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The Effect of Hashimoto's Thyroiditis on the Development of Thyroid Carcinoma

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ABSTRACT

Purpose: We aimed to investigate whether Hashimoto's Thyroiditis (HT) affects the development of thyroid carcinoma or not.

Methods: We examined 772 patients' files between January 2000 and December 2010 retrospectively at Istanbul University Cerrahpasa Medical School Endocrinology and Metabolism Clinic, where fine-needle aspiration biopsy (FNAB) was applied. We noted the patient's demographic findings, anti-thyroglobulin antibody (anti-TG) and anti-thyroperoxidase antibody (anti-TPO) levels, ultrasonography (US), and cytology reports. We compared the findings of HT patients without Hashimoto's as a control group.

Results: 393 patients with a mean age of 46.11 ± 12.53 of whom 39 were male and 354 were female with HT and thyroid nodules (HT group) were compared with 379 patients with a mean age of 47.5 ± 12.6 of whom 53 were male and 326 female with nonautoimmune thyroid disease and nodules (control group). We found the prevalence of differentiated thyroid carcinoma 6.6% in the HT group and backward 12.9% in the control group (p=0.03). There were not any distinguishing US findings between groups. Anti-TPO positivity was significantly higher in benign nodules (p=0.008).

Conclusion: Our findings did not point out an increased risk of Hashimoto's nodules in terms of differentiated thyroid carcinoma development.

Keywords: Hashimoto's Thyroiditis, Thyroid Carcinoma, Thyroid nodules, Fine-needle aspiration biopsy

ÖZET

Amaç: Amacımız Hashimoto tiroiditinin (HT), tiroid karsinomu gelişimi üzerine etkisini incelemektir.

Yöntem: İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Endokrinoloji ve Metabolizma kliniğinde Ocak 2000- Aralık 2010 tarihleri arasında ince iğne aspirasyon biyopsisi (İİAB) uygulanan 772 hastanın dosyası geriye dönük olarak incelendi. Hastaların demografik bulguları, anti-tiroglobulin antikoru (anti-TG) ve anti-tiroperoksidaz antikoru (anti-TPO) düzeyleri, ultrasonografi (US) ve sitoloji raporları kaydedildi. Hashimoto Tiroiditi (HT) hastalarının bulguları hashimoto olmayan kontrol grubu ile kıyaslandı.

Bulgular: Ortalama yaşı 46.11 ± 12.53 olan, 39 erkek 354 kadın toplam 393 HT hastası (HT grubu), ortalama yaşı 47.5 ± 12.6 olan, 53 erkek ve 326 kadın toplam 379 hasta (kontrol grubu) ile karşılaştırıldı. Diferansiye tiroid karsinomu prevelansı HT grubunda %6.6, kontrol grubunda ise %12.9 saptandı (p=0.03). Gruplar arasında ayırt edici US bulgusu saptanmadı. Anti-TPO pozitifliği benign nodüllerde anlamlı olarak daha yüksekti (p=0.03).

Sonuç: Hashimoto tiroiditi nodüllerinde diferansiye tiroid karsinomu gelişimi yönünden artmış bir risk tespit edilmedi.

Anahtar kelimeler: Hashimoto tiroiditi, Tiroid karsinomu, Tiroid nodülü, İnce iğne aspirasyon biyopsisi

Hashimoto thyroiditis (HT) was first described more than a hundred years ago, now known as one of the most common autoimmune diseases that affects women predominantly (1). It is clear that HT is a risk factor for thyroid lymphoma development but its relationship with differentiated thyroid carcinoma has been debated since the cases Dailey documented in 1955 (2). Thyroid nodules are common in clinical practice and detected differentiated thyroid cancer is increasing worldwide (3). So, the clinician needs to detect suspicious conditions without overdiagnosing.

It is a debated topic if a nodule in HT patients differs from a nodule in a patient without thyroid autoimmunity in terms of malignancy development risk. In the literature, HT was found significantly associated with differentiated thyroid carcinoma in many retrospective studies (4, 5, 6, 7). But strikingly we can notice that studies that support the relationship are postsurgical series without a control group. Since surgery is performed on suspicious nodules, analyses of surgical series may easily lead to selection bias. Also, the immune response elicited towards tumor antigens can not be distinguished.

In the literature, FNAB-based studies are more limited and do not show a significant correlation between HT and DTC (8,9,10).

