folia medica

Folia Medica 67(1)
DOI: 10.3897/folmed.67.e138135

Original Article

The effect of the presence of Hashimoto's thyroiditis on the frequency of papillary thyroid carcinoma subtypes

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Received: 29 September 2024 ♦ **Accepted:** 2 January 2025 ♦ **Published:** 25 February 2025

Citation: Şahin ZB, Sayiner ZA, Akarsu E. The effect of the presence of Hashimoto's thyroiditis on the frequency of papillary thyroid carcinoma subtypes. Folia Med (Plovdiv) 2025;67(1): e138135. doi: 10.3897/folmed.67.e138135.

Abstract

Aim: Papillary thyroid carcinoma (PTC) subtypes are known to differ from each other in terms of the features associated with each subtype. The aim of this study was to determine whether the incidence of PTC subtypes differs in the presence or absence of Hashimoto's thyroiditis.

Materials and methods: A total of 1195 patients were included and evaluated for the presence of nodules, divided into two groups: those with Hashimoto's thyroiditis and thyroid nodules (HT) and those with thyroid nodules only (non-HT). The two groups were compared with respect to demographics, clinical, ultrasonographic and cytological characteristics of thyroid nodules, and the presence of PTC.

Results: Of the patients, 943 (78.9%) were diagnosed with thyroid nodules without HT (non-HT group) and 252 (21.1%) with thyroid nodules with HT (HT group). The incidence of indeterminate cytology (Bethesda category III) was significantly higher in the HT group than in the non-HT group (18.60% vs. 10.80%, p=0.001). The incidence of PTC was also statistically significantly higher in the HT group than in the non-HT group (22.2% vs. 5.7%, p=0.001). However, no correlation was observed between the histopathological subtypes of PTC and the presence of Hashimoto's thyroiditis.

Conclusion: Hashimoto's thyroiditis did not appear to alter the incidence of PTC subtypes. However, PTC was more frequently observed in thyroid nodules associated with HT compared to those without HT.

Keywords

Hashimoto thyroiditis, papillary thyroid carcinoma, thyroid nodule

Introduction

Recent studies have suggested that lymphocytic infiltration and immunological factors observed in Hashimoto's thyroiditis (HT) may lead to an increased risk of developing papillary thyroid cancer. HT is the most common autoimmune thyroid disease, affecting 2%–15% of the world's population, and the most common cause of hypothyroidism.[1] The process of autoimmune destruction of the thyroid gland by apoptosis of thyroid epithelial cells has been observed in cases of Hashimoto's thyroiditis, a condition which frequently results in the development of hypothyroidism. Almost all HT patients have high serum concentrations of antibodies against one or more thyroid

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antigens and diffuse lymphocytic infiltration of the thyroid gland, consisting predominantly of thyroid-specific B and T cells.[2,3] Dailey et al.[4] were the first to speculate on the relationship between HT and thyroid cancer in 1955. They linked Hashimoto's with PTC, and it has been reported that patients with thyroid cancer survive significantly longer when HT is associated with PTC.[4] Chronic inflammation and lymphocytic infiltration in HT have been suggested to be risk factors for thyroid cancer.[5] However, in later studies, the effects of the combination of HT and nodules on the development of thyroid carcinoma were not clearly demonstrated. The World Health Organization revised its classification of differentiated thyroid carcinoma in 2022. They suggested using the term subtype instead of the term variant.[6] The impact of Hashimoto's thyroiditis on the risk of PTC and the relationship between differentiated PTC subtypes and the presence of HT remains unclear.

Aim

The aims of this study were to determine the clinical, sonographic, and cytological findings in patients with thyroid nodules with HT, whether there is a difference from the findings in patients with thyroid nodules without HT diagnosis, and whether there is an association between PTC risk and PTC subtypes in the presence of HT and thyroid nodules.

Materials and methods

In this retrospective study, patients who were treated at the Department of Endocrinology and Metabolism at Gaziantep University Medical School were diagnosed with nodular thyroid disease and underwent fine needle aspiration biopsy of thyroid nodules. The study was approved by the decision of the Clinical Research Ethics Committee. Patients aged 18-80 were included in the study. Patients taking anti-thyroid drugs, patients who had previously received radioactive iodine (to rule out Graves' disease), patients who had received radiotherapy to the head and neck, and patients who had taken drugs (glucocorticoids, lithium, etc.) that could affect thyroid function were excluded from the study. Thus, 1195 patients were included in the study. The decision to proceed with surgery was based on the results of the nodule cytology, the detection of compression findings and the expressed preference of the patient. The findings were obtained by retrospective collection of data regarding the characteristics of the nodules that were histopathologically confirmed as papillary thyroid carcinoma or noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFT-P)

The age, sex, history of radiotherapy to the neck region, history of additional cancer, history of previous thyroid surgery, and history of thyroid cancer in first-degree relatives of the patients were examined. The free triiodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormone (TSH), and anti-thyroid peroxidase (anti-TPO) levels in the 6 months prior to fine needle aspiration biopsy (FNAB) were recorded as the data closest to the biopsy date.

