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Total Thyroidectomy for the Treatment of Hashimoto's Thyroiditis Coexisting With Papillary Thyroid Carcinoma

Osman Kurukahvecioglu, MD
Ferit Taneri, MD
Osman Yüksel, MD
Altan Aydin, MD
Ekmel Tezel, MD, PhD
Erhan Onuk, MD
Gazi University Medical School
Department of General Surgery
Ankara, Turkey

ABSTRACT

The coexistence of Hashimoto's thyroiditis (HT) and papillary thyroid carcinoma (PTC) is controversial. This study was conducted to evaluate the correlation between HT and PTC and to identify predictive factors for the coexistence of PTC and HT. A total of 922 patients underwent surgery for thyroid disorders between January 2001 and August 2005. In all, 199 patients had been diagnosed with PTC, 37 of whom had coexistent HT; in 689 patients, benign thyroid disease had been diagnosed. Patients' age and sex, as well as histopathology, tumor size, nodal involvement status, multicentricity, presence of metastasis, and serum thyroglobulin levels, were retrospectively reviewed. A significant correlation was observed between HT and PTC, although no statistical significance was noted between PTC and HT type (nodular or diffuse). Most patients with PTC+HT were female and younger (<40 y old) than those with PTC only. The rate of occult tumor in patients with PTC+HT was higher than that in patients with PTC alone. Data indicate the coexistence of PTC and HT and suggest that PTC may develop even in cases of diffuse HT. Total thyroidectomy is the surgical procedure of choice, especially in young, female patients with HT.

Keywords: Hashimoto's thyroiditis; papillary thyroid carcinoma; total thyroidectomy; thyroglobulin

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Address correspondence to
Ferit Taneri, MD
Gazi Üniversitesi Tip Fakültesi
Genel Cerrahi Anabilim Dali
06500 Besevler, Ankara, Turkey
E-mail: ferittaneri@yahoo.com

INTRODUCTION

Hashimoto's thyroiditis (HT), an autoimmune disease that occurs in female patients of middle age, is characterized by lymphocytic infiltration, fibrosis, and parenchymal atrophy. Treatment for HT is generally medical, especially in patients who suffer from symptoms of hypo- or hyperthyroidism. Surgical therapy is indicated when glandular volume increases, causing compressive symptoms, or when suspected neoplastic degeneration of 1 or more nodules is detected.[1] The association between HT and papillary thyroid carcinoma (PTC) was first described by Dailey et al in 1955.[2] The coexistence of these 2 diseases has remained controversial since that time. In a population-based study, Crile and Hazard[3,4] reported only 1 case of PTC during follow-up of more than 1000 patient-years in 200 patients with HT; however, Holm et al[5] found an association between thyroid lymphoma and HT and reported a 69 times increased risk of lymphoma. Recent studies have identified an increased prevalence of coexistent HT in patients with PTC.[6-8] The association of HT with PTC has been reported in many studies; the prevalence of reported coexistence has ranged from 0.5% to 38%.[2,7,9-13]

Some investigators have reported that the presence of lymphocytic infiltration in papillary thyroid cancer is associated with a better prognosis, a lower recurrence rate, and less advanced disease at presentation.[6,7,14,15] Although an association among morphologic, immunohistochemical, and biomolecular features of HT and PTC has been suggested, the pathologic significance and possible clinical implications of this association are not yet fully understood.[1] Besides possible ethnic, geographic, and sex differences observed in the prevalence of both diseases, differences in patient selection for thyroidectomy and in histopathologic interpretation of HT also contribute to this variability.[6]

PATIENTS AND METHODS

A total of 922 patients underwent surgery for thyroid disorders between January 2001 and August 2005. The histopathologic diagnosis of these patients was reviewed for HT and PTC. PTC had been diagnosed in 199 patients; in 37 of these cases, HT reportedly coexisted with PTC. Benign thyroid disease (BTD), including nodular goiter, diffuse goiter, hyperthyroidism, and HT, was diagnosed in 689 patients. In 34 cases, follicular, medullary, or anaplastic carcinoma was diagnosed. The purpose of this study was to evaluate the correlation between HT and PTC. Toward this goal, investigators performed a retrospective analysis of patients in whom PTC, with or without HT or BTD, had been diagnosed. In all cases, a routine preoperative diagnostic workup, including thyroid hormone assay, ultrasound examination of the thyroid, and thyroid scintigraphy, had been performed. The clinical diagnosis of HT was based on increased serum antithyroglobulin and antiperoxidase levels. Fine needle aspiration (FNA) was performed in all cases characterized by clinically suspicious nodules.

Total thyroidectomy was performed in all cases, except those with unilateral nodular goiters with benign frozen examination results. The histopathologic diagnosis of HT was based on the presence of diffuse mononuclear cell infiltration with fibrosis, occasional well-developed germinal centers, and enlarged follicular cells

with abundant eosinophilic, granular cytoplasms. Peritumoral inflammatory response was not considered to indicate HT.