So, in our study, we compared the malignancy rate of HT nodules with non-hashimoto nodules in the control group with cytological criteria obtained by FNAB. The study aimed to determine the impact of HT on the development of differentiated thyroid carcinoma (DTC).

Material and Methods

The medical records of the patients with thyroid gland disorders who were followed up in the Cerrahpasa Medical School, Endocrinology and Metabolism clinic between January 2000 and December 2010 were retrospectively reviewed. The patients with one or more thyroid nodules, whose thyroid autoantibody level was checked, and who underwent nodule fine needle aspiration biopsy (FNAB) were evaluated.

The ethical approval was obtained from the Ethical Board Instution of Cerrahpasa Medical Faculty in Istanbul, Turkey (approval ID:16386). Patients with signs of hyperthyroidism, history of antithyroid drug use, radioactive iodine treatment or radiation exposure, FNAB cytology reporting medullary carcinoma, FNAB cytology results suspected or nondiagnostic but not confirmed, diagnosed with Graves disease or a different form of autoimmune thyroiditis were excluded from the study.

Hashimoto thyroiditis was defined as the patients who met one or more of the following criteria and at least one thyroid autoantibody positivity;

1- The patients with diffuse gland enlargement

2- The patients with heterogeneous parenchyma and echogenic septations were identified on ultrasound (US).

3- The patients with clinically euthyroid, subclinical hypothyroidism, or hypothyroidism with or without thyroid hormone replacement therapy.

4- The patients who have serum anti-thyroglobulin antibody (antiTG) with 0-40 u/ml reference range and/or anti-thyroperoxidase antibody (anti-TPO) with 0-35 u/ml reference range levels were obtained.

772 patients with FNAB cytology reported as lymphocytic thyroiditis, non-atypical thyrocyte, papillary carcinoma, and follicular carcinoma were evaluated. Three hundred ninety-three patients constituted the Hashimoto group while the patients with negative autoantibody levels and without defined clinical or US findings constituted the control group (n=379).

Demographic characteristics and US features of the patients were recorded. The number of the nodules (single, two, three, or more), size (1 cm and below, between 1-2 cm, 2 cm and above), echogenicity (hyperechoic, hypoechoic, isoechoic, mixed echo), nature (solid, predominant, cystic predominant), calcification form (eggshell, coarse, microcalcification), presence of peripheral halo were all noted. Cytology results were evaluated as benign and malignant. Gender, age, ultrasonography findings, and cytology results of HT patients were compared with the control group.

The patients in the Hashimoto group who were found to be benign and patients who were found to be malignant as a result of FNAB were compared in terms of demographic characteristics, ultrasonographic findings, and autoantibody positivity. Besides, the characteristics of the patients with benign and malignant nodules in the whole cohort were studied.

Statistical analyses were performed using SPSS software version 17. Descriptive analyses presented means and standard deviations for normally distributed variables.

The Chi-square test and Fisher's exact test were used to compare proportions and the Student's t-test was used to compare the parameters between groups. A P value of less than 0.05 was considered to show statistical significance.

Results

The mean age of 772 patients included in the study was 46.79 ± 12.57 (18-86) years. 88.1% (n= 680) of the patients were female and 11.9% (n= 92) were male. FNAB of the nodules resulted as 90.3% (n= 697) benign and 9.7% (n= 75) malignant.

Table 1 presents the demographic and US characteristics of the HT and control groups. The mean gender and age of the groups were found to be compatible with each other.

US findings

When US findings were compared, in both groups' multiple nodules of 1-2 cm in size, with similar echogenicity with excess cystic components mostly detected. The presence of a peripheral halo in Hashimoto's nodules was found significant (p=0.001). No significant difference was observed between the groups in terms of calcification content, but eggshell calcification was more common in the Hashimoto group and microcalcification was more common in the control group. The presence of 1-2 cm in size, single or two nodules in the Hashimoto group; three or more nodules smaller than 1 cm and above 2 cm in the control group was found to be statistically higher (p=0.002).

