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Original Article

Hashimoto's Thyroiditis is Not a Negative Contributor to Papillary Thyroid Cancer

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ABSTRACT

Objective: Hashimoto's thyroiditis is the most common autoimmune thyroid disease. Papillary thyroid cancer is the most common thyroid cancer. Whether Hashimoto's thyroiditis is a predisposing factor for papillary thyroid cancer remains unclear. In this study, the frequency of papillary thyroid cancer was investigated in patients with Hashimoto's thyroiditis who underwent total thyroidectomy.

Methods: In this study, 534 patients were screened retrospectively. Preoperative thyroid function tests, anti-thyroid antibodies, ultrasonography findings, fine-needle aspiration biopsies, and thyroidectomy pathology results were examined. According to the pathology, 139 patients had Hashimoto's thyroiditis. Patients with Hashimoto's thyroiditis (group 1) and non-Hashimoto's thyroiditis (group 2) were compared.

Results: Papillary thyroid cancer was found in 70 patients (50.4%) in group 1 and 156 patients (39.5%) in group 2 ($P = .026$). The odds ratio was 1.59 (95% CI; 1.07-2.34). There was no difference for sex, age, tumor size, microcarcinoma–macrocarcinoma distribution, subtype, number of tumor focus, lymph node metastasis, vessel invasion, and extrathyroidal spread.

Conclusion: We found more papillary thyroid cancer and less capsular invasion in patients with Hashimoto's thyroiditis, but we did not find any differences between groups in terms of age, gender, tumor size, vascular invasion, and metastasis. According to these findings, Hashimoto's thyroiditis may be a risk factor for papillary thyroid cancer.

Keywords: Hashimoto's thyroiditis, risk, papillary

INTRODUCTION

Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disease. Therefore, it is the most prevalent cause of hypothyroidism.[1] Hashimoto's thyroiditis leads to diffuse lymphocytic infiltration, fibrosis, and parenchymal atrophy in the thyroid gland.[2] Hashimoto's thyroiditis is a histopathologic diagnosis, but it can also be diagnosed by physical examination and laboratory tests. It affects 0.3-1.5 people per 1000 people and women constitute the majority of them.[3]

According to the Surveillance, Epidemiology, and End Results database, the prevalence of thyroid cancer in 2002 was 8.7/100 000 people. Papillary thyroid cancer (PTC) is the most common subtype and its prevalence is 7.7/100 000 according to the same database.[3] High-resolution thyroid ultrasonography (USG) and ultrasound-guided fine-needle aspiration biopsy are becoming more common and histopathological evaluation can be performed in more detail. These may be the underlying causes of PTC increase.[4]

The relationship between HT and PTC was first discussed in 1955. Since then, a number of studies have been conducted trying to show the relationship between these 2 diseases, but this is still not clear. Studies have shown that the co-occurrence of HT to PTC is associated with a better prognosis. These studies have given importance to the subject.[5] The aim of this study was to determine whether HT is a predisposing factor for PTC.

METHODS

Exclusion criteria: Patients younger than 18 years old who underwent subtotal thyroidectomy or lobectomy were not included. Patients whose histopathology revealed a malignancy other than well-differentiated thyroid cancer, who had preoperative hyperthyroidism, and/or who had no preoperative thyroid USG were excluded. Between July 2014 and July 2016, 850 patients who underwent bilateral total thyroidectomy by the general surgery department were retrospectively analyzed.

The patients were divided into 2 groups as with and without HT according to histopathology. Demographic characteristics, preoperative thyroid function tests, anti-thyroid antibodies, thyroid USG findings, thyroid fine-needle aspiration biopsies, and bilateral total thyroidectomy pathology results were evaluated.

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We could not detect all patients' anti-thyroid antibodies, so we did not evaluate them. In addition, tumor size, tumor number, the presence of invasion, extrathyroidal spread, and lymphatic metastasis were obtained from the hospital database.

