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Influence of Lymphocytic Thyroiditis on the Prognostic Outcome of Patients with Papillary Thyroid Carcinoma

KEH-CHUAN LOH, FRANCIS S. GREENSPAN, FANG DONG, THEODORE R. MILLER, AND PETER P. B. YEO

Division of Endocrinology (K.-C.L., F.S.G., P.P.B.Y.), Department of Medicine, University of California-San Francisco, San Francisco, California 94143; Endocrine Unit (K.-C.L.), Department of Medicine, Tan Tock Seng Hospital, Republic of Singapore; Biostatistics Consultancy Unit (F.D.), National University Medical Institute, Republic of Singapore; and Department of Pathology (T.R.M.), University of California-San Francisco, San Francisco, California 94143

ABSTRACT

Both the association between lymphocytic thyroiditis (LT) and papillary thyroid carcinoma (PTC), and the prognostic significance of lymphocytic infiltrate in patients with thyroid malignancy, remain controversial. We examine the above relationships by retrospectively reviewing our series of patients treated for differentiated nonmedullary thyroid carcinoma at University of California-San Francisco over a 25-yr period (1970–1995). Of the 631 patients with complete data for analysis, 128 patients (20.3%) showed concomitant histologic evidence of LT and 503 patients (79.7%) had no evidence of LT. Prognostic outcome was assessed using Kaplan-Meier survival plots and analysis of risk factors by Cox's proportional-hazard modeling. The cohort with LT revealed a higher frequency of PTC (97.7% *vs.* 87.3%) and female patients (85.2% *vs.* 66.8%), a lower frequency of extrathyroidal invasion (7.8% *vs.* 23.3%) and nodal metastases (25.8% *vs.* 43.3%), and absence of distant metastases (0% *vs.* 4.8%), respectively, compared with those without LT. At initial surgery, a significantly greater proportion of patients with LT belonged to lower pathological tumor-node-metastasis stages, compared with those without LT (stage 1, 86.7% *vs.* 73%; stage 2, 4.7% *vs.* 8.3%; stage 3, 8.6% *vs.* 15.3%; and stage 4, 0% *vs.* 3.4%). Over a mean ± SE follow-up period of 11.1 ± 0.4 yr, patients with LT had significantly lower cancer recurrence rate (6.3% *vs.* 24.1%; $P < 0.0001$) and cancer mortality rate (0.8% *vs.* 8.0%; $P = 0.001$), respectively, compared with those without LT. In summary, our series showed a relatively common occurrence of LT in patients with PTC, and we believed that lymphocytic infiltration developed mainly in response to the tumor itself. We also found a more favorable course of PTC in the presence of LT; this supports the hypothesis that lymphocytic infiltration represents a form of immune reaction to control tumor growth and proliferation. (*J Clin Endocrinol Metab* **84:** 458–463, 1999)

THE ASSOCIATION between lymphocytic thyroiditis (LT) and papillary thyroid carcinoma (PTC) seems intriguing. Since the first documentation by Dailey *et al.* in 1955 (1), the coexistence of these two diseases has been variously reported to range from 0.3–38% (2–8). Besides possible ethnic, geographic, and gender differences in the prevalence of both diseases, differences in patient selection for thyroidectomy and histopathologic interpretation of LT also contribute to this variability (7–9). The occurrence of LT in patients with PTC has also been reported to predict fewer recurrences and an improved survival.

The aim of our study is to determine a definite statistical relation between these two entities, from a retrospective review of our series of 735 patients with differentiated nonmedullary thyroid carcinoma treated at the University of California-San Francisco (UCSF) from 1970–1995. We have previously reported on the utility of pathological tumor-node-metastasis staging classification in predicting disease-free survival and cancer-specific survival in this series of patients (10). In this study, we compare the characteristics of patients with and without histological evidence of LT, and we examine the influence of LT on survival outcome.

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Address all correspondence and requests for reprints to: Keh-Chuan Loh, Endocrine Unit, Department of Medicine, Tan Tock Seng Hospital, Moulmein Road, Singapore 308433, Republic of Singapore. E-mail: keh_chuan_loh@notes.ttsh.gov.sg.

