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Effects of Chronic Lymphocytic Thyroiditis on the Clinicopathological Features of Papillary Thyroid Cancer

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Keywords
Papillary thyroid cancer · Chronic lymphocytic thyroiditis · Disease persistence

Abstract
Background: The effects of chronic lymphocytic thyroiditis (CLT) on the presentation and outcome of papillary thyroid carcinoma (PTC) have long been a topic of controversy. ***Objective:*** To evaluate the effect of coexistent CLT on the clinicopathological features of PTC. ***Design:*** Retrospective study. ***Patients:*** All patients with PTC who had been followed by the 2 co-investigators (Juan Rivera and Richard J. Payne) between 2006 and 2011 were included. ***Results:*** CLT was present in 35% (166) of the included patients and was associated with a higher proportion of patients with TNM stage I ($p = 0.027$) and fewer patients with persistent disease ($p = 0.014$) in comparison with the PTC-only group. Analysis of the data based on age (<45 or >45 years) revealed that in the older group, the presence of CLT was associated with fewer patients with persistent disease ($p = 0.03$) and capsular invasion ($p = 0.05$). However, in patients <45 years of age, the presence of CLT was associated with more capsular invasion ($p = 0.003$) and extrathyroidal extension ($p = 0.004$) compared with the PTC-only group. ***Conclusions:*** CLT in patients with PTC was associated with lower-stage disease and less disease persistence in patients >45 years of age. In patients <45 years, the presence of CLT appeared to be associated with unfavorable pathological features.

Introduction

Papillary thyroid cancer (PTC) is the most common form of thyroid cancer, comprising approximately 80% of all thyroid cancers [1, 2]. Chronic lymphocytic thyroiditis (CLT) is an autoimmune disease characterized by widespread lymphocytic infiltration, fibrosis, and late-stage parenchymal atrophy of thyroid tissue. It is the most common inflammatory disorder of the thyroid gland [3].

The association between CLT and PTC was first described by Daily et al. in 1955 [4]. Since then, the association between both diseases has remained controversial, and the percentage of PTC patients with CLT has been reported to range from 0.5 to 38% [4–6]. The pathogenic mechanism explaining why PTC and CLT develop concurrently remains controversial, although a number of

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theories have been suggested. One suggestion is that CLT may represent the host's immune response to preexisting PTC. Conversely, PTC may be induced or triggered by preexisting CLT. Alternatively, both diseases may result from an imbalance between apoptotic and antiapoptotic pathways [7].

Several previous reports have shown that the coexistence of CLT with PTC is associated with a better prognosis, a lower recurrence rate, and a less aggressive clinical presentation [5, 8–11]. However, other investigators have reported that the coexistence of CLT has no protective effect on patient outcome [12, 13].

The aim of this study was to determine differences in clinicopathological variables related to the prognosis of PTC patients with or without concomitant CLT.

Patients and Methods

This study was a retrospective analysis of PTC patients seen in McGill University-based hospitals in the city of Montreal (QC, Canada).

In September 2011, we reviewed the thyroid cancer database of 2 co-investigators (Juan Rivera and Richard J. Payne). Patients who were included in the analysis were recruited between 2006 and 2011. Only patients with PTC were included, whereas all other types of thyroid cancer were excluded. PTC patients with autoimmune diseases other than CLT and patients with a history of radiation exposure were also excluded.

Following ethics committee approval, the medical records of the patients were reviewed, and clinicopathological parameters, including age, gender, tumor size, multifocality, vascular invasion, capsular invasion (CI), extrathyroidal extension (ETE), and lymph node (LN) and distant metastases, were analyzed according to the presence or absence of CLT.

Initial Treatment of the Patients

Total thyroidectomy was performed in all patients with malignancy or suspicious for malignancy confirmed by preoperative fine-needle aspiration biopsy. Patients in whom the initial surgical procedure was lobectomy underwent completion thyroidectomy after histopathological confirmation of PTC. Ipsilateral central LN dissection was performed in all patients. If the patient had evidence of lateral LN metastases in the preoperative evaluation, modified lateral neck dissection was performed. Radioactive iodine (RAI) was given within 6–12 weeks after surgery. Indication for RAI ablation was based on 2006 and 2009 American thyroid association guidelines [14, 15]. A post-ablation scan was taken 5–7 days following RAI therapy. All patients received suppressive treatment with levothyroxine. Patient follow-up was based on physical examination, neck ultrasound (US), and serum thyroglobulin and thyroglobulin antibody (TgAb) measurements at intervals 6–12 months and iodine whole-body scan 9–12 months after RAI treatment.