Table 1. The demographic and ultrasonographic characteristics of the patient and control groups

	Hashimoto's Thyroiditis	Control group	p-value
Number (%)	393 (50.9)	379 (49.1)	
Sex F/M	354 (90.1) / 39 (9.9)	326 (86) / 53 (14)	0.082
Age ± mean	46.11 ± 12.53	47.5 ± 12.6	0.127
Number of nodules			
One	70 (20.9)	48 (15)	
Two	49 (14.6)	27 (8.4)	**0.002**
Three or more	216 (64.5)	246 (76.6)	
Nodule size, cm			
<1 cm	5 (1.4)	6 (1.9)	
1-2 cm	322 (90.2)	250 (80.9)	**0.002**
>2 cm	30 (8.4)	53 (17.2)	
Echogenicity			
Hypoechoic	47 (27.6)	34 (29.6)	
İsoechoic	46 (27.1)	33 (28.7)	0.572
Hyperechoic	38 (22.4)	18 (15.7)	
Mixed echo	39 (22.9)	30 (26.1)	
Calcification form			
Eggshell	3 (10)	1 (2.6)	
Coarse	11 (36.7)	14 (36.8)	0.428
Microcalcifications	16 (53.3)	23 (60.5)	
Peripheral halo			
presence	77 (19.6)	41 (10.8)	**0.001**
absence	316 (80.4)	338 (89.2)	
Composition			
Solid predominant	11 (18.6)	10 (13.9)	0.46
Cystic predominant	48 (81.4)	62 (86.1)	

FNAB results

The comparison of the cytology results of the Hashimoto group with the control group is given in Table 2. When we analyzed the results of FNAB, we found that 6.6% of the patients in the Hashimoto group and 12.9% of those in the control group resulted as malignant. The malignancy rate was significantly higher in the control group, and nearly twice as high in the Hashimoto group (p=0.03).

Table2. Fine needle aspiration biopsy results of Hashimoto and control groups

Number (%)	Hashimoto's Thyroiditis	Control group	p-value
Benign	367 (93.4)	330 (87.1)	**0.003**
Malignant	26 (6.6)	49 (12.9)	

Comparison of benign-malignant nodules

Table 3 presents the demographic characteristics and US findings of the nodules. When we compare the cases according to cytology results; there was no difference between the mean age and gender distribution of benign and malignant nodules. While both measured autoantibodies were found to be positive at a higher rate in the benign group; AntiTPO positivity of benign nodules was also statistically significant (p=0.008). 1 cm or less and 2 cm and above in size, the presence of hypoechogenicity and microcalcification in the malign nodules; the presence of peripheral halo around benign nodules was found to be statistically significant.

Table3. Demographic and ultrasonographic characteristics due to cytology results

	Benign	Malignant	p-value
Number (%)	697 (90.3)	75 (9.7)	
Sex F/M	611 (87.7) / 86 (12.3)	69 (92) / 6 (8)	0.270
Age ± mean	46.9 ± 12.46	45.8 ± 13.6	0.490
Anti-TPO positivity	322 (46.3)	22 (30.1)	**0.008**
Anti - TG positivity	187 (29.1)	16 (23.9)	0.366
Number of nodules			
One	111 (18.0)	7 (17.9)	
Two	73 (11.8)	3 (7.7)	0.634
Three and more	433 (70.2)	29 (74.4)	
Nodule size, cm			
<1 cm	7 (1.1)	4 (10.3)	
1-2 cm	544 (86.8)	28 (71.8)	**0.001**
>2 cm	76 (12.1)	7 (7.9)	
Echogenicity			
Hypoechoic	68 (26.1)	13 (54.2)	
Isoechoic	76 (29.1)	3 (12.5)	**0.028**
Hyperechoic	53 (20.3)	3 (12.5)	
Mixed acho	64 (24.5)	5 (20.8)	
Calcification			
Eggshell	4 (6.7)	0 (0.0)	
coares	25 (41.7)	0 (0.0)	**0.034**
Microcalcifications	31 (51.7)	8 (100)	
Peripheral halo			
presence	116 (16.6)	2 (2.7)	**0.001**
absence	581 (83.4)	73 (97.3)	
Composition			
Solid predominant	19 (15.2)	2 (33.3)	0.237
Cysticpredominant ağırlıklı	106 (84.8)	4 (66.7)	

The characteristics of Hashimoto's nodules

Table 4 shows the demographic characteristics, US findings, and distribution of autoantibody positivity within the HT group according to cytology results. When we compared the patients of the Hashimoto group, whose FNAB results were found to be benign, and those whose results were found to be malignant; we found that they generally reflect the characteristics of benign and malignant nodules of the whole population. It was found statistically significant that benign HT nodules were between 1-2 cm in size and contained a peripheral halo. Of the 30 Hashimoto patients whose calcification features could be evaluated, 4 of whom cytology was found to be malignant also contained microcalcifications, whereas all kinds of calcifications could be seen in benign nodules. Malignant HT nodules were found to be more hypoechoic than other malignant nodules. Besides, ≤1 cm and≥2 cm in size, microcalcification, and containing predominantly solid components were found to be significant. Although there was no statistically significant difference between the groups in terms of autoantibody positivity, more antiTG positivity was found in malignant HT nodules.