The diagnosis of HT was made based on the following two criteria:

- Those who are diagnosed with chronic lymphocytic thyroiditis as a result of pathological examination (lymphocytic infiltrate with germinal center formation, predominantly T lymphocytes and polyclonal plasma cells, capsule limited fibrosis, lobulation of thyroid tissue by fibrotic bands) (patients with thyroid lymphoma or tumor associated lymphocytic infiltration were excluded from the study).
- TPO-Ab positivity and HT findings on ultrasonography (heterogeneous echotexture, presence of hypoechoic micronodules [1-6 mm] with surrounding echogenic septations).[7]

The patients were evaluated in two groups: HT and non-HT. Demographic data (age and sex), sonographic features of the thyroid gland and thyroid nodules, and nodule cytology features of patients in both groups were compared. Cytological and histological parameters were based on a report review only. The number of thyroid cancers was compared between the two groups. Age, sex, and PTC pathological findings, which were the most common thyroid cancers in both groups, were compared.

The pathological parameters evaluated included tumor diameter (cm), lymph node invasion (yes or no), vascular invasion (yes or no), distant metastasis (yes or no), extrathyroidal involvement (present or absent), multifocal involvement, histopathological reports, PTC subtype (follicular, classical, tall cell, NIFTY, trabecular subtype, insular, oncocytic, or hobnail cell subtype), and presence of concomitant chronic lymphocytic thyroiditis.

Statistical analysis

The conformity of the numerical variables to the normal distribution was tested using the Shapiro-Wilk test. Mann Whitney U test was used to compare the non-normally distributed variables in two groups. The chi-square test was used to test the relationships between categorical variables. Numerical variables were indicated by means and standard deviations, and categorical variables were presented as numbers and percentages. The SPSS 22.0, Windows version package program was used in the analysis. Statistical significance was set at $p<0.05$.

Results

The study included 1195 patients. Of these, 943 (78.9%) were in the group with thyroid nodules without HT (non-HT group) and 252 (21.1%) were in the group with thyroid nodules with HT (HT group). The age, sex, history of radiotherapy to the neck region, history of additional cancer,

history of previous thyroid surgery, and history of thyroid cancer in first-degree relatives of the patients were examined. These variables were similar in both groups, except for the TSH values. TSH levels were higher in the HT group than in the non-HT group, and those with high TSH values had more total thyroidectomies ($p<0.001$) **(Table 1)**. The mean age of the patients in the non-HT and HT groups was 47±13 years and 46±13 years, respectively. Of the patients in the non-HT group, 84.9% were women and 15.1% were men. Of the patients in the HT group, 89.3% were women and 10.7% were men.

There was no statistical difference between the patient groups in preoperative thyroid ultrasound evaluation according to TIRADS classification ($p>0.05$). The distribution of nodule cytology according to Bethesda classification of patients in the non-HT and HT groups is shown in **Table 2**. When we compared the FNAB results of the patients according to the Bethesda classification, the frequency of suspected malignancy was significantly higher in the HT group than that in the non-HT group (7.5% vs. 1.9%, $p=0.001$), and the frequency of benign nodules was significantly lower (42.5% vs. 58.1%, $p=0.001$). There was no difference in terms of malignant cytology between HT and non-HT group (2.8% vs. 1.7%, $p=0.236$)

The incidence of histopathologically proven PTC was found to be statistically significantly higher in the HT group than in the non-HT group (HT and non-HT: 22.2% vs. 5.7%, $p=0.001$). PTC was observed in only two patients classified under Bethesda category II. The two individuals under consideration were assigned to the HT cohort. PTC was observed in 1.8% (2/107) of patients who exhibited benign cytology **(Table 2)**.

There was no statistically significant difference between the incidence of PTC subtypes in the HT and non-HT groups ($p=0.990$). The most common papillary thyroid carcinoma subtype was follicular thyroid carcinoma in both groups **(Table 3)**.

Sonographic nodule characteristics in patients with PTC were compared between the two groups, and no statistical significance was found ($p>0.05$) **(Table 4)**.

The prognostic pathological features of PTC in both groups were compared. No statistically significant differences were found in lymph node invasion, vascular invasion, extrathyroidal involvement, multifocal involvement, and tumor size, which are considered prognostic variables.