Definitions

CLT was defined histologically as diffuse lymphoplasmacytic and plasma cell infiltration, lymphoid follicle formation with germinal centers, varying degree of fibrosis, parenchymal atrophy, and the presence of large follicular cells with abundant oxyphilic cell changes [5].

Disease persistence was defined as persistently elevated thyroglobulin or a positive neck US or whole-body scan 6–12 months after RAI ablation. In patients with positive TgAb, disease persistence was defined as a positive finding in neck US or iodine whole-body scan 6–12 months after ablation or failure of TgAb to decline >50% versus the baseline value [16].

Recurrence was defined as the reappearance of disease after complete ablation of thyroid remnants either biochemically by elevated thyroglobulin or TgAb or structurally by a positive finding in neck US or whole-body scan.

Laboratory Studies

Thyroglobulin level was measured by the chemiluminescence assay (Immulite 2000, Siemens Corp). The functional sensitivity for the thyroglobulin assay was 0.9 μg/L, and the analytical sensitivity was 0.2 μg/L. TgAb levels were also determined by a chemiluminescent assay (Immulite 2000 Anti-Tg Ab; Siemens) and considered negative when <20 IU/mL.

Statistical Analysis

Associations between variables were analyzed using contingency tables and the χ^2 test. Accordingly, the Wilcoxon rank sum test was used to compare continuous variables, such as age and tumor size, between subgroups. The relative importance of prognostic factors was presented as odds ratios and 95% confidence intervals. The difference between 2 values was considered significant when $p < 0.05$. All tests were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Among the 475 patients, 166 (35%) had coexistent CLT. The mean age of patients with and without CLT was 48 ± 13.8 and 49.3 ± 13.9 years, respectively. Female gender was more prevalent in the CLT group (88%) ($p = 0.06$). The mean tumor size was 1.96 ± 1.53 cm in patients with CLT and 2.06 ± 1.62 cm in patients without CLT. TgAb were present in 18.7% of patients with PTC only and in 42.2% of patients with PTC and CLT. The mean follow-up with and without CLT was 24.6 months (range 6–80) and 25.5 months (range 6–81), respectively (Table 1).

Effect of CLT on the Whole Group

There was a significantly higher proportion of patients in the CLT group who presented with TNM stage I ($p = 0.027$) and a lower proportion of patients with CLT who presented with disease persistence ($p = 0.014$). There was a trend towards more multifocal tumors in patients with CLT than patients without CLT (49.4 vs. 41.1%, respectively; $p = 0.08$), and a trend towards larger tumor size in

Table 1. Clinicopathological parameters of 475 patients with papillary thyroid carcinoma (PTC) stratified by the presence of chronic lymphocytic thyroiditis (CLT)

Variables	PTC only (%)	PTC with CLT (%)	Odds ratio (95% CI)	*p* value
Total *n*	309 (65)	166 (35)		
Sex				
Female	258 (81.2)	146 (88)	1.67 (0.98–2.9)	0.061
Male	58 (18.8)	20 (12)		
Age				
Mean (SD), years	49.3±13.87	48±13.78		
Patients <45 years	128 (41.4)	78 (47)		0.24
Patients >45 years	181 (58.6)	88 (53)		
Thyroglobulin antibody	58 (18.7)	70 (42.2)	3.51 (2.3–5.8)	<0.0001
Mean tumor size (SD), cm	2.06 (1.62)	1.96 (1.53)		0.08
Vascular invasion	35 (11.3)	20 (12)	1.07 (0.6–1.9)	0.83
Capsular invasion	85 (27.5)	39 (23.5)	0.81 (0.5–1.3)	0.34
Extrathyroidal extension	64 (20.7)	39 (23.5)	1.17 (0.74–1.8)	0.49
LN metastasis	75 (24.3)	46 (27.7)	1.19 (0.78–1.8)	0.41
Lateral LN	25 (8.1)	19 (11.4)	1.47 (0.8–2.8)	0.23
Multifocality	127 (41.1)	82 (49.4)	1.4 (0.96–2.0)	0.08
Bilaterality	119 (38.5)	67 (40.1)	1.1 (0.72–1.5)	0.73
Distant metastasis	6 (1.94)	1 (0.6)	0.31 (0.04–2.6)	0.27
Aggressive histology	10 (3.2)	8 (4.8)	1.5 (0.6–3.9)	0.39
Stage				
I	192 (62.2)	120 (71.9)	1.34 (1.02–1.8)	0.027
II	47 (15.2)	16 (9.6)	0.59 (0.33–1.08)	0.09
III	51 (16.5)	24 (14.4)	0.85 (0.5–1.4)	0.5
IV	19 (6.1)	6 (3.6)	0.57 (0.2–1.5)	0.24
Persistent disease	24 (7.8)	3 (1.8)	0.22 (0.06–0.73)	0.014
Recurrent disease	1 (0.3)	3 (1.8)	5.67 (0.58–54.9)	0.13
Mean follow-up (SD), months	25.5 (19.5)	24.6 (16.3)		0.08