Subjects and Methods

Patient selection

Among 735 patients treated for papillary or follicular thyroid cancer (including the Hürthle cell variant) at the UCSF Medical Center during the period 1970–1995, 631 patients (male:female = 1:2.4) with sufficient nonneoplastic thyroid tissue for histopathological examination were included in this study. One hundred twenty-eight subjects (20%) showed evidence of lymphocytic infiltration of the neoplastic or nonneoplastic thyroid tissue, whereas this was absent in the remaining 503 patients (80%) that we evaluated. A majority of the patients received treatment of thyroid carcinoma according to accepted protocol involving total or near-total thyroidectomy, adjuvant radioactive ^{131}iodine ablation of residual thyroid tissue, and postoperative L-thyroxine suppressive therapy as appropriate to their disease status, as reported previously (10).

Histological classification

All specimens obtained at surgery or outside histology slides were reviewed by a senior pathologist (T. R. Miller) or an associate. The histological classification for thyroid carcinoma was made according to the World Health Organization criteria (11). The diagnosis of LT was taken from a review of the pathology reports on each patient. The degree of lymphocytic infiltration varied from islands of lymphocytic infiltration in or around the papillary carcinomas, or in thyroid tissue surrounding follicular carcinomas, to heavy infiltration of lymphocytes (including germinal centers) in the papillary carcinomas or in surrounding thyroid tissue. Patients with classical Hashimoto's thyroiditis, characterized by the presence of Hürthle cells and varying degree of acini atrophy in addition to the above findings, were included in the cohort

with LT (12). Unfortunately, serum thyroglobulin antibody or thyroperoxidase antibody titers were not available in most of these patients.

Observed end-point

Prognostic outcome was obtained from follow-up examinations and the UCSF Cancer Registry. Follow-up duration was calculated from the time of last evaluation or the time of death. The study end-point was either cancer recurrence or death from thyroid cancer. Tumor recurrence was defined as new evidence of locoregional disease or distant metastases occurring more than 6 months after successful primary treatment. Hence, this was evaluated only in patients who had undergone a potentially curative operation, followed by successful ^{131}iodine ablative therapy in those with residual tumor.

Data analysis

Data were analyzed using the Statistical Package for Social Science (SPSS, Inc., Chicago, IL). Risk factor analyses were performed on various prognostic factors, including LT. Time-dependent variables were analyzed by the Cox's proportional-hazard model and the Kaplan-Meier product limit estimates of survival curves (13, 14). The log-rank test was used for comparison of survival curves. Observed differences are assumed statistically significant if the probability of chance occurrence is $P < 0.05$.

Results

Patient and tumor characteristics

Table 1 compares patient and tumor characteristics between the cohorts with the presence and absence of LT, respectively, at the initial surgical treatment. Histological evidence of LT was found in 128 (20%) of the 631 patients evaluated. The mean or median age at diagnosis did not differ between the cohorts; our series showed that LT could be identified in thyroid or thyroid carcinoma tissue from patients from all ages, with the highest prevalence noted in the third to fifth decades of life. However, a greater female preponderance was noted in the cohort with LT. Whereas the majority (89%) of patients in our overall series had PTC, this constituted an overwhelming 98% of the cohort with LT. At diagnosis, patients with LT tend to have more limited disease, with a significantly lower frequency of extrathyroidal invasion (7.8% *vs.* 23.3%), nodal metastases (25.8% *vs.* 43.3%), and distant metastases (0% *vs.* 4.8%), compared with those without LT. Correspondingly, the cohort with LT had a higher proportion of patients with stage 1 disease and lower proportion of subjects in stage 2 or higher pTNM classification, compared with those without LT.