Discussion

Thyroid nodules are a common condition. The frequency of thyroid nodules in autopsy results of individuals without known thyroid disease was found to be 50%, and this rate

Table 1. Baseline characteristics of participants

Parameters	Groups				*P* values
	Non-HT		HT		
	Count	Mean	Count	Mean	
Age (years)	943	47±13	252	46±13	0.688
TSH (mU/mL)	943	1.50±2.07	252	2.24±2.42	0.001*
Free T3 (ng/dl)	943	0.89±0.17	252	0.87±0.19	0.687
Free T4 (µg/dl)	943	3.67±0.53	252	3.67±0.57	0.677
Nodule diameter (cm)	943	2.7±1.1	252	2.7±1.3	0.766
Tumor diameter (cm)	52	1.73±1.49	56	1.67±1.50	0.753

Table 2. Distribution of nodule cytology according to Bethesda classification of patients and the frequency of histopathologically proven PTC of patients in non-HT and HT groups

Nodule cytology	Non-HT n (%)	HT n (%)	*P*
Benign	548 (58.1)	107 (42.5)	0.001*
Atypia of undetermined significance	70 (7.4)	26 (10.3)	0.122
Follicular neoplasm/suspicious for follicular neoplasm	8 (0.8)	2 (0.8)	0.990
Suspicious for malignancy	18 (1.9)	19 (7.5)	0.001*
Malignant	16 (1.7)	7 (2.8)	0.236
Non diagnostic/unsatisfactory	252 (26.7)	82 (32.5)	0.540
Histopathologically proven papillary thyroid carcinoma	54 (5.7)	56 (22.2)	0.001*

*$p<0.05$ was considered significant

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Table 3. Distribution of papillary thyroid carcinoma subtypes

Papillary thyroid carcinoma subtypes	Non-HT group n (%)	HT group n (%)	*P* values
Follicular	26 (50.0)	29 (52.7)	0.85
Classical	10 (19.2)	10 (18.2)	0.99
Tall cell	7 (13.5)	7 (12.7)	0.99
NIFTP	4 (7.7)	3 (5.5)	0.87
Trabecular	2 (3.8)	1 (1.8)	0.89
Hobnail	1 (1.9)	1 (1.8)	0.99
Insular	1 (1.9)	2 (3.6)	0.86

NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features; $p<0.05$ was considered significant

Table 4. Sonographic nodule characteristics with PTC

	Non-HT n (%)	HT n (%)	*P*
Nodule echogenicity			0.569
Hypoechoic	11 (20.4)	11 (19.6)	
Hyperechoic	1 (1.9)	2 (3.6)	
Mixechoic	39 (72.2)	36 (64.3)	
Isoechoic	3 (5.6)	7 (12.5)	
Margin irregularity presence	14 (25.9)	13 (23.2)	0.741
Microcalcification	6 (11.1)	5 (8.9)	0.703
Solidity	1 (1.9)	1 (1.8)	0.979
Nodule diameter			0.765
<2 cm	33 (63.5)	38 (67.9)	
2-4 cm	15 (28.8)	13 (23.2)	
>4 cm	4 (7.7)	5 (8.9)	

$p<0.05$ was considered significant

varies between 19% and 67% in ultrasound scans of healthy individuals.[8,9] The relationship between chronic inflammation and the risk of malignancy has long been known, and HT, a chronic inflammatory disease, may be associated with an increased risk of thyroid cancer. Many studies have been conducted on this association, but the results are uncertain.[5,10-12] It has been shown that the presence of HT affects the evaluation of nodule cytology. HT may result in reactive atypia mimicking papillary thyroid cancer, such as increased nuclear size and nuclear contour irregularities, which may result in false positivity for malignancy in FNAB specimens.[13] The most comprehensive study demonstrating a relationship between HT and PTC was the 20-year prospective study conducted by Silva de Morais et al.[5] In this study, 9851 patients were evaluated (10168 non-HT nodules and 3895 HT nodules), and the prevalence of indeterminate cytology was higher in the HT group than in the non-HT group (indeterminate: 26.3% vs. 21.8%, respectively, $p<0.001$).[5] In our study, the frequency of indeterminate cytology was higher in the HT group, but the difference was not statistically significant. In contrast, the frequency of category V (suspected malignancy) according to the Bethesda classification was significantly higher in the HT group than in the non-HT group (7.5% vs. 1.9%, $p=0.001$). On AUS or FLUS cytology, most cells in the cases appeared benign, but some showed nuclear enlargement, pale chromatin, and irregular nuclear contours. This histological appearance is more common in Hashimoto's patients, which supports the higher AUS/FLUS result in fine-needle aspirations from patients with chronic lymphocytic thyroiditis in the literature. However, no such relationship was observed in this study. Nuclear changes seen in follicle cells in lymphocytic thyroiditis may include focal enlargement, clefts, nucleolar prominence, and chromatin clarification. Although this may also be observed in cell groups reported as suspected papillary carcinoma, the abundance of lymphocytes and plasma cells does not exclude the possibility of accompanying PTC.[13,14] Therefore, the cellular and structural changes observed in lymphocytic thyroiditis may have common features with PTC, and this supports the increase in the rate of suspicion of papillary carcinoma in biopsies performed on nodules diagnosed with HT.