Numbers of patients are shown except where indicated otherwise. LN, lymph node metastasis. Aggressive histological subtypes include insular, diffuse sclerosing, solid, and tall cell variants.

patients with PTC only (*p* 0.08), but this trend did not reach statistical significance. There was no difference between the 2 groups regarding the prevalence of vascular invasion or CI, ETE, LN, or distant metastasis, and aggressive histological subtypes (Table 1), and in the MACIS score (Table 2).

Changes in the Thyroglobulin Level during Follow-Up

Among patients with persistent disease, TgAb tests were positive in 5 patients in the PTC-only group (20.3%) and in 3 patients (100%) in the PTC-CLT group. In 3 of those patients, TgAb level failed to decline and in 5 patients TgAb level increased during follow up; in all of those 8 patients, disease persistence was confirmed by a positive finding in neck US or iodine whole-body scan.

Among patients with disease recurrence, the patient with recurrence in the PTC-only group had negative TgAb. In the PTC-CLT group, 1 of the 3 patients with recurrence had positive TgAb. This patient was operated in 2007, and initial evaluation showed declining TgAb level as well as negative neck US and iodine whole-body scan; however, 3 years later, TgAb started to rise. Structural recurrence was confirmed by neck US (PTC metastasis to lateral cervical LN confirmed by fine needle aspiration biopsy), which was confirmed histologically after LN dissection.

In the remainder of the patients with positive TgAb (53 patients in the PTC-only group and 66 patients in PTC-CLT group), TgAb level decreased during follow-up and disappeared in patients followed up for >3 years (35%).

Table 2. MACIS score in patients with papillary thyroid cancer (PTC) and chronic lymphocytic thyroiditis (CLT) and in patients with PTC only

MACIS score	PTC only (%)	PTC and CLT (%)	Odds ratio (95% CI)	*p* value
Mean (SD)	5.0 (1.28)	4.9 (1.12)		0.69
<6	254 (82.2)	137 (82.5)	1.02 (0.62–1.68)	0.93
6–6.99	32 (10.4)	23 (13.9)	1.39 (0.79–2.47)	0.26
7–7.99	13 (4.2)	4 (2.4)	0.56 (0.18–1.75)	0.32
>8.0	10 (3.2)	2 (2.5)	0.36 (0.09–1.68)	0.19
<7	286 (92.6)	160 (96.4)	2.14 (0.86–5.4)	0.10
>7	23 (7.4)	6 (3.6)		

Table 3. Clinicopathological parameters of 269 patients with papillary thyroid cancer (PTC) >45 years of age, stratified by the presence of chronic lymphocytic thyroiditis (CLT)