Table 4. Demographic, ultrasonographic, and autoantibody findings of Hashimoto Group due to cytology results

	Benign HT	Malignant HT	p-value
Number (%)	367 (93.4)	26 (6.6)	
Sex F/M	331 (90.2) / 36 (9.8)	23 (88.5) / 3 (11.5)	0.776
Age ± mean	46.2 ± 12.49	44.6 ± 13.05	0.528
Anti - TPO	322 (88.0)	22 (84.6)	0.613
Anti - TG	187 (58.8)	16 (69.6)	0.310
Number of nodules			
One	66 (20.9)	4 (21.1)	
Two	46 (14.6)	3 (15.8)	0.988
Three and more	204 (64.6)	12 (63.2)	
Nodule size, cm			
<1 cm	3 (0.9)	2 (10.0)	
1-2 cm	309 (91.7)	13 (65.0)	**0.001**
>2 cm	25 (7.4)	5 (25.0)	
Echogenicity			
Hypoechoic	40 (25.6)	7 (50.0)	
Isoechoic	44 (28.2)	2 (14.3)	0.243
Hyperechoic	35 (22.4)	3 (21.4)	
Mixed echo	37 (23.7)	2 (14.3)	
Peripheral halo			
presence	76 (20.7)	1 (3.8)	**0.036**
absence	291 (79.3)	25 (96.2)	
Composition			
Solid predominant	9 (16.1)	2 (66.7)	**0.028**
Cystic predominant	47 (83.9)	1 (33.3)	

Discussion

In our study, while the rate of DTC was 6.6% in the HT group, it was found to be significantly higher at 12.9% in the control group. To our knowledge, our study was the first study in which DTC was found to be twice as low in HT patients compared to a matched control group. Also, our study showed that the risk of DTC development was not increased in nodules on HT. A similar result was also shown in the study conducted by Yue Jie et al. (11). Even the patients with DTC in the aforementioned study were diagnosed with HT via pathological examination. It should be kept in mind that the most important issue here is whether the inflammation in the pathological specimen is a peritumoral inflammatory reaction or a finding of Hashimoto's thyroiditis.

Although some studies report that malignant HT nodules are detected more frequently in females or younger patients; in this study, similar to many other studies in the literature, we did not find the difference between groups in terms of age or gender (4, 6, 9, 12).

In a multicenter study in which sonographic analysis of HT was performed, very similar to our study, the mean age was 49 and 89% were female, and their nodules were reported to be between 1-2 cm in size, but the presence of peripheral halo was not found to be significant for HT in the study (13). In the study of Anil C et al., the presence of multiple nodules with similar echogenicity in their study population and the presence of peripheral halo in the HT group support the findings of our study (8). In the study of Ohmori N et al., while nodule echogenicity was similar in both groups, it was reported that more coarse calcifications were observed in patients with malignant HT (14). Gul K et al. found that hypoechogenicity, microcalcification, and solitary nodules were more common in the HT group; whereas they reported that microcalcification and halo loss were higher in control patients (4). The common point of all these studies is that the stated US findings did not represent a statistically significant difference between the groups and it should be underlined that there was no typical and distinctive US finding for HT nodules.

The features of malignant nodules in our study, such as being significantly hypoechoic, containing microcalcification, and size are consistent with the US features of suspected malignant nodules defined in the thyroid nodules approach guidelines. Besides, the fact that malignant nodules are predominantly solid components and benign nodules contain peripheral halo is an expected finding (3). It is consistent with the literature that HT nodules reflect the characteristics of malignant or benign nodules in the general population, and that they do not show any additional distinguishing features (12).

HT-DTC coexistence was found in 17.7% of 35 cases documented by Dailey et al. for the first time (2). The link between HT and DTC has long been a topic of controversy. There are conflicting reports; some suggest that these two are positively correlated, whereas other studies report no relationship. The mean prevalence rate can change from 1.2% in FNAB studies to 36.6% in thyroidectomy studies (15).

