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Research paper

Coexistence of Hashimoto's thyroiditis with papillary thyroid carcinoma. A retrospective study

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ABSTRACT

OBJECTIVE: The association between Hashimoto's thyroiditis (HT) and papillary thyroid carcinoma (PTC) remains controversial in medical bibliography. The main objective of our study was to determine the prevalence of PTC and HT coexistence in histopathologic material of thyroidectomized patients. DESIGN: In a retrospective study, the clinicohistopathologic data of 140 patients (19 males/121 females), who underwent a total or near total thyroidectomy for any thyroid pathology from January 2005 to December 2009 at the Naval Hospital of Crete, were analysed. The mean age of the patients was 52 years (range 16-74). RESULTS: HT was detected in 42 (30%) and PTC in 32 (22.9%) specimens. Coexistence of HT with PTC was present in 12 (8.6%) specimens. Among 32 specimens with PTC, the prevalence of HT was 37.5%. Among 42 specimens with HT, the prevalence of PTC was 28.6%. There was no statistically significant difference between the presence of PTC and HT in histopathologic material. CONCLUSIONS: The prevalence of PTC and HT coexistence in histopathologic material of 140 thyroidectomized patients was 8.6%, whereas the difference between PTC and HT was not statistically significant.

Key words: Cancer, Hashimoto's thyroiditis, Papillary thyroid carcinoma, Thyroid

INTRODUCTION

Hashimoto's thyroiditis (HT), also called chronic lymphocytic or autoimmune thyroiditis, is part of the spectrum of autoimmune thyroid diseases (AITD) and is associated with various degrees of thyroid hypofunction and circulating antibodies to thyroid antigens.[1,2] By strict criteria, it is a histologic diagnosis that was first described by Hakaru Hashimoto, a Japanese surgeon working in Berlin, Germany.[3] The cause of HT is thought to be a combination of genetic susceptibility and environmental factors.[4] The incidence of HT is estimated to be 10-15 times higher in

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females; its annual incidence worldwide is estimated to be 0.3-1.5 cases per 1000 individuals.[5] In clinical practice, patients (especially women) with HT and a firm, solitary, "cold" thyroid nodule on radionuclide scanning should have an ultrasound-guided fine needle aspiration biopsy (FNAB) because of the potentially increased risk of a concurrent thyroid cancer (TC).[1] Although the link between chronic inflammation and cancer is well established, the association between HT and papillary thyroid carcinoma (PTC) has been controversial in medical bibliography since its initial description by Dailey et al in 1955.[6-21] The aim of our study was to determine the prevalence of PTC and HT coexistence in histopathologic material of thyroidectomized patients.

PATIENTS AND METHODS

In a retrospective study, we analyzed clinico-histopathologic data of 140 patients (19 males/121 females), mean age 52 (range 16-74) years, who underwent a total or near total thyroidectomy for any thyroid pathology from January 2005 to December 2009 at the Naval Hospital of Crete, Chania, Greece. All patients were from the region of Chania. The diagnosis of TC was confirmed either by the re-evaluation of histopathology sections, when available, or from reviews of the pathology reports. TC classification was based on the TNM classification system.[22] Coexistent HT was defined as the presence of diffuse lymphocytic and plasma cell infiltrate, oxyphilic cells and the formation of lymphoid follicles and reactive germinal centres; the infiltrate had to occur in a normal region of the thyroid gland, distinct from the site of the TC. Peritumoural inflammatory response was not designated as HT. Tumour recurrence was defined as new evidence of TC (locoregional or distant metastasis) after successful tumour resection in which postoperative serum thyroglobulin levels were normal for at least six months or the postoperative radioiodine scan was negative (or both). Persistent TC was defined as an elevated postoperative serum thyroglobulin or persistent uptake on the postoperative radioiodine scan after thyroidectomy and radioiodine ablation treatment. The potential association of PTC with HT in histopathologic material was assessed by the use of the χ^2-test. Time-independent variables were evaluated using Student's *t*-test. The differences were considered statistically significant at $p<0.05$.

RESULTS

The reasons for thyroidectomy and the prevalence of histopathologic diagnoses among the 140 thyroidectomized patients are presented in Tables 1 and 2. 32 of the 33 thyroidectomized patients with TC had PTC. The stage of PTC (TNM system) at the time of diagnosis was I (4 patients with T1aN0M0 and 28 patients with T1bN0M0; T1a: tumour diameter 1cm or less, T1b: tumour diameter of more than 1cm but not more than 2cm, N0: no regional lymph node matastasis, M0: no distant metastasis). The association of PTC with HT in histopathologic material in

Table 1. Reasons for total or near total thyroidectomy.