Variables	PTC only (%)	PTC with CLT (%)	Odds ratio (95% CI)	*p* value
Total *n*	181 (67.3)	88 (32.7)		
Sex				
Female	114 (77.9)	79 (89.7)		
Male	40 (22.1)	9 (10.2)		
TgAb	35 (19.3)	38 (43.2)	3.1 (1.8–5.6)	0.0001
Vascular invasion	21 (11.6)	7 (7.95)	0.65 (0.27–1.6)	0.36
Capsular invasion	60 (33.2)	19 (21.6)	0.55 (0.31–1.01)	0.05
Extrathyroidal extension	44 (24.3)	16 (18.2)	0.69 (0.37–1.3)	0.26
LN metastasis	40 (22.1)	16 (18.2)	0.78 (0.4–1.5)	0.46
Lateral LN	13 (7.2)	4 (4.6)	0.64 (0.2–2)	0.41
Multifocality	82 (45.3)	39 (40.9)	0.84 (0.5–1.4)	0.5
Bilaterality	71 (39.2)	34 (39.0)	0.98 (0.6–1.6)	0.93
Distant metastasis	1 (0.55)	0	0.68 (0.03–16.9)	0.81
Aggressive histology	4 (2.2)	3 (3.4)	1.56 (0.34–7.1)	0.57
Stage				
I	71 (39.2)	42 (47.7)	1.4 (0.84–2.4)	0.19
II	40 (22.1)	16 (18.2)	0.59 (0.31–1.1)	0.95
III	51 (28.2)	24 (27.1)	0.95 (0.5–1.7)	0.87
IV	19 (10.5)	6 (6.8)	0.62 (0.2–1.6)	0.33
MACIS				
<6	131 (72.4)	61 (69.3)	0.86 (0.5–1.5)	0.6
6–6.99	31 (17.1)	22 (25)	1.6 (0.87–3.0)	0.13
7–7.99	12 (6.7)	3 (3.4)	0.49 (0.14–1.8)	0.28
>8	7 (3.9)	2 (2.3)	0.58 (0.16–2.8)	0.5
Persistent disease	15 (8.3)	0	0.04 (0.003–0.7)	0.03
Recurrent disease	1 (0.55)	2 (2.3)	4.2 (0.37–46.8)	0.24

LN, lymph node; TgAb, thyroglobulin antibody. Aggressive histological subtypes include insular, diffuse sclerosing, solid, and tall cell variants.

Effect of CLT in Patients >45 Years

There were 269 (56.6%) patients >45 years, among whom 88 (32.7%) were in the PTC-CLT group and 181 (67.3%) were in the PTC-only group.

There were significantly fewer patients with persistent disease in the PTC-CLT group compared with the PTC-only group (0 vs. 8.29%, respectively; $p = 0.03$), and a lower incidence of CI in the PTC-CLT group compared with

Table 4. Clinicopathological parameters of 206 papillary thyroid carcinoma (PTC) patients <45 years, stratified by the presence of chronic lymphocytic thyroiditis (CLT)

Variables	PTC only (%)	PTC with CLT (%)	Odds ratio (95% CI)	*p* value
Total *n*	128 (62.1)	78 (37.9)		
Sex				
Female	110 (85.9)	67 (85.9)		
Male	18 (14.1)	11 (14.1)		
TgAb	23 (17.9)	32 (41.0)	3.18 (1.7–6.0)	0.0004
Capsular invasion	25 (19.5)	30 (38.5)	2.58 (1.37–4.8)	0.003
Extrathyroidal extension	20 (15.6)	23 (29.5)	2.76 (1.38–5.5)	0.004
LN metastasis	35 (27.3)	30 (38.5)	1.66 (0.9–3.0)	0.099
Lateral LN	12 (9.4)	15 (19.2)	2.23 (0.98–5.1)	0.054
Multifocality	45 (35.3)	46 (59)	2.65 (1.5–4.7)	0.001
Bilaterality	48 (37.5)	33 (42.3)	1.22 (0.69–2.2)	0.49
Distant metastasis	5 (3.9)	1 (1.3)	0.26 (0.03–2.24)	0.22
Aggressive histology	6 (4.7)	5 (6.4)	1.4 (0.4–4.7)	0.59
Stage				
I	123 (96.1)	77 (98.7)	3.1 (0.36–27.3)	0.3
II	5 (3.9)	1 (1.3)	0.32 (0.03–2.8)	0.3
MACIS				
<6	122 (95.3)	76 (97.4)	1.9 (0.4–9.5)	0.45
6–6.99	2 (1.6)	1 (1.3)	0.8 (0.07–9.2)	0.9
7–7.99	1 (0.78)	1 (1.3)	1.6 (0.1–26.7)	0.72
>8	3 (2.3)	0	0.23 (0.01–4.5)	0.33
Persistent disease	9 (7.03)	3 (3.9)	0.52 (0.14–2.02)	0.35
Recurrent disease	0	1 (1.3)	4.9 (0.2–123)	0.32

LN, lymph node; TgAb, thyroglobulin antibody. Aggressive histological subtypes include insular, diffuse sclerosing, solid and, tall cell variants.

the PTC-only group (21.6 vs. 33.2%, respectively; $p = 0.05$) (Table 3).