The reason for the wide distribution of HT-DTC association rates found in the literature may be due to the design of the studies, and the ethnic or geographical characteristics of the selected patients (16). Most of the retrospective-designed surgical case series without a control group reflect high rates of HT-DTC association (4, 5, 6). Thyroidectomy indications of these patients may differ. Surgery is generally performed when thyroid nodules are suspicious of malignancy. More importantly, the presence of reactive lymphocytic thyroiditis around the tumor and primary lymphocytic thyroiditis could not be distinguished from each other in the histopathological examination. The detected thyroiditis may be only a peritumoral inflammatory response (7, 15, 17, 18, 19).

A higher rate of positive detection of antibodies against both TPO and TG in patients with benign cytology results was a predictable result since the HT group also consisted of patients with benign cytology at a high rate. Generally, statistical significance was shown between anti-TPO positivity and benign cytology in our patients. The fact that anti-TPO is a more specific antibody for autoimmune thyroiditis than anti-TG may explain our finding of anti-TPO positivity and HT together at a higher rate in the benign group. Only 4 to 6 of the approximately 40 epitopes of thyroglobulin can be recognized by B cells and besides, TG which was synthesized due to the immune response in the presence of thyroid carcinoma contains epitopes different from those produced in the background of autoimmune thyroiditis may explain the coexistence of antiTG positivity and thyroid carcinoma. At the same time, this supports us in detecting more antiTG positivity in malignant HT nodules (9, 20, 21). AntiTG positivity may be more significant than anti-TPO positivity for a suspected malignant HT nodule. According to the 1638 patient comprehensive FNAB study published by Kim E.S et al., HT-DTC association was not found significant; while no difference was reported between malignant and benign nodules in terms of the number of nodules, gender of the patients, and anti-TPO positivity, on the contrary it was shown that malignant nodules were smaller and more anti-TG positive (9).

In a postsurgery study of 140 thyroidectomized patients, the prevalence of DTC and HT coexistence was 8.6% and Mazakopakis et all did not find a statistically significant difference between DTC and HT (22).

The results of Casagna et al's did not found a relationship between autoimmune thyroiditis with nodules and thyroid cancer. They also indicate that surgical series that found a correlation between cancer and autoimmune thyroiditis consists of patients who underwent surgery due to more suspicious nodules and this condition leads to selection bias (23).

We can see that there is not enough evidence to claim that HT is a risk factor for DTC, and more tissue studies are needed to carefully distinguish peritumoral lymphocytic reaction from primary lymphocytic thyroiditis. The significantly higher rates of HT-DTC coexistence in surgical series and much lower rates in the few FNAB studies also support this idea. In our opinion thyroiditis, which is detected mostly, is an immune response to the tumor and occurs in response to tissue damage caused by the tumor, so it should be evaluated as a secondary lymphocytic reaction rather than a predisposing lesion. Therefore, there is a bias depending on whether the study performs due to FNAB or post-surgery results (15). The immune response is likely elicited towards tumor antigens in cancer patients which are shared with normal thyroid tissues thereby inducing specific thyroid autoimmunity.

The main limitation of our study is that the diagnosis of Hashimoto was not confirmed pathologically in the surgical specimen. However, we believe that our results may not have been affected by the increased false positivity of the diagnosis of HT in surgical specimens secondary to the peritumoral lymphocyte infiltration.

Conclusion

In our study, the fact that the diagnosis of HT was not based on histopathological examination but it was based on clinical findings and autoantibody positivity, and also the presence of the sex-age matched control group prevented false positive results. Thus, the frequency of DTC in patients with HT was found to be 1.95 times lower than in patients without HT. HT nodules did not show any additional features that would require us to change our approach to suspected malignant nodules. Prospective-designed studies with longer follow-up periods are needed to further elucidate this relationship.

Declarations

Funding

None

Conflicts of interest/Competing interests

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Ethics approval

Institutional Ethical Board of Cerrahpasa Medical Faculty in Istanbul, Turkey (approval ID:16386; 09/05/2011)

Availability of data and material

The data that support the findings of this study are available from the corresponding author, [SDÇ], upon reasonable request.

Authors' contributions

The authors confirm their contribution to the paper as follows: study conception and design: ÖA, ÖÇ; data collection: SDÇ; analysis and interpretation of results: SDÇ, ÖÇ; draft manuscript preparation: SDÇ. All authors reviewed the results and approved the final version of the manuscript.

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