Laboratory

Serum thyroid-stimulating hormone (TSH) (normal range: 0.34-5.6 mIU/mL), free thyroxine (normal range: 0.61-1.2 ng/dL) and free triiodothyronine (normal range: 2.5-4.2 pg/mL), anti-thyroid peroxidase antibody (normal range: 0-9 IU/mL), and anti-thyroglobulin antibody (normal range: 0-4 IU/mL) levels were determined. Not all autoantibodies were available in all patients so they were not studied. It was found that these measurements were studied with the chemiluminescence immunoassay method in UniCel DxI 800 (Beckmann-Coulter, Brea, Calif, USA) device.

Thyroid Fine-Needle Aspiration Biopsy

Thyroid fine-needle aspiration biopsies (TFNAB) were examined. The results had been reported according to Bethesda system[6] as non-diagnostic (I), benign (II), unspecified atypia (AUS)/indeterminate follicular lesion (AUFL) (III), follicular neoplasm (FN) or suspicious for FN (IV), suspicious for malignancy (V), and malignant (VI).

Ethics Committee Approval: The local ethics committee approved this study from Ankara Education and Research Hospital. (Date: October 27, 2015, Decision number: 617/2015) All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki eclaration and its later amendments or comparable ethical standards.

Indications for Thyroidectomy

Thyroid fine-needle aspiration biopsies with AUS/AUFL, FN/suspicious for FN, suspicious for malignancy, malignant, and TFNABs with 2 times non-diagnosed were the causes for total thyroidectomy. Also, patients with multinodular goiter, giant thyroid nodule (>4 cm), and primary hyperparathyroidism + multinodular goiter underwent total thyroidectomy.

Histopathological Diagnosis

Histopathological diagnosis of HT was based on total thyroidectomy material. For the diagnosis of HT, infiltration of the gland by lymphocytes and plasma cells and destruction of follicles due to this infiltration are required. Some epithelial cells become eosinophilic granular cytoplasm and are called askanazy or hurtle cells. The diagnosis of HT was confirmed by examining the thyroid parenchyma according to the above criteria, independent of tumor tissue.[7]

Main Points

- According to our study, Hashimoto's thyroiditis is a predisposing factor for papillary thyroid cancer.
- Capsule invasion and vascular invasion are less likely in papillary thyroid cancer in people with Hashimoto's thyroiditis.
- Hashimoto's thyroiditis does not lead to more severe papillary thyroid cancer.

Statistical Analysis

Statistical analyses were made using Statistical Package for the Social Sciences version 22.0. (IBM SPSS Corp.; Armonk, NY, USA). Numerical variables were summarized with mean ± standard deviation or median (min-max). Categorical variables were indicated by number and percentage. The chi-square test or Fisher's exact test was used to determine whether there was any difference between the groups in terms of categorical variables. The Kolmogorov–Smirnov test was used to determine whether the normal variables showed normal distribution, and the homogeneity of the variance was examined by Levene's test. Differences between 2 independent groups in terms of numerical variables, the differences between the 2 independent groups were approached as follows: When the parametric test assumptions are met, the t-test used for independent groups. In the absence of parametric test assumptions, Mann–Whitney U test was used. Post hoc analysis was used to compare more than 2 groups. The significance level was taken as $P < .05$.

RESULTS

This study included 534 patients who met the study criteria. The group of patients with HT (group 1) consisted of 139, and the group without HT (group 2) consisted of 395 patients (Table 1). Hashimoto's thyroiditis was diagnosed according to thyroidectomy results.

Around 94.2% (131) of the group 1 were female, while 82.8% (327) of the group 2 were female ($P = .001$). There was no difference in the mean age between the 2 groups ($P = .574$) (Table 1).

Thyroid-stimulating hormone level, thyroid status, thyroid volume, thyroid parenchymal echogenicity, the number of nodules, and suspicious nodules were significantly different between the groups ($P < .001$).