Reasons for thyroidectomy	Number of patients (%) (N=140)
Bilateral symptomatic nodular non-toxic goiter	57 (40.7)
Graves' disease	2 (1.4)
Large goiter with or without obstructive symptoms	26 (18.6)
Equivocal or positive FNAB for malignant process of a nodule or mass within the thyroid gland	55 (39.3)

FNAB: Fine Needle Aspiration Biopsy

Table 2. Histopathologic diagnosis among 140 thyroidectomized patients.

Histopathologic diagnosis	Number of patients (%) – Gender: female/male
PTC	20 (14.3) – 16/4
HT	30 (21.4) – 26/4
PTC & HT	12 (8.6) – 9/3
Other	78 (55.7) – 70/8
Nodular goiter	57 (40.7) – 55/2
Graves' disease	02 (1.4) – 2/0
Hyperplastic nodules	14 (10.0) – 10/4
Adenoma	04 (2.9) – 3/1
MTC	01 (0.7) – 0/1
Total	140

HT: Hashimoto's Thyroiditis, PTC: Papillary Thyroid Carcinoma, MTC: Medullary Thyroid Cancer

our patients is presented in Table 3. HT was found in 42 (30%) of the 140 specimens (7 males, 16.7% and 35 females, 83.3%). PTC was found in 32 (22.9%) of the 140 specimens, (7 males, 21.9% and 25 females, 78.1%). Coexistence of HT and PTC was detected in 12 (8.6%) of the 140 specimens, (3 males, 25% and 9 females, 75%). Among 32 specimens with PTC, the prevalence of HT was 37.5%, which is higher than the prevalence of HT in other specimens without PTC (27.7%). Among 42 specimens with HT, the prevalence of PTC was 28.6%, which is higher than the prevalence of PTC in other specimens without HT (20.4%). However, there was no statistically significant difference (χ^2=1.11, df=1, p=0.29) between the presence of PTC in specimens with HT and the presence of PTC in other HT negative specimens (Table 3). The majority of thyroidectomized patients with HT or PTC were females (35 females versus 7 males and 25 females versus 7 males, respectively); there was no statistically significant gender difference (χ^2=0.49, df=1, p=0.48) or PTC (χ^2=2.43, df=1, p=0.12).

The available clinicopathologic features of the 32 PTC patients with and without HT are summarized in Table 4. The majority of PTC patients were females (25 female versus 7 male); there was no statistically significant gender difference between PTC patients with and without HT (χ^2=0.11, df=1, p=0.74). In addition, there was no significant difference in age (t=1.36, df=30, p=0.18) or tumour size (χ^2=0.305, df=1, p=0.58) at the time of diagnosis between PTC patients with and without HT. The number of PTC patients with tumour size ≤10mm was the same among the two groups (HT present and HT absent). Follow-up data revealed no persistent or recurrent PTC. No deaths were observed among patients with PTC from the time of diagnosis to the last follow-up examination (mean±SD is 3.7±1.6 years).

Table 3. Association between PTC and HT among 140 thyroidectomized patients.

Histopathologic diagnosis	HT present	HT absent	Total
PTC present	12	20	32
PTC absent	30	78	108
Total	42	98	140

χ^2-test: p >0.05, HT: Hashimoto's Thyroiditis, PTC: Papillary Thyroid Carcinoma

Table 4. Clinicopathologic characteristics of 32 PTC patients with and without HT.

Characteristics	HT present (N=12)	HT absent (N=20)
Age (years) mean ± SD at diagnosis	49.25 ± 10.21	54.70 ± 11.42
Gender (female/male)	9/3	16/4
Stage (TNM) Stage I	2 T1aN0M0 10 T1bN0M0)	2 T1aN0M0 18 T1bN0M0)
Tumour size (cm)		
≤1	2	2
>1 but ≤2	10	18
Family history of TC	0	0
Persistent or recurrent PTC	0	0
Deaths	0	0

HT: Hashimoto's Thyroiditis, TC: Thyroid Cancer, PTC: Papillary Thyroid Carcinoma, T1a: tumour diameter 1cm or less, T1b: tumour diameter more than 1cm but not more than 2cm, N0: no regional lymph node matastasis, M0: no distant metastasis. For statistical evaluation see text

DISCUSSION

Our findings showed a low rate (8.6%) of PTC and HT coexistence and no statistically significant relationship between the presence of HT and the presence of PTC in histopathologic material of 140 thyroidectomized patients. Several retrospective studies have revealed a strong correlation between these two diseases, whereas other clinical and cytological studies have failed to show any significant increase in the incidence of PTC or TC in cohorts of patients with HT, as was also shown in our study.[6-21] Pertinent data from various studies are presented in Table 5. In a study by Larson et al, patients with HT were three times more likely to have differentiated thyroid cancer (DTC) than patients without HT, suggesting a strong link between HT and DTC.[19] The link was supported by the immunohistochemical evidence of increased phosphorylated Akt, Akt1, and Akt2 expression in regions of HT and thyroid cancer compared with regions of normal surrounding thyroid tissue.[19] Wirtschafter et al identified the presence of RET/PTC genetic aberrations in 15 patients with HT, in the absence of any clinically detectable thyroid cancer.[23]

Table 5. Coexistence of HT with PTC or TC. Brief literature review.

