gland were enlarged in all patients with thyroid nodules, and various echogenicities and vascularity

were detected. Of the 20 patients with thyroid nodules, 11 (11/20, 55%) had nodules without suspicious features and nine (9/20, 45%) had suspicious nodules. Of the 11 nodules without suspicious features, eight (8/11, 72.7%) had colloid cysts on US. No new nodules or suspicious features were observed in any of the patients with colloid cysts during follow up. FNAB was performed in three (3/11, 27.3%) patients with solid nodules without suspicious features because of their family history of thyroid cancer. Cytopathology revealed two cases as category II and one as category IV (suspicious for follicular neoplasm). The pathology report for the hemi Thyroidectomy specimen with a category IV nodule revealed follicular adenoma. Follow-up US were performed on the remaining two patients with category II nodules, and no new suspicious features or significant size increases warranted repeat biopsy. FNAB was performed on nine patients with suspicious nodules. The results revealed category II nodules (lymphocytic Thyroiditis) in two patients. One patient, diagnosed with lymphocytic Thyroiditis on FNAB, underwent lobotomy for confirmatory diagnostic purposes because her thyroid gland showed asymmetrical enlargement with multiple echogenic foci, which was suspicious for micro calcifications. The surgical specimen also showed lymphocytic Thyroiditis. The second case, diagnosed as lymphocytic Thyroiditis on FNAB, presented with a focal ill-defined hypo echoic thyroid nodule

with non-parallel orientation, which was followed up without interval change (Figure 1) Of the remaining seven patients with suspicious features, three patients presented with focal suspicious nodules (Figure 2) and four patients presented with a diffusely enlarged gland with numerous micro calcifications (Figure 3). FNAB revealed two patients with category III (follicular lesion of undetermined significance) and five with category V (suspicious for malignancy; suspicious for papillary carcinoma) findings. All of the seven patients with suspicious nodules presented with suspicious lymph nodes along the lateral neck at preoperative US, and subsequent FNAB for lymph nodes was performed. Three of the seven patients showed distant (lung) metastasis at the initial presentation. Aspiration cytology of lateral neck nodes revealed metastatic papillary carcinoma in two patients with category III nodules. All seven cases (six girls and one boy) underwent surgery; all had papillary thyroid carcinoma with microscopic extra thyroidal extension and lateral neck lymph node metastasis. Five patients had diffuse sclerosing variant of PTC (DSVPTC) and two patients had conventional PTC. None of the patients with thyroid cancer died during the follow up (median 38 months, range 12 - 64 months). All seven patients underwent radioactive iodine therapy after surgery. Four patients are on follow up without evidence of recurrence. Three patients are on follow up with Residual tumors in the lung. Figure 4 shows the number of patients with thyroid nodules on US and the pathological results.

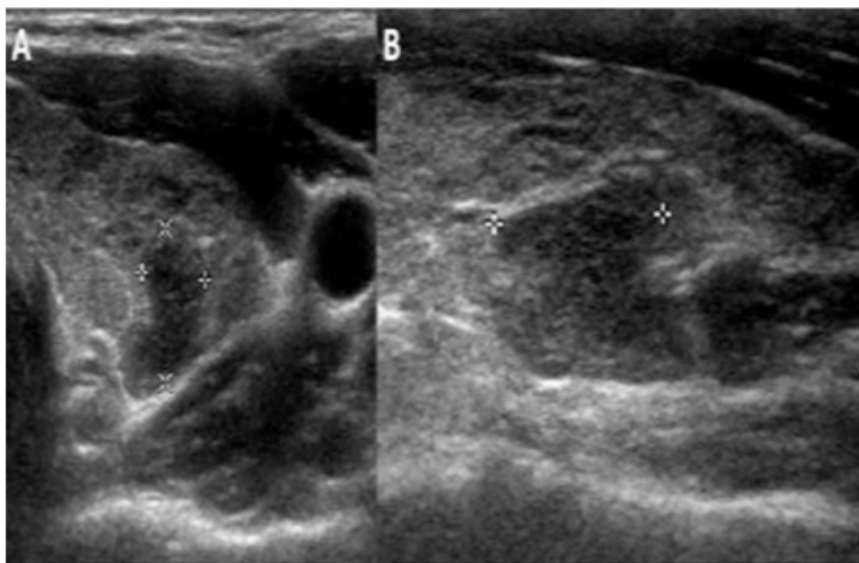


Figure 1: A 17-year-old boy with goiter. Transverse (A) and longitudinal (B) scans show heterogeneous hypoechoic parenchyma. An ill-defined marked hypoechoic thyroid nodule with nonparallel orientation is seen in the left thyroid lobe. Subsequent fine-needle aspiration biopsy (FNAB) results were lymphocytic Thyroiditis. He was diagnosed at the age of 13 years.