The sonographically suspicious nodules were 201 in group 1 and 750 in group 2. Their location, echogenicity, the presence of microcalcification and macrocalcification, marginal arrangement, and the ratio of anterior–posterior diameter to transverse diameter of the nodule were not different between the groups. But there was a significant difference in terms of nodule volume and the presence of cystic content ($P = .03$) and nodule biopsy results ($P < .001$) (Table 2).

There was a difference between the groups in terms of total thyroidectomy indications ($P < .001$). Post hoc analysis showed that the difference was caused by the indication groups of multinodular goiter (MNG), TFNAB:AUS/AUFL, and suspicious for malignancy (Table 3).

Papillary thyroid cancer was detected in 70 patients of group 1 and 156 patients of group 2 ($P = .026$). The odds ratio was 1.59 (95% CI; 1.07-2.34). There were no differences between the groups in terms of age and gender distributions, tumor diameter, tumor subtype, number of focus, microcarcinoma–macrocarcinoma

Table 1. Demographic, Biochemical, and Ultrasonographic Features of Patients

		HT Group (Group 1) (n=139)	Non-HT Group (Group 2) (n=395)	*P*
Gender	Female, n (%)	131 (94.2)	327 (82.8)	.001*
	Male, n (%)	8 (5.8)	68 (17.2)	
Age		48.0 ± 12.5	47.3 ± 12.3	.574
TSH		1.84 (0.35-17.9)	1.12 (0.13-14.2)	<.001*
Thyroid status	Euthyroid, n (%)	129 (92.8)	393 (99.5)	<.001*
	Hypothyroid, n (%)	10 (7.2)	2 (0.5)	
Presence of MNG, n (%)		103 (74.1)	339 (85.8)	.002*
TSH	Normal, n (%)	129 (92.8)	393 (99.5)	<.001*
	High, n (%)	10 (7.2)	2 (0.5)	
Number of patients with autoantibodies viewed, n (%)		64 (46)	176 (44.5)	.68
Thyroid right lobe volume, mL		9609.6 (594.9-60 889.9)	11 771 (611.5-312 000)	.018*
Thyroid left lobe volume, mL		8255.5 (0-172 380)	10 978.2 (2051.1-182 520)	<.001*
Parenchymal echogenicity	Homogeneous, n (%)	3 (2.2)	92 (23.3)	<.001*
	Mild heterogeneous, n (%)	13 (9.4)	127 (32.2)	
	Mild to moderate heterogeneous, n (%)	15 (10.8)	16 (4.1)	
	Moderate heterogeneous, n (%)	64 (46)	147 (%)	
	Moderate to advanced heterogeneous, n (%)	16 (11.5)	2 (0.5)	
	Advanced heterogeneous, n (%)	28 (20.1)	11 (2.8)	
Number of nodules per patient, n		2 (0-14)	3 (1-16)	<.001*
Pathological-looking number of nodules per patient, n		1 (0-5)	2 (0-5)	<.001*

HT, Hashimoto's thyroiditis; TSH, thyroid-stimulating hormone; MNG, multinodular goiter.

distribution, lymphatic metastasis, and extrathyroidal spread. Vascular invasion of the tumor was not detected in the HT group. The mean preoperative TSH level and hypothyroidism tendency were more pronounced in group 1 as expected. There were significant differences between the groups in terms of thyroid volume, MNG presence, parenchymal echogenicity, the number of nodules, and the number of suspicious nodules. As a result, while PTCs were more in group 1, the capsular invasion of the tumor was more prominent in group 2, no difference was observed in other features (Table 4).

DISCUSSION

Since the contribution of chronic inflammation to tumor development it has been shown in many tissues that chronic inflammation leads to tumor development. From this point of view, it has been investigated in many studies whether autoimmune thyroiditis also causes thyroid cancer. In some studies, HT has been shown to be a risk factor for PTC, while others have not shown it to be a risk factor. These studies are retrospective or prospective studies based on total thyroidectomy or TFNAB results.[1] Since HT was diagnosed primarily with histopathology, in our study, patients with and without HT were retrospectively evaluated based on bilateral total thyroidectomy.