Outcome and survival characteristics

Treatment outcome and follow-up data are summarized in Table 2. Initial cure, post primary treatment of thyroid cancer, was achieved in 100% of the cohort with LT and 92% of those without LT. After a mean follow-up interval of 11.0 yr in both cohorts, thyroid cancer recurrence was recorded in 6.3% of patients with LT, compared with 24% of patients without LT ($P < 0.0001$). Similarly, deaths from thyroid cancer occurred in only <1% of the cohort with LT, compared with 8% in those without LT ($P = 0.001$).

Data on disease-free survival and cancer-specific survival for the respective cohorts, with and without LT, were tabulated by Kaplan-Meier product-limit estimates of survival. Fig. 1 compares the disease-free survival of patients with and without LT, showing a distinct separation of the survival plots at all time points assessed ($P < 0.0001$, by log-rank test). Fig. 2 shows the cancer-specific survival plots between the two cohorts; a significant (but less marked) separation of the survival plots at all time points is noted ($P = 0.003$, by log-rank test). Using pTNM classification to compare sur-

TABLE 1. Clinical characteristics in differentiated thyroid carcinoma associated with or without LT at the initial surgical treatment

	LT		Comparison between with- and without-LT [a] *P* value
	Present (n = 128)	Absent (n = 503)	
Age in yr			
Mean	38.0	40.6	NS (0.08)
SE	1.2	0.8	
Range	14.4–78.2	5.2–97.0	
Sex			
Male/female	19/109	167/336	<0.0001
Ratio	1:5.7	1:2.0	
Tumor type			
Papillary	125 (97.7%)	439 (87.3%)	0.003
Follicular[b]	3 (2.3%)	64 (12.7%)	
Extrathyroidal invasion	10 (7.8%)	117 (23.3%)	<0.0001
Multifocal tumor	54 (42.2%)	257 (51.1%)	NS (0.08)
Nodal metastases	33 (25.8%)	218 (43.3%)	0.003
Distant metastases	0 (0%)	24 (4.8%)	0.004
pTNM staging			
Stage 1	111 (86.7%)	367 (73.0%)	
Stage 2	6 (4.7%)	42 (8.3%)	0.007
Stage 3	11 (8.6%)	77 (15.3%)	
Stage 4	0 (0%)	17 (3.4%)	

[a] Comparison made using Mann-Whitney test for age, Pearson chi-square test for pTNM staging, and Fisher exact test for all other characteristics. NS, nonsignificant.

[b] Includes Hurthle cell carcinoma.

TABLE 2. Treatment outcome in differentiated thyroid carcinoma associated with or without LT

	LT		Comparison between with- and without-LT *P* value
	Present (n = 128)	Absent (n = 503)	
Follow-up duration[a]			
Median in yr	10.9	10.0	NS
Mean in yr	11.0	11.0	
SE in yr	0.4	0.3	
Patients with initial cure	128 (100%)	463 (92.0%)	0.0001
Cancer recurrence			
No. of patients	8 (6.3%)	121 (24.1%)	<0.0001
Time to recurrence[a]			
Median in yr	2.0	3.0	NS
Mean in yr	4.9	4.7	
SE in yr	1.9	0.5	
Cancer deaths			
No. of patients	1 (0.8%)	40 (8.0%)	0.001
Time to death[a]			
Median in yr	0.8	6.3	NS
Mean in yr	0.8	8.5	
SE in yr	—	1.2	

[a] Comparison of time-dependent variables (follow-up duration, time to recurrence, and time to death) was by Mann-Whitney test; comparison of proportions, by Fisher exact test.