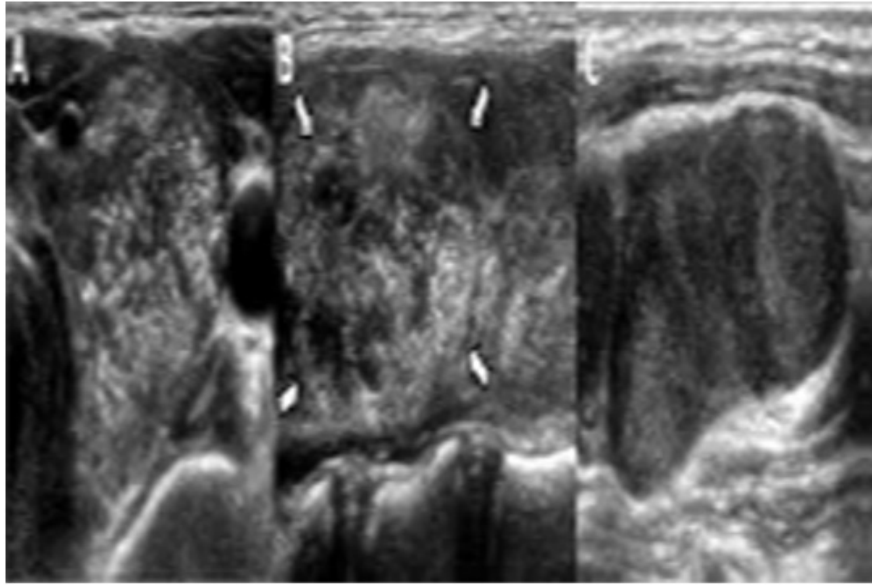


Figure 2: A 12-year-old girl with Hashimoto's Thyroiditis and papillary thyroid cancer (PTC). Transverse (A) and longitudinal (B) scan show heterogeneous echogenic nodules (arrows) with numerous micro calcifications in the upper portion of the left thyroid lobe. The lower aspect of the involved gland also shows scattered echogenic micro calcifications (C) Longitudinal scan of ipsilateral neck shows metastatic lymph nodes.

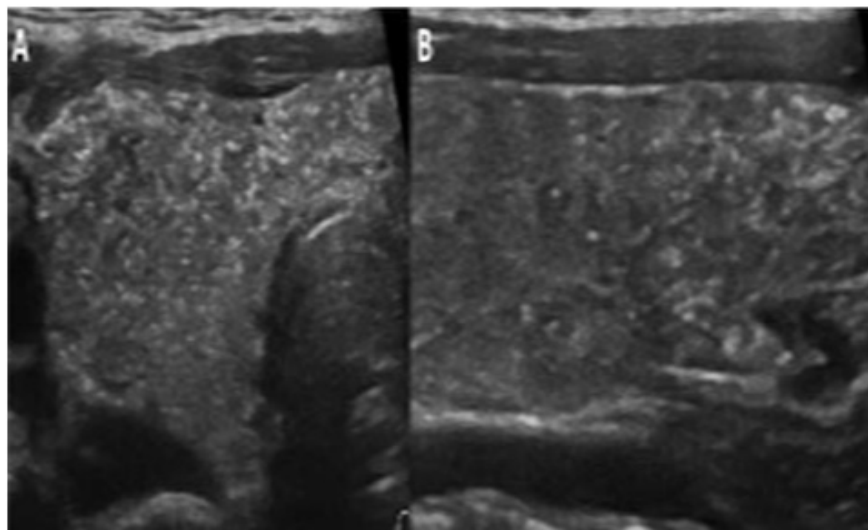


Figure 3: A 18-year-old girl with Hashimoto's Thyroiditis and papillary thyroid cancer (PTC). Transverse (A) and longitudinal image (B) shows diffuse enlargement of both thyroid lobes with scattered innumerable microcalcifications.