In our study, patients who underwent bilateral total thyroidectomy were divided into 2 groups based on histopathology as those with and without HT. Similar to the literature, prominent female gender dominance, hypothyroidism tendency, low volume of the thyroid gland, and low parenchymal echogenicity in patients with HT were detected.[8-10] Pathologic ultrasonographic findings such as hypoechogenicity, solid structure, and the presence of microcalcifications in malignant nodules developing on the basis of nodular HT are similar to the general population.[11,12] In our study, although the number of sonographically suspicious nodules was higher in the non-HT group (Table 1), in the detailed analysis of these nodules, no significant difference was found between the 2 groups except that the cystic content and nodule volume were lower in the HT group (Table 2).

Table 2. Characteristics of Sonographically Suspicious Nodules

Nodule		HT Group (Group 1) (n=201)	Non-HT Group (Group 2) (n=750)	*P*
Volume, mL		1091.7 (12-35 490)	1582.6 (22.1-114 400)	.030*
Location, n (%)	Right	108 (53.7)	373 (49.7)	
	Left	82 (40.8)	329 (43.9)	.587
	Isthmus	11 (5.5)	48 (6.4)	
Echogenicity, n (%)	Isoechoic	38 (18.9)	129 (17.2)	
	Hypoechoic	51 (25.4)	149 (19.9)	
	Iso-hypoechoic	21 (10.4)	79 (10.5)	.102
	Mixed	83 (41.3)	380 (50.7)	
	Hyperechoic	5 (2.5)	9 (1.2)	
	Iso-hyperechoic	3 (1.5)	4 (0.5)	
Ratio of anterior-posterior diameter to transverse diameter, n (%)	<1	192 (95.5)	696 (92.8)	.223
	>1	9 (4.5)	54 (7.2)	
Edge layout, n (%)	Regular margin	173 (86.1)	673 (89.7)	.141
	Irregular margin	28 (13.9)	77 (10.3)	
Central vascularity, n (%)	No	177 (88.1)	645 (86)	.449
	Yes	24 (11.9)	105 (14)	
Cystic content, n (%)	No	176 (87.6)	609 (81.2)	.035*
	Yes	25 (12.4)	141 (18.8)	
Microcalcification, n (%)	No	154 (76.6)	579 (77.2)	.861
	Yes	47 (23.4)	171 (22.8)	
Macrocalcification, n (%)	No	170 (84.6)	652 (86.9)	.386
	Yes	31 (15.4)	98 (13.1)	

HT, Hashimoto's thyroiditis.

Table 3. Indications for Total Thyroidectomy

Indication	HT Group (Group 1) (n=139)	Non-HT Group (Group 2) (n=395)	*P*
MNG, n (%)	**19 (13.7)**	**136 (34.4)**	
TFNAB, n (%)	93 (66.9)	177 (44.8)	
Malignant	16 (11.5)	32 (8.1)	
AUS/AUFL (1 or 2 times)	**47 (33.8)**	**83 (21)**	
suspicious for malignancy	**12 (8.6)**	**8 (2)**	<.001
ND (2 times)	14 (10.1)	39 (9.9)	
FN/suspicious for FN	4 (2.9)	15 (3.8)	
Giant nodule, n (%)	19 (13.7)	74 (18.7)	
MNG + parathyroid lesion, n (%)	7 (5.7)	8 (2)	

MNG, multinodular goiter; TFNAB, thyroid fine-needle aspiration biopsy, AUS, unspecified atypia; AUFL, indeterminate follicular lesion; ND, non-diagnosed; FN, follicular neoplasia.