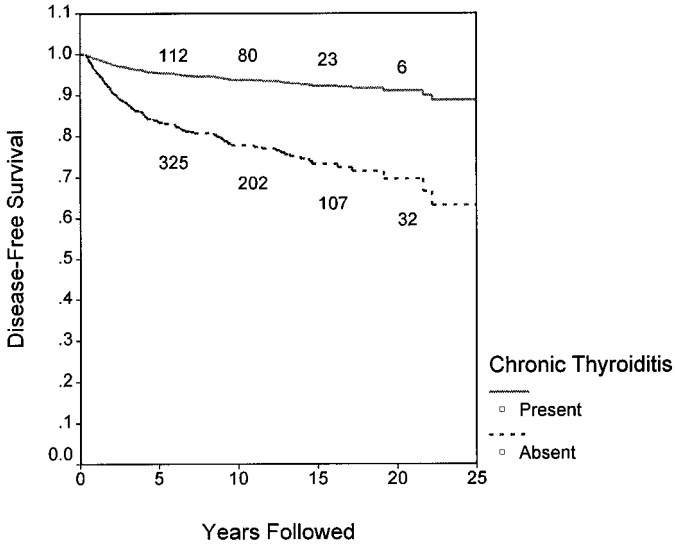

FIG. 1. Kaplan-Meier plot for disease-free survival, comparing the cohorts with and without concomitant LT ($P < 0.0001$, by log-rank test).

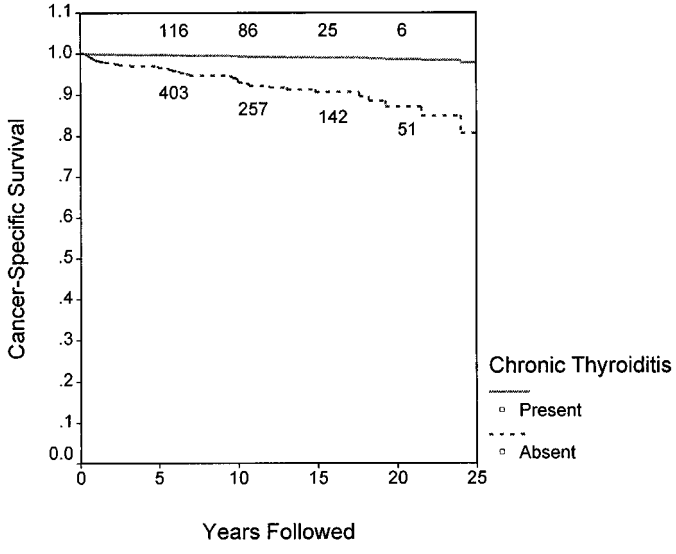

FIG. 2. Kaplan-Meier plot for cancer-specific survival (patients who did not succumb to thyroid cancer), comparing the cohorts with and without concomitant LT ($P = 0.003$, by log-rank test).

vival outcome between the cohorts with similar tumor staging, the disease-free survival was significantly better in patients with LT, compared with those without LT. However, the difference in cancer-specific survival between the cohort with LT and those without LT was not statistically significant, when analyzed according to pTNM staging.

Analysis of prognostic factors

Table 3 presents the Cox proportional-hazards model for cancer recurrence and cancer mortality, respectively, showing the risk ratio (RR) and 95% confidence interval (CI) for the prognostic variables studied. Variables used in TNM staging (age cut-off at 45 yr, tumor size, extent of primary tumor, and presence of nodal or distant metastases) uniformly depicted a significant association with both cancer recurrence and cancer mortality. Besides the variables assessed in TNM staging, gender, tumor focality and LT were found to be additional factors influencing the risk of cancer recurrence; whereas gender, tumor type, and LT were significantly associated with thyroid cancer mortality.

Table 4 presents the Cox proportional-hazards model for cancer recurrence and cancer mortality, respectively, by multivariate analysis of factors found to be significant in the univariate model (apart from variables used in TNM staging, because the pTNM staging itself was included in the model). In the multivariate model, the presence of LT remained a significant favorable prognostic factor for cancer recurrence (RR = 0.4; 95% CI = 0.2–0.9), whereas gender and tumor focality did not confer an independent

TABLE 3. Risk factors for cancer recurrence and cancer mortality by univariate analysis