In our study, no difference was found in terms of cytological diagnosis of malignancy between the HT and non-HT groups (2.8% vs. 1.7%, p=0.236). In a study conducted by Matesa-Anić et al. from Croatia, the FNAB of 10508 consecutive patients who were treated at the outpatient clinic was analyzed. While the prevalence of PTC in patients with HT was 1.9%, the prevalence of PTC in patients without HT was 2.7%; no significant relationship was found between HT and PTC in this study.[15] In addition, in a retrospective study conducted by Erdoğan et al.[16], the FNAB of 769 patients was examined, and the prevalence of PTC in patients with HT was 2%, similar to the study by Matesa-Anić et al.[15] In our study, the incidence of histopathologically proven PTC was significantly higher in the HT group than in the control group. The incidence of PTC was 5.7% and 22.2% in the non-HT and HT groups, respectively. Similarly, in a study by Graceffa et al., the incidence of PTC in patients with HT was 28.6%.[17] According to these results, some of the patients in the other groups in the presence of HT according to FNAB evaluation appear to have a PTC diagnosis when evaluated histopathologically. PTC was observed in only two patients classified under Bethesda category II. The two individuals under consideration were assigned to the HT cohort. PTC was observed in 1.8% (2/107) of patients who exhibited benign cytology.

In a study by Ohmori et al., in which US features of papillary thyroid cancer were compared between patients with and without HT, many US features were reported to be similar.[18] In addition, in a study by Özdemir et al.[19], 317 patients had HT and 602 patients did not. PTC was evaluated, and no differences were found in terms of nodule diameter, structure, echogenicity, presence of halo, irregular margins, microcalcification, and vascularization. In our study, no difference was found between the US features of the nodules between the HT and non-HT groups.

Many studies have emphasized that HT is a protective factor against poor prognosis in PTC. It is argued that the immune response, which occurs especially on the basis of HT or chronic lymphocytic thyroiditis and causes destruction of the thyroid parenchyma, also destroys tumoral cells in the same way, thus partially inhibiting tumor spread; ultimately, the tumor has a less aggressive course.[20] In a meta-analysis of 71 observational studies by Moon et al.[21] in 2018, HT was found to be associated with better clinicopathological features and prognosis among patients with PTC. According to this study, lymph nodes, vascular, and distant metastases were found to be lower in the HT group than in the non-HT group.[21] In this study, malignant pathological features and poor prognosis determinants such as tumor size, lymph node invasion, vascular invasion, extrathyroidal involvement, multifocal involvement, and distant metastasis were compared in both groups, and no significant differences were detected. Studies that examine the complex pathophysiological processes of both conditions in more detail are needed to clarify the conflicting results in the literature regarding the presence of HT and PTC aggressiveness.

Our study had several limitations. First, we studied patients retrospectively; therefore, our results cannot be generalized to the general population and do not reflect large-scale epidemiological data on HT or thyroid cancer. Second, confounding variables may have influenced our results. Detection of mutations in PTC cells: as the current research is a retrospective study and real-time evaluation of ultrasonography findings is impossible, the findings cannot be evaluated in real time. Therefore, the interpretation may vary between operators. However, this limitation does not diminish the significance of this investigation, as all preoperative sonograms were interpreted by two experienced endocrinologists.

Conclusion

In conclusion, the relationship between HT and thyroid cancer remains controversial, despite numerous studies. In our study, PTC was found to be significantly more common in nodules with Hashimoto thyroiditis. In thyroid nodule evaluation, Hashimoto's disease does not seem to affect papillary thyroid carcinoma subtypes. In addition, the presence of HT in the ultrasonographic features of thyroid nodules did not seem to affect the frequency of PTC diagnoses.

Author contributions

E.A., Z.A.S., and Z.B.Ş. gathered and analyzed data; Z.A.S. wrote the article; Z.A.S. and E.S. supervised the article.

Acknowledgements

The authors have no support to report.

Funding

The authors have no funding to report.

Competing Interests

The authors have declared that no competing interests exist.

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