Patients' age and sex, along with histopathology, tumor size, nodal involvement status, multicentricity, presence of distant metastasis, and serum thyroglobulin levels, were reviewed retrospectively in the hospital records.

Statistical Analysis

Prognostic and demographic parameters were evaluated with the Mann-Whitney *U* test or the χ^2 test. Prognostic parameters were assessed through a test of multivariate logistic regression. All statistical analyses were performed with the Statview (SAS Inc., Cary, NC) dataset program.

RESULTS

In the 199 patients (159 women and 40 men) in whom PTC was diagnosed, the mean age was 46.6±13.5 y (range, 19–95 y); 562 women and 127 men with a mean age of 47.1±12.3 y (range, 20–85 y) were diagnosed with BTD. The differences between these 2 groups in terms of age and sex distribution were statistically insignificant (for each parameter, $P>.05$).

Of 199 patients in whom PTC was diagnosed, 37 (18.5%) had coexistent HT, and of 689 patients with BTD, 64 also had HT (9.2%). The difference between these rates was statistically significant ($P=.006$). The association between HT and PTC, therefore, was significantly greater with a diagnosis of PTC than with a diagnosis of BTD.

In 101 patients with HT, the presence of a dominant mass with incomplete regression on suppressive therapy (n=76), the progression of thyromegaly despite suppressive therapy (n=23), and the appearance of compressive symptoms (n=2) were indications for surgical intervention. Among this group of patients, 76 had nodular HT and 25 had diffuse HT. Of the 76 patients with nodular HT, PTC was diagnosed in 30, whereas 7 of 25 patients with diffuse HT had coexistent PTC. The difference between these 2 groups was not statistically significant ($P=.3468$). The data suggest that PTC may develop even in cases of diffuse HT.

When patients with PTC were examined for the presence of coexistent HT, it was found that 35% of patients were younger than 40 y in the PTC+HT group, whereas 9% of those with PTC alone were younger than 40 ($P=.015$). There was only 1 male patient (2.7%) in the PTC+HT group, but there were 39 males (22.2%) in the PTC group ($P=.002$). When the groups were compared in terms of tumor size, about half of patients in the PTC+HT group had occult PTC (tumor size <1 cm), and the difference between the 2 groups was statistically significant ($P=.019$). No difference was reported in terms of multicentricity, nodal involvement, or distant metastasis. It is interesting to note that 10.8% of patients with PTC+HT and 22.8% of those with PTC alone had follicular variant PTC, but this histopathologic parameter did not reach statistical significance. Preoperative serum thyroglobulin levels were higher in the PTC group than in the PTC+HT group (40.7±13.4 µg/L and 163±27.9 µg/L, respectively) ($P=.003$). Demographic and prognostic parameters for both groups are shown in the Table.

Most of those with PTC coexistent with HT were younger, female patients with a tumor generally smaller than 1 cm and lower serum thyroglobulin levels. Multivariate logistic regression testing revealed that the most important characteristics for

PTC+HT are young age (<40) and small tumor size (<1 cm) (P=.02, P=.007, respectively).

Clinicopathologic Features of Study Patients

Characteristics	Group I (PTC+HT) (n=37)	Group II (PTC) (n=162)	*P* Value
Age <40 y*	35 (13/24)	9 (15/147)	.015
Sex, M*	2.7 (1/36)	22.2 (39/123)	.002
Tumor size*			
<1 cm	51.4 (19)	48.6 (18)	.019
≥1 cm	29.6 (48)	70.4 (114)	.019
Nodal involvement*	10.8 (4/33)	7.4 (12/150)	NS
Distant metastasis*	0	0	NS
Multicentricity*	13.5 (5/32)	11.1 (18/144)	NS
Follicular variant*	10.8 (4/33)	22.8 (37/125)	NS
Thyroglobulin level, μg/L†	40.7±13.4	163±27.9	.003
(range)	(0.2–204)	(0.1–1500)	.003

*Values are expressed as percentage (n).
†Values are expressed as means±standard deviation.
NS=nonsignificant.