Variable	Cancer recurrence		Cancer mortality	
	Risk ratio (95% CI)	*P* value	Risk ratio (95% CI)	*P* value
Age				
<45 yr	1		1	
≥45 yr	1.7 (1.2–2.4)	0.0048	9.5 (4.3–21.1)	<0.0001
Sex				
Male	1		1	
Female	0.5 (0.4–0.7)	0.0001	0.3 (0.2–0.5)	0.0001
Tumor type				
Papillary cancer	1		1	
Follicular cancer	1.3 (0.7–2.2)	NS (0.43)	6.4 (3.2–12.7)	<0.0001
Tumor size				
T1: ≤10 mm	1		1	
T2: 10–40 mm	3.5 (1.5–8.0)	0.0035	2.8 (0.3–26.6)	NS (0.38)
T3: >40 mm	12.1 (3.5–41.4)	0.0001	19.3 (1.2–309)	0.0370
T4: extrathyroidal invasion	17.4 (7.8–38.6)	<0.0001	54.5 (7.2–395)	0.0001
Tumor focality				
Unifocal	1		1	
Multifocal	1.9 (1.2–3.2)	0.0120	2.7 (0.9–7.7)	NS (0.07)
Nodal metastases				
N0: negative	1		1	
N1: positive	4.4 (2.8–6.8)	<0.0001	2.7 (1.2–5.9)	0.0160
Distant metastases				
M0: negative	1		1	
M1: positive	4.1 (2.2–7.7)	<0.0001	20.3 (10.4–39.3)	<0.0001
pTNM staging				
Stage I	1		1	
Stage II	1.1 (0.5–2.3)	NS (0.89)	10.3 (3.1–33.9)	0.0001
Stage III	3.5 (2.3–5.2)	<0.0001	21.0 (8.1–54.3)	<0.0001
Stage IV	7.5 (3.9–14.6)	<0.0001	73.3 (27.0–199)	<0.0001
Lymphocytic thyroiditis				
Absent	1		1	
Present	0.2 (0.1–0.5)	0.0001	0.1 (0.0–0.8)	0.026

Variable assigned risk ratio of 1 are used as reference for the Cox model.

risk. Conversely, the presence of LT was not an independent predictor for cancer mortality in the multivariate model.

Discussion

In our study of subjects with LT, we include both patients with Hashimoto's thyroiditis and those with simply a cellular lymphocytic infiltrate around a thyroid neoplasm. Because thyroid antibody titers were not available in the majority of patients studied, this was excluded from our evaluation. The presence of LT was noted in one-fifth of our series of patients with differentiated nonmedullary thyroid carcinoma. In particular, LT was recorded in 125 of 564 patients (22%) with PTC histology, compared with 3 of 67 patients (4.5%) with follicular or Hürthle cell histology. We found that patients with LT almost uniformly had PTC, consistent with the observation by other investigators (6–9). The etiologic relationship between thyroid carcinoma and LT still remains a point of dispute, because it is unclear whether thyroiditis is induced secondarily by neoplasm (8, 15) or that thyroiditis predisposes the patient to the development of thyroid carcinoma (16–18). Although some authors reported that thyroid carcinomas occur with significantly greater frequency in patients with Hashimoto's thyroiditis (16, 17, 19), it is generally believed that Hashimoto's thyroiditis is not a premalignant lesion.

Conversely, nonspecific cellular lymphocytic infiltration is commonly recognized adjacent to a thyroid neoplasm (3, 7, 8, 15, 20). One may therefore postulate that thyroiditis associated with thyroid carcinoma, in most cases, is secondary to the neoplasm, representing the reaction induced by an antigen from the neoplasm itself. Our observation that patients with LT have a lower TNM score at diagnosis is consistent with the hypothesis that lymphocytic response limits tumor growth and metastases. It is postulated that the infiltrated lymphocytes from patients with PTC are likely to be cytotoxic T cells, with natural killer or lymphokine-associated killer activity acting as carcinoma cell killers (21). These antitumor lymphocytes may also secrete cytokines, such as interleukin-1, that inhibit thyroid carcinoma growth (22).