In patients with nodules requiring fine-needle aspiration biopsy in the general population, the risk of thyroid cancer was 9-13%.[13,14] Which nodules require biopsy is decided based on ultrasonographic appearance. The risk is determined according to the presence of microcalcification, hypoechoic structure, edge irregularity, central vascularity, solid component, and irregular and thick halo. In the presence of a cystic component, spongiform appearance, hyperechogenicity, fine and regular halo, comet artifact, and the likelihood of the nodule being a benign nodule increase, thus biopsy is not necessary.[15-17] Simply, a biopsy is recommended for intermediate-high suspicion nodules with a size of >1 cm. But, non-risky nodules other than size are recommended to follow without biopsy.[18] The association of benign and malignant nodules in HT is well known, however, specific guidelines for the approach to these nodules are not available today, they are approached as in the general population.[15] In studies conducted, an approach similar to the general population seems to be sufficient for HT.[11] In our study, the nodules with suspicious appearance in the HT group were evaluated based on the current guidelines and were found to have lower volume and less cystic content compared to the non-HT group. In the general population, cystic content is less in malignant nodules, but as the volume increases, the risk of malignancy increases.[19] In our study, since all of these nodules did not undergo fine-needle aspiration biopsy in all groups, these differences could not be evaluated.

Indications for total thyroidectomy can be grouped under 3 main headings: malignant thyroid nodule/nodules, non-toxic nodular/multinodular goiter, and hyperthyroidism. The most common cause is malignant nodule/nodules and the most common benign cause is non-toxic multinodular goiter. Thyroid cancer risk is the most common cause of total thyroidectomy in HT.[20,21] In our study, bilateral total thyroidectomy indications were different between the groups. We did post hoc analysis to see where the difference stems from; this difference was due to MNG, AUS/AUFL, and suspicion for malignancy groups. The most common operation indication was biopsy results in both groups. There was a significant difference between the groups with a detailed examination of the biopsy results; HT patients were most frequently operated on due to the biopsy result of the AUS/AUFL.

The issue of whether HT caused thyroid cancer since 1955 is constantly discussed. Some studies supported this thesis and some argued that there was no such relationship. Since the development of neoplasia on the basis of chronic inflammation is already known, the chronic inflammatory process present in HT may be causing cancer development. The inflammatory process can lead to DNA damage through reactive oxygen mediators resulting in cancer development. Helper and cytotoxic T lymphocytes, and high amounts of anti-thyroid antibodies lead to papillary cell damage by administering this inflammatory response. On the other hand, the presence of accompanying HT in cases with thyroid cancer may be an incidental condition.[1] According to data from a large number of meta-analyses, PTC is seen 3 times more in HT patients. The incidence of HT with PTC varies between 0.5% and 58% in various populations and this association has increased significantly in the last 20 years. Of course, both the increase in the frequency of autoimmune diseases, the spread of USG and biopsy, and the increase of awareness are important factors in this increase.[21] As in the literature, in our study, PTC was more common in HT patients (50.35% vs. 39.49%, $P = .026$) and the odds ratio was detected as 1.59.

According to the literature, HT and PTC are seen more often, are more focused, and are smaller (usually <1 cm) in younger women.[22-24] In our study, PTC was found to be more common in females but there was no difference between the groups in terms of gender and age distribution. The mean tumor size was <1 cm in both groups. Papillary thyroid cancer was found as a single focus in more than 50% of patients in both groups, but no statistically significant difference was observed ($P = .432$, Table 4).

One of the hypotheses to explain the causal relationship between HT and PTC is the high level of TSH. High levels of TSH contribute to the development of papillary cancer by inducing follicular epithelial proliferation in patients with hypothyroidism.[25] In our study, the mean TSH level was higher in group 1 and the tendency to hypothyroidism was higher ($P < .001$).

There are studies showing that PTCs accompanied by HT have a better prognosis. In the study performed by Ahn et al.[26] HT and PTC showed smaller tumor size, single focus, less lymph node metastasis, and better survival. Also, in a more recent study by Borowczyk27, chronic lymphocytic thyroiditis decreases the stage of differentiated thyroid cancer. There are several hypotheses to explain why HT has a better prognosis for PTC. In HT, follicular cells express Fas and Fas ligand, which induce Fas-related apoptosis and cause destruction in thyroid tissue. Because PTC originates from follicular cells, the immune response caused by the common antigen may cause the destruction of tumor cells.[28] The BRAF mutation is also lower in PTC with HT, which is associated with a good prognosis.[29] In our study, the vascular invasion was not seen in group 1, while it was seen in 7 patients of group 2, but the statistical comparison was not possible because of scarcity. The capsular invasion was found to be low in the HT group close to significance ($P = .061$). Lymphatic metastasis and extrathyroidal spread were detected in both groups but no difference was found.