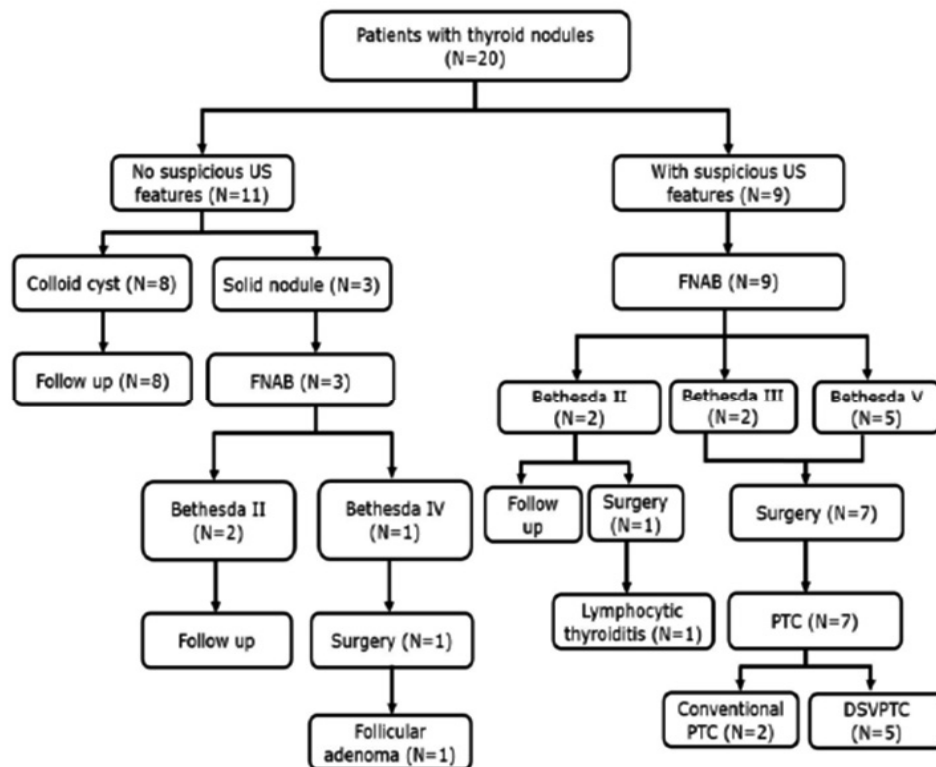


Figure 4: Flow chart of nodule characteristics and results of cytopathology. US, ultrasonography; FNAB, fine-needle aspiration biopsy; FLUS, follicular lesion of undetermined significance; PTC, papillary thyroid carcinoma; DSVPTC, diffuse sclerosing variant of papillary thyroid carcinoma.

Discussion

In this study, the prevalence of thyroid nodules and cancer in children and adolescents with HT were 22.4% and 7.9%, respectively. The malignancy rate among the detected thyroid nodules was 35%. Among the seven patients with a malignancy, all were PTC: five patients with DSVPTC and two with conventional PTC. TSH and thyroid autoantibody levels did not differ between patients with or without thyroid nodules. Thyroid cancer is the most common pediatric endocrine malignancy but is still rare, constituting 0.5% to 3% of all pediatric malignancies [15,16]. As pediatric thyroid cancer presents with more advanced disease and a greater frequency of metastasis than in adults, these cases warrant careful evaluation and a more proactive diagnostic approach [17]. Because chronic inflammation is thought to predispose a patient to neoplastic transformation and autoimmune disease, which are associated with several kinds of malignancies [18], investigators have focused on the correlation between HT and thyroid cancer since it was first described by Dailey, et al. [6] some studies have reported a positive correlation [6,19], while others have failed to demonstrate an association [8,20,21]. To date, few reports have been published about the prevalence of thyroid nodules and cancer in children and adolescents with HT. An Italian population had 31.5% (115/365) thyroid nodule prevalence, 3.0% (11/365) malignancy prevalence, and 9.6%