Authors (reference)	Patients studied	HT patients with PTC n (%)
Dailey et al, 1955 (6)	278 with TC	35 (12.6)
Crile and Hazard, 1962 (7)	200 with HT	1 (0.5)
Ott et al, 1985 (8)	146 with HT and solitary cold nodules	47 (32)
Ott et al, 1987 (9)	161 with TC	61 (38)
Eisenberg et al, 1989 (10)	120 with TC	13 (10.8)
Sclafani et al, 1993 (11)	48 with HT	8 (17)
Schaffler et al, 1998 (12)	153 with TC	10 (6.5)
Loh et al, 1999 (13)	631 with DTC	128 (20.3)
Singh et al, 1999 (14)	388 with PTC	57 (15)
Kebebew et al, 2001 (15)	136 with PTC	41 (30)
Cipolla et al, 2005 (16)	71 with PTC	19 (26.7)
Labidi et al, 2006 (17)	78 with HT	11 (14.1)
Costanzo et al, 2006 (18)	282 thyroidectomized (46 DTC, 28 HT)	11 (3.9)
Larson et al, 2007 (19)	98 resected thyroid specimens with HT	43 (43.8)
Repplinger et al, 2008 (20)	1198 thyroidectomized (217 HT, 293 PTC)	63 (5.3)
Matesa-Anic et al, 2009 (21)	10508 undergoing FNAC	42 (0.4)
Mazokopakis et al, 2010	140 thyroidectomized (32 PTC, 42 HT)	12 (8.5)

HT: Hashimoto's Thyroiditis, TC: Thyroid Carcinoma, PTC: Papillary Thyroid Carcinoma, DTC: Differentiated Thyroid Carcinoma, FNAC: Fine Needle Aspiration Cytology

In a Sicilian series of 282 patients thyroidectomized for any pathology, the rate of histologically detected HT in patients with DTC was 24%; the presence of DTC in patients with histologically detected HT was 39%.[18] The outcome and prognosis of PTC appears to be improved with the presence of coexistent HT;[13-15] McConahey et al found mortality from thyroid cancer to be strongly associated with the absence of HT.[24] In 373 patients with struma lymphomatosa diagnosed by FNA cytology (FNAC) not a single instance of TC was found.[25] Matesa-Anic et al did not find any statistically significant relationship between HT and PTC in FNA cytologic material collected from 10,508 patients; coexistence of HT and PTC was recorded in 42 (0.4%) of all patients undergoing FNAC.[21]

The observed variability in the prevalence of the coexistence of HT and PTC in published studies could be explained by ethnic, geographic, and gender differences in the prevalence of either disorder, as well as differences in patient selection (gender, age, and history of thyroid disorders). Moreover, the variability could be attributed to the indications for thyroidectomy, differences in the pathologic definitions and histopathologic interpretation of HT, such as the level of histological examination.[13,15] This variability does not allow firm conclusions as to the relationship between HT and TC.

As expected, the majority of thyroidectomized patients, such as HT patients, were women. It is known that women express thyroid autoimmunity more frequently than men and this tendency is even more obvious in the postmenopausal period.[1] However, our study did not reveal a statistically significant difference in age or gender between PTC patients with and without HT, in contrast to other studies.[15] The lack of gender difference could be attributed to the small number of males in our cohort.

HT was a common histopathologic finding in our material (30%), indicating a high frequency of this disease in Crete. In a previous Greek study from Athens University among 264 thyroidectomized patients, the histopathologic diagnosis of HT was 3.8%.[26]

One of the most common reasons for thyroidectomy in our patients was the equivocal or positive FNAB results for malignant process of a nodule or mass within the thyroid gland. FNAB is useful for diagnosing PTC in patients with HT-associated thyroid lesions, with a sensitivity of more than 90%.[14] Moreover, the American Thyroid Association (ATA) recommends FNAB as the procedure of choice for evaluating thyroid nodules and selecting candidates for surgery.[27] FNA biopsy has resulted in improved diagnostic accuracy, a higher malignancy yield at the time of surgery, and significant cost reductions.[28,29]

Our study was a retrospective study that included patients who underwent a total or near total thyroidectomy and therefore a) was limited by the availability and content of the medical records and b) was subject to potential selection bias. Further longitudinal prospective studies of patients with HT are required to determine the potential association between these disorders, if any, and the pathogenetic mechanism involved. Until we have more solid data of such association, HT patients should periodically undergo careful clinical and laboratory examination.

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