CONCLUSION

Papillary thyroid cancer was found to be significantly higher in HT patients. Papillary thyroid cancer was more common in females in both groups and age distribution was similar. Hence, different effects of HT on age and gender were not detected. In the HT group, the tumor was less prone to capsular invasion and did not perform vascular invasion, which was a favorable result. The effect of HT on tumor size and the number of foci were not observed. Finally, since our study is a cross-sectional study, it is currently not possible to tell the effect of HT on PTC prognosis; however, long-term follow-up is predicted to reach a meaningful outcome.

Limitations

We could not detect all patients' anti-thyroid antibodies so we did not evaluate them. We could not tell if there is any relationship between thyroid autoantibodies and PTC. Unfortunately,

Table 4. Comparison of Papillary Carcinomas Detected in the Resected Thyroid Tissue of the 2 Groups

			Group 1 (HT)	Group 2(non-HT)	*P*
Number, n (%)			70 (50.35)	156 (39.49)	.026*
gender, n (%)	Female		65 (92.9)	133 (85.3)	.166
	Male		5 (7.1)	23 (14.7)	
age			46.8 ± 12.4	46.1 ± 12.8	.705
Preoperative TSH			1.99 (0.36–17.9)	1.22 (0.13–14.2)	<.001
Thyroid function status, n (%)	Euthyroid		62 (88.6)	155 (99.4)	.001*
	Hypothyroid		8 (11.4)	1 (0.5)	
MNG presence, n (%)			51 (72.9)	133 (85.3)	.042*
Right thyroid lobe volume, mL			7920.1 (1560.0–60 889.9)	9684.5 (611.5–140 874.2)	.028*
Left thyroid lobe volume, mL			7271.7 (338.3–172 380)	8616.9 (2355.0–88 058.9)	.044*
Parenchymal echogenicity,	Homogeneous, n		1 (1.4)	36 (23.1)	<.001*
	Heterogeneous		69 (98.6)	120 (76.9)	
Nodule number, n			2 (1–11)	3 (1–16)	.001*
Suspicious nodule number, n			1 (0–5)	1 (0–5)	<.001*
Tumor diameter, mm			9 (0.6–45)	9 (0.4–68)	.899
Diameter group, n (%)	Microcarcinoma		47 (67.1)	97 (62.2)	.473
	Macrocarcinoma		23 (32.9)	59 (37.8)	
Tumor subtype, n (%)	Classic		60 (85.7)	132 (84.6)	.093
	Follicular		7 (10)	23 (14.7)	
	Tall cell		0 (0)	1 (0.6)	
	Hurtle cell		2 (2,85)	0 (0)	
	Oncocytic cell		1 (1,42)	0 (0)	
Capsular invasion, n (%)			2 (2.9)	18 (11.5)	.061
Vascular invasion, n (%)			–	7 (4.5)	.102
Extrathyroidal spread, n (%)			4 (5.7)	17 (10.9)	.321
Lymphatic metastasis, n (%)			10 (14.3)	20 (12.8)	.930
Focus number, n (%)		Single focus	36 (51.4)	89 (57.1)	.432
		>1 focus	34 (48.6)	67 (42.9)	

HT, Hashimoto's thyroiditis; TSH, thyroid-stimulating hormone; MNG, multinodular goiter.

the biopsy of every nodule with sonographically suspicious appearance was not done.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Education and Research Hospital. (Date: October 27, 2015, Decision number: 617/2015).

Informed Consent: The written informed consent obtained form all the participants.

Peer-review: Externally peer-reviewed.

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