DISCUSSION

PTC, the most common thyroid cancer, is associated with a relatively good prognosis.[16] Patient age at the time of diagnosis, stage of PTC, tumor size, the presence of cervical node or distant metastasis, extrathyroidal tumor extension, and extent of thyroidectomy have been previously shown to influence patient outcome.[16] An association between HT and differentiated thyroid carcinoma has been reported by several authors since the 1950s, along with variable incidence rates, probably due not only to the different genetic and environmental factors involved, but above all to the various anatomopathologic definitions of HT that are used in clinical studies.[1] Meta-analysis showed that the incidence rate of HT is 2.77 times higher in patients with PTC than in patients affected by BTD.[8] Furthermore, in patients with thyroid carcinoma, the incidence rate of association with HT is 1.99 times higher in those with PTC than in patients with other histopathologic forms of thyroid carcinoma.[1]

Although the association between HT and differentiated thyroid carcinoma has been the topic of many reports, this association and the pathogenesis of HT and PTC remain unclear; it is unknown whether these thyroid disorders share a common origin, and

whether the presence of HT affects the biologic behavior of PTC.[15] The association of HT with PTC has been reported in many studies; the prevalence of coexistence has ranged from 0.5% to 38%.[2,7,9-13] In the present study, it was found that HT and PTC coexist at a rate of 4%. Association with HT was reported in 37 (18.5%) of 199 patients with PTC and in 64 (9.2%) of 689 patients with BTD; this finding confirmed that there is a significantly higher association with HT in patients with PTC than in those with BTD ($P<.05$).

According to the literature, patient demographic characteristics and prognostic variables at presentation are not influenced by the presence of HT.[8] Several studies have reported female predominance among patients with HT-associated thyroid cancer, reflective of the overall population with HT.[8] In the current study, patients with PTC+HT were younger than age 40, and most were female.

Several studies regarding the effects of certain factors such as race and sex on the presence of lymphocytic infiltrates in PTC, which is indicative of autoimmune thyroiditis, have shown that this is significantly more prevalent among Japanese patients of both sexes and among white and black American women with PTC than in the same populations affected by multinodular goiter and follicular adenoma.[17] Okayasu et al[17] showed that patients from different ethnic backgrounds and various geographic regions may have higher rates of coexistent PTC and HT in endemic regions (~19%). With regard to their clinical course, thyroid tumors associated with HT do not seem to be more aggressive than nonassociated forms. In previous studies, none of the patients in whom PTC and HT were diagnosed experienced metastasis.[18] In the present study, differences in parameters such as lymph node involvement and the presence of distant metastasis indicate that the aggressiveness of PTC was not statistically significant.

HT, an autoimmune disease that commonly results from thyromegaly, may coexist with benign or malignant thyroid disease. The thyroid gland in HT is usually diffusely enlarged and, less commonly, is asymmetric or nodular.[19,20] In HT, surgery is indicated to identify coexistent neoplasia in cases in which (1) the presence of a dominant mass with incomplete regression on suppressive therapy suggests cancer or lymphoma, (2) thyromegaly progresses despite suppressive therapy, (3) historic or physical findings (eg, irradiation, multiple endocrine neoplasia syndrome, nerve paralysis, pain, tracheal compression, stipple calcification, cervical lymph node enlargement) suggest malignancy, and (4) findings on needle biopsy are indeterminate (eg, lymphoma vs thyroiditis).[21]

It has been reported that PTC is more likely to occur with the nodular type of HT than with the diffuse type.[1] Results reported here do not support this observation. Investigators in the present study found no difference between nodular and diffuse types of HT in terms of incidence of PTC. Because an increased incidence of thyroid carcinoma among patients with the nodular form of HT has been reported in the literature, HT might well be considered a precursor of the disease.[22,23] There are no data in the literature, however, prior to those of the current study, that suggest that occult tumors are observed more frequently in patients with PTC+HT.[15] Rates of occult carcinoma in PTC+HT and PTC were reported as 51.4% and 29.6%, respectively. In the PTC+HT group, 13.5% had multicentric tumor, as did 11.1% in the PTC group. Occult carcinoma and multicentricity rates of PTC+HT were higher than those of PTC alone, and statistical analysis yielded *P* values of .003 and .7, respectively. Nevertheless, it has been reported that cases in which PTC coexists with HT

are much more frequently multicentric (93%) compared with cases of the nonassociated form of PTC (50%).[24] These results suggest that surgical treatment should always consist of total thyroidectomy, even in patients with diffuse type HT because the data show no clear correlation between nodular-type HT and PTC.

It is anticipated that preoperative thyroglobulin levels may be higher in patients with PTC. In the present study, the serum thyroglobulin level was higher in PTC, as was expected. This finding may alert surgeons to the possible presence of PTC. Serum thyroglobulin is an established tumor marker that is used in the treatment of patients with a diagnosis of differentiated thyroid carcinoma.[25,26]

PTC and HT share several morphologic and immunohistochemical features. It is difficult for investigators to define which features indicate PTC during follow-up for HT. In a young (<40 y), female patient with HT with small nodules (<1 cm), the possibility of carcinoma should not be overlooked. Preoperative screening and other diagnostic methods such as FNA biopsy may not yield information about these nodules. When surgical treatment is indicated in such patients, total thyroidectomy should be chosen because most occult carcinomas cannot be detected preoperatively, and these nondetectable small tumors may remain after the surgical procedure has been completed, unless total thyroidectomy is performed.

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