Effect of CLT in Patients <45 Years

There were 206 (43.4%) patients <45 years: 128 patients (62.1%) in the PTC-only group and 78 (37.9%) in the PTC-CLT group.

There was a significant number of patients in the PTC-CLT group with CI ($p = 0.003$) and ETE ($p = 0.004$). In addition, the PTC-CLT patients tended to have multifocal disease ($p = 0.001$). There was a trend for PTC-CLT patients to have more LN ($p = 0.099$) and lateral LN metastases ($p = 0.05$) (Table 4).

Discussion

The protective effect of CLT in PTC has long been a matter of debate. Several previous reports have shown that the coexistence of CLT with PTC is associated with a better prognosis, a lower recurrence rate and less aggressive clinical presentation [5, 8–11]. However, other investigators have reported that the coexistence of CLT has no protective effect on patient outcome [12, 13]. Factors that could explain the contradictory results from different studies include differences in the definition of CLT, poor reporting on the presence of CLT in subjects where the dominant finding is PTC, and differences in the impact of CLT on different age or ethnic groups [5, 9].

In our study, 35% of patients with PTC had lymphocytic thyroiditis, a frequency that is consistent with other reports (0.5–38%) [5, 6, 17]. We also found that patients with PTC and CLT presented at a younger age and had a greater female preponderance. This result is consistent with other reports [5, 18]. The coexistence of CLT was associated with fewer patients with persistent disease and a larger number with early-stage disease. However, when we analyzed the data separately based on age, we found that in patients >45 years, those with CLT had significantly less persistent disease and a lower incidence of CI. However, in the group of patients <45 years, the presence of CLT was associated with more CI and ETE. Further-

more, in this age group, PTC associated with CLT tended to be multifocal. However, there was no effect of the distant metastases, disease persistence, or recurrence.

Our results from patients >45 years are in agreement with the emerging literature that suggests a protective effect of CLT in patients with PTC. In a large retrospective study, Bie-Yu et al. [11] reported a higher percentage of TNM stage 4 in PTC-only patients ($p = 0.0459$) and a higher recurrence rate ($p = 0.0148$). The thyroid-cancer-specific survival rate for PTC-only patients compared with PTC-CLT patients was 95.7 and 98.7% at 10 years and 91.8 and 98.7% at 20 years, respectively. Another large study by Kashima et al. [5] reported a 0.7% cancer-specific mortality rate and a 95% relapse-free 10-year survival rate in patients with CLT compared to a 5% mortality and 85% relapse-free 10-year survival rate for those without CLT. Furthermore, CLT patients tended to have less frequent ETE ($p = 0.0029$) and frequent intrathyroidal multiple lesions ($p = 0.018$). Loh et al. [8] found that patients with CLT had a lower frequency of ETE (7.8 vs. 23.3%) and nodal metastases (25.8 vs. 43.3%) and an absence of distant metastases (0 vs. 4.8%) compared with patients without CLT. Compared with patients without CLT, in those with CLT cancer recurrence (6.3 vs. 24.1%; $p < 0.0001$) and cancer mortality rate were significantly lower (0.8 vs. 8%; $p = 0.001$). These studies differ from our study, as they had a larger sample size and a longer duration of follow-up.

Singh et al. [12] reported that coexistent Hashimoto thyroiditis did not alter the prognostic variables at the time of diagnosis of PTC or the approach to management. However, a meta-analysis suggested a positive correlation between CLT and the length of disease-free survival. Kebebew et al. [10] reported that 56% of patients with PTC and CLT had multicentric PTC compared with 25.3% of the patients without CLT ($p < 0.001$). There was no significant difference in tumor size, LN metastases, distant metastass, or the incidence of recurrent or persistent disease among the patients with PTC and CLT compared with patients with PTC only.