(11/115) malignancy prevalence among thyroid nodules [5] whereas our subjects had a lower prevalence of thyroid nodules (22.4%), but a higher malignancy rate (35%). Our rates for both thyroid nodules and malignancy in patients with HT were much higher than those reported in a study by Keskin, et al. [11] in a Turkish population; they reported 13% (39/300) thyroid nodule prevalence, a 0.67% (2/300) malignancy prevalence, and a 5.12% (2/39) malignancy rate among thyroid nodules. Several hypotheses may explain these differences. First, the role of iodine status may have affected the difference in cancer rates in pediatric HT. Iodine deficiency is well known to be a risk factor for thyroid nodules and the follicular histological type of thyroid cancer [22]. However, the association between PTC and excessive iodine intake remain unclear. One study suggested that high iodine uptake may increase the risk of the papillary thyroid cancer [23,24]. Italy and Turkey are countries with mild to moderate iodine deficiency, whereas INDIA is an iodine-sufficient region [25] Because of the limitations of the retrospective design, this was difficult to assess, but a difference in iodine status may have influenced the prevalence of thyroid nodules and malignancy. Second, the role of TSH should be discussed. There has long been a controversy in the literature about a positive correlation between HT and PTC. Kim, et al. [26] reported a very strong correlation between PTC and HT, and proposed Tg-Ab as an independent risk

factor for thyroid cancer. Many previous studies have indicated that higher serum TSH concentrations are associated with an increased frequency of benign and malignant thyroid nodules in patients without autoimmune Thyroiditis [8,9,30]. A study by Fiore et al. also showed that the risk of thyroid cancer increases when serum TSH was high, regardless of thyroid autoantibody status [27]. The prevalence of malignancy in this retrospective study was much higher (35%) than the 5% to 15% malignancy risk expected for thyroid nodules [29]. In this study, patients with thyroid nodules had lower TSH levels than HT patients without thyroid nodules and there were no significant differences in the levels of auto antibodies observed between the patient groups. Our results contradict many previous studies, which may indicate that the mechanisms underlying the relationship between increased serum TSH and thyroid cancer are different from those affecting the link between autoimmune Thyroiditis and thyroid malignancy. However in our study, TSH levels obtained from patients with HT and data of comparable healthy controls were not available. Small patient numbers may also partly explain this contradiction with previous studies. In similar studies of Italian and Turkish populations, the most common type of HT merger thyroid cancer was PTC, but further histological subtypes were not described [5,11]. In this study, all seven patients with thyroid cancer had PTC: five had DSVPTC and two had conventional PTC. Among the five patients with DSVPTC, four presented with the diffuse infiltrating form of PTC, and the other presented with nodular lesions. Even though the patient presented with nodular lesions, the remaining thyroid parenchyma had numerous micro calcifications. To date, there is no established relationship between HT and DSVPTC, so additional studies are required. Molecular biological studies about DSVPTC suggest that it exhibits different expression patterns of galectin 3, epithelial membrane antigen, p53, p64, and cell adhesion molecules compared to conventional PTC. A genetic analysis revealed that activation of rearranged during transfection (RET)/PTC rearrangements is common in DSVPTC with a lack of BRAFV600E and RAS mutations [31,32]. The association between HT and thyroid cancer is not well understood, but several authors have suggested the role of RET/PTC rearrangement in the association between PTC and HT. Previous studies have suggested that chronic inflammation might facilitate the RET/PTC rearrangement, or vice versa [33-35]. Additionally, Muzza, et al. [36] and Kim, et al. [37] reported that the BRAFV600E mutation, a common genetic alteration, is associated with a lower frequency of PTC in the background of HT. Therefore, we presumed that these common genetic features of increased RET/PTC rearrangement and fewer BRAFV600E mutations might be a link between DSVPTC and HT. However, molecular studies were not performed in our study, so further studies are needed to validate this hypothesis. This study had several limitations. First, it included only a small number of HT merger malignant thyroid disease cases. In fact, this limitation arises from the significantly lower incidence of HT in children. Therefore, a larger series must be conducted to verify our results. Second, our analysis was retrospective, and the study population was limited to patients with HT who had US examinations at a single institution, which could lead to selection biases. Third,

FNAB was not performed on colloid cysts. Two patients with benign FNAB results did not undergo a surgical biopsy. However, patients who did not undergo FNAB and patients with benign cytological results were followed up for at least 24 months without changes; therefore, we believe our nodular prevalence well reflects the actual incidence.

Conclusion

The prevalence of thyroid nodules and malignancy were 22.4 % and 7.9%, respectively, in children and adolescents with HT. The malignancy rate among thyroid nodules was 35%. The malignancy risk of thyroid nodules developing in an HT background is higher than the 26% rate generally reported for children with nodules. All patients with thyroid cancer presented with advanced disease. Specifically, 71.4% of patients with thyroid cancer had DSVPTC. Therefore, clinicians should be aware of the high malignancy risk of thyroid nodules in children and adolescents with HT, and US might be helpful to survey known or suspected thyroid nodules in these patients.

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