Over a mean follow-up period of 11 yr, we reported a significantly better cancer recurrence and cancer mortality rates in the cohort with LT, compared with those without LT. Our risk factor analyses showed that variables used in TNM staging (age at time of initial assessment, tumor size, presence of extrathyroidal invasion, and initial nodal or distant metastases) are all important prognostic factors for recurrence or death from thyroid cancer. In the univariate model,

TABLE 4. Risk factors for cancer recurrence and cancer mortality, by multivariate analysis

Variable	Cancer recurrence		Cancer mortality	
	Risk ratio (95% CI)	*P* value	Risk ratio (95% CI)	*P* value
Sex				
Male	1		1	
Female	0.9 (0.5–1.5)	NS (0.58)	0.5 (0.2–1.1)	NS (0.06)
Tumor type				
Papillary cancer			1	
Follicular cancer	ND		3.0 (1.4–6.4)	0.0041
Tumor focality				
Unifocal	1			
Multifocal	1.6 (0.9–2.7)	NS (0.10)	ND	
pTNM staging				
Stage I	1		1	
Stage II	1.0 (0.4–2.9)	NS (0.94)	9.5 (2.4–37.0)	0.0012
Stage III	2.2 (1.1–4.3)	0.0224	20.2 (6.3–64.5)	<0.0001
Stage IV	4.7 (1.6–13.3)	0.0040	55.0 (16.5–183)	<0.0001
Lymphocytic thyroiditis				
Absent	1		1	
Present	0.4 (0.2–0.9)	0.0311	0.4 (0.0–2.8)	NS (0.34)

Variables assigned risk ratio of 1 are used as reference for the Cox model (ND, Not done because of nonsignificant risk ratios obtained from univariate analysis).

the presence of LT is similarly associated with a significantly lower risk of cancer recurrence (RR = 0.2; 95% CI = 0.1–0.5) and cancer deaths (RR = 0.1; 95% CI = 0.0–0.8). Using the multivariate model with inclusion of pTNM staging, the relative risk for cancer recurrence still remains significantly lower in patients with LT (RR = 0.4; 95% CI = 0.2–0.9). This suggests that, besides predicting more limited disease at diagnosis, the presence of LT also predicts favorable long-term outcome. This is represented by the Kaplan-Meier survival plots, showing a significantly better disease-free survival and cancer-specific survival in the cohort with presence of LT.

Despite some controversy, there is an emerging literature on the prognostic value of LT in patients with PTC (6–8). In a review of 1533 patients with a long postoperative duration of follow-up, Kashima *et al.* (7) reported a 5% cancer-specific mortality and a 85% relapse-free 10-yr survival rate in patients without LT, compared with 0.7% mortality and 95% relapse-free 10-yr survival rate, respectively, in those with LT (a finding very similar to ours). In a longitudinal follow-up of 95 patients with PTC for 10 yr, Matsubayashi *et al.* (8) found a significantly reduced incidence of tumor recurrence in the group with histologic evidence of lymphocytic infiltration (2.8%), compared with the group without (18.6%). In another study, Ott *et al.* (16) reported no evidence of recurrence or deaths over a 4.7-yr follow-up period in 47 patients diagnosed with thyroid carcinoma, from a specific subpopulation with Hashimoto's thyroiditis and solitary cold nodule.

The improved prognosis associated with the presence of LT has also been reported in patients with more aggressive thyroid tumor types. In a review of seven cases of thyroid carcinoma, in patients with concomitant Hashimoto's thyroiditis that were identified from a large cohort of 590 patients, Segal *et al.* (5) reported the absence of tumor invasion beyond the thyroid gland capsule, cervical or distant metastases in all 7 patients. The limited disease noted in the group with Hashimoto's thyroiditis was evident despite most patients having a more aggressive tumor type [four with follicular thyroid carcinomas (one of which was associated with anaplastic area) and one medullary thyroid carcinoma]. Interestingly, all seven patients were alive and disease free after 7–17 yr of follow-up, as contrasted with the 9% mortality in their total series of thyroid cancers, even in patients with low-grade malignancy.

In conclusion, our finding suggests a more favorable course of PTC in patients with associated histopathologic evidence of lymphocytic infiltration around the neoplastic gland. The presence of LT may be considered as a form of immune reaction to control tumor growth and proliferation.

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