Hypotheses concerning the mechanism by which PTC with CLT leads to a better prognosis have been addressed in different ways. Giordano et al. [19] reported that follicular cells in CLT express both FAS (apoptosis antigen 1) and FAS ligand, which are thought to activate the FAS-mediated apoptosis pathway, causing the destruction of the thyroid tissue as well as promoting cancerous growth. The immune response in CLT may lead to the destruction of thyroid tissue. Coexisting CLT in patients with PTC may be involved in the destruction of tumor cells in much the same way as in patients with advanced CLT. Such an immune response against the tumor may be associated with less aggressive biological behavior in patients with PTC and CLT. Kimura et al. [20] reported that interleukin-1 secreted by infiltrating lymphocytes inhibits human thyroid carcinoma cell growth. In studies on BRAF v600E, Kim et al. [21] reported a significantly lower prevalence of BRAF mutations in patients with PTC and Hashimoto thyroiditis, suggesting that Hashimoto thyroiditis is less likely to be associated with a poor prognostic outcome.

Muzza et al. [22] investigated the relationship between histological and clinical features (including outcome) of PTC and the expression of inflammatory-related genes, e.g., the expression of genes encoding interleukin-8 (CXCL8) and chemokine ligand 20 (CCL20), in samples from PTC, thyroiditis, and normal thyroid tissue. PTC specimens showed a significantly greater expression of CCL20 and CXCL8 with respect to both normal thyroid and thyroiditis tissue. Interestingly, these differences were independent of the specific genetic lesion harbored by the tumor (BRAF, RET/PTC, or unknown genetic alterations) and of the presence or absence of associated autoimmune thyroiditis. Since CXCL8 recruits leukocytes and promotes angiogenesis, its role in tumor invasion and metastatic spread appears to be reasonable. However, no association between CXCL8 expression of and tumor staging or patients' outcome was found, likely because of the poor aggressive behavior of PTC [23].

A possible explanation for the controversy regarding the effect of CLT in the outcome of PTC might be related to the subtypes of lymphocytes present in the background thyroiditis. Cunha et al. [24] found that the presence of CD68+, CD4+, CD8+, CD20+, FoxP3+, and Th17 lymphocytes, but not MDSCs (myeloid-derived suppressor cells), was associated with clinical and pathological features of lower tumor aggressiveness and a more favorable patient outcome.

No previous study has demonstrated the effects of CLT stratified by age. This is the first report suggesting that the potential protective effect may be attenuated in younger patients. A possible explanation is that more locally spread PTC (multifocal, with CI and ETE) in younger patients may trigger the immune response resulting in CLT. Alternatively, CLT may just be a common bystander with little impact on PTC outcome.

While younger age was found to be associated with more CI and ETE in our patients with PTC and CLT, the prognosis of PTC is better in younger patients irrespective of whether they had CLT or not as manifested in our

study by early-stage disease, lower MACIS score, and lower persistent and recurrent disease in comparison to older patients (Tables 3, 4).

In conclusion, our study showed that concomitant CLT and PTC is associated with a better clinical stage and lower disease persistence. However, this protective effect was not found in patients <45 years.

Disclosure Statement

There is no conflict of interest for all authors

References

1 Robbins J, Merino MJ, Boice JD Jr, Ron E, Ain KB, Alexander HR, Norton JA, Reynolds J: Thyroid cancer: a lethal endocrine neoplasm. Ann Intern Med 1991;115:133–147.
2 Ain KB: Papillary thyroid carcinoma. Etiology, assessment, and therapy. Endocrinol Metab Clin North Am 1995;24:711–760.
3 Hodgson NC, Button J, Solorzano CC: Thyroid cancer: is the incidence still increasing? Ann Surg Oncol 2004;11:1093–1097.
4 Daily ME, Lindsay S, Skahen R: Relation of thyroid neoplasm to Hashimoto's disease of the thyroid gland. AMA Arch Surg 1955;70: 291–297.
5 Kashima K, Yokoyama S, Noguchi S, Murakami N, Yamashita H, Watanabe S, Uchino S, Toda M, Sasaki A, Daa T, Nakayama I: Chronic thyroiditis as a favorable prognosis factor in PTC. Thyroid 1998;8:197–202.
6 Matsubayashi S, Kawai K, Matsumoto Y, Mukuta T, Morita T, Hirai K, Matsuzuka F, Kakudoh K, Kuma K, Tamai H: The correlation between papillary thyroid carcinoma and lymphocytic infiltration of the thyroid. J Clin Endocrinol Metab 1995;80:3421–3424.
7 Antonaci A, Consorti F, Mardente S, Giovannone G: Clinical and biological relationship between chronic lymphocytic thyroiditis and papillary thyroid cancer. Oncol Res 2009;17: 495–503.
8 Loh KC, Greenspan FS, Dong F, Miller TR, Yeo PP: Influence of lymphocytic thyroiditis on the prognostic outcome of patients with PTC. J Clin Endocrinol Metab 1999;84:458–463.
9 Meier DW, Woolner LB, Beahrs OH, McConahey WM: Parenchymal findings in thyroid carcinoma: pathologic study of 256 cases. J Clin Endocrinol Metab 1959;19:162–171.
10 Kebebew E, Treseler PA, Ituarte PH, Clark OH: Coexisting chronic lymphocytic thyroiditis and papillary thyroid cancer revisited. World J Surg 2001;25:632–637.
11 Bie-yu H, Chuen H, Tzu- Chieh C: Well differentiated thyroid carcinoma with concomitant Hashimoto's thyroiditis present with less aggressive clinical stage and low recurrence rate. Endocr Pathol 2011;22:144–149.
12 Singh B, Shaha AR, Trivedi H, Carew JF, Poluri A, Shah JP: Coexistent Hashimoto's thyroiditis with papillary thyroid carcinoma: impact on presentation, management and outcome. Surgery 1999;126:1070–1076.
13 Del Rio P, Cataldo S, Sommaruga L, Concione L, Arcuri MF, Sianesi M: The association between papillary carcinoma and chronic lymphocytic thyroiditis: does it modify the prognosis of cancer? Minerva Endocrinol 2008;33: 1–5.
14 Copper D, Doherty G, Haugen B, Kloos R, Lee S, Mandel S, Mazzaferri E, Mclver B, Sherman B, Tuttle M: Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109–142.
15 American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper D, Doherty G, Haugen B, Kloos R, Lee S, Mandel S, Mazzaferri E, McIver B, Pacini F, Schlumberger M, Sherman I, Steward L, Tuttle M: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–1214.
16 Verburg FA, Luster M, Cupini C, Chiovato L, Duntas L, Elisei R, Feldt-Rasmussen Rimmel H, Seregni E, Smit JW, Theimer C, Giovanella L: 2013 implications of thyroglobulin antibody positivity in patients with differentiated thyroid cancer. Thyroid 2013;23:1211–1225.
17 Braverman LE: Iodine and thyroid: 33 years of study. Thyroid 1994;4:351–356.
18 Ahn D, Heo SJ, Park JH, Kim JH, Sohn JH, Park JY, Park SK, Park J: Clinical relationship between Hashimoto's thyroiditis and papillary thyroid cancer. Acta Oncol 2011;50: 1228–1234.
19 Giordano C, Stassi G, De Maria R, Todaro M, Richiusa P, Papoff G, Ruberti G, Bagnasco M, Testi R, Galluzzo A: Potential involvement of FAS and its ligand in the pathogenesis of Hashimoto's thyroiditis. Science 1997;275: 960–963.
20 Kimura H, Yamashita S, Namba H, Tominaga T, Tsuruta M, Yokoyama N, Izumi M, Nagataki S: Interleukin-1 inhibits thyroid carcinoma cell growth. J Clin Endocrinol Metab 1992;75:596–602.
21 Kim SK, Song KH, Lim SD, Lim YC, Yoo YB, Kim JS, Hwang TS: Clinical and pathological features and BRAF mutation in patients with papillary thyroid carcinoma with and without concurrent Hashimoto thyroiditis. Thyroid 2009;19:137–141.
22 Muzza M, Degl'Innocenti D, Colombo C, Perrino M, Ravasi E, Rossi S, et al: The tight relationship between papillary thyroid cancer autoimmunity and inflammation: clinical and molecular studies. Clin Endocrinol 2010;72: 702–708.
23 Rotondi M, Coperchini F, Chiovato L: CXCL8 in thyroid disease: from basic notions to potential applications in clinical practice. Cytokine Growth Factor Rev 2013;24:539–546.
24 Cunha LL, Morari EC, Guihen AC, Razolli D, Gerhard R, Nonogaki S, Soares FA, Vassallo J, Ward LS: Infiltration of a mixture of immune cells may be related to good prognosis in patients with differentiated thyroid carcinoma. Clin Endocrinol (Oxf) 2012;77:918–925.