TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2017) 47: 1173-1179
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doi:10.3906/sag-1604-83

Relationship of paratracheal lymph nodes with the progression of chronic autoimmune thyroiditis: 5-year follow-up results

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Received: 22.04.2016 • **Accepted/Published Online:** 20.03.2017 • **Final Version:** 23.08.2017

Background/aim: To examine changes in paratracheal lymph nodes (PLNs) and the relationship with the course of the disease in patients with chronic autoimmune thyroiditis (CAT) 5 years after diagnosis.

Materials and methods: A total of 169 patients with newly diagnosed CAT and 53 healthy subjects were included in the study. All patients underwent ultrasonographic (US) examinations of the thyroid, paratracheal regions, and examined thyroid function tests. Eighty-four patients who were euthyroid at baseline and who were contacted 5 years after the diagnosis were reevaluated by US and thyroid function tests.

Results: The PLNs frequency was significantly higher in the CAT group than the controls (75.1 % vs. 30.1 %, $P < 0.001$). Among the 84 patients who were euthyroid at the time of diagnosis and were contacted again after 5 years, 15 developed hypothyroidism. Initially, PLNs were present in all patients who developed hypothyroidism and were significantly higher than in those who remained euthyroid (respectively 100% vs. 68.7%, $P = 0.009$). PLN presence and PLN volume in patients who were euthyroid at baseline predicted hypothyroidism at the end of 5 years.

Conclusion: PLNs may be used as an indicator of disease progression. In addition, patient age and baseline TSH levels are other factors that predict the development of hypothyroidism in time.

Key words: Chronic autoimmune thyroiditis, paratracheal lymph nodes, ultrasonography, antithyroid antibodies, hypothyroidism

1. Introduction

Chronic autoimmune thyroiditis (CAT) has a high prevalence in the general population (1,2). The diagnosis of CAT is usually based on clinical findings, positive antithyroperoxidase antibody (TPOAb) or cytological results and appearance on thyroid ultrasonography (US) (3). However, none of the laboratory tests seem to be ideal. The validity of using reduced thyroid echogenicity as a predictor of possible CAT, in general, was very good. However, the rate of diagnostic verification seems to be lower when the history of thyroid disease is brief or when the reduction in thyroid echogenicity is mild (4). It is now known that not only the thyroid gland but also the peripheral lymph nodes (LNs) contain lymphoid follicles in autoimmune thyroid diseases (5–7). While LNs identified in CAT patients were previously thought to be malignant, it has been understood that the LNs in CAT patients are inflammatory (8,9). Paratracheal lymph nodes (PLNs) are seen commonly in patients with autoimmune thyroiditis. However, no study has examined the effects of PLNs on the course of CAT.

In the current study, we aimed to investigate the changes in PLNs and the relationship with the course of the disease in CAT patients 5 years after diagnosis.

2. Materials and methods

This study was undertaken in the outpatient endocrinology clinic between January 2008 and January 2009, with the approval of the local ethics committee. A total of 169 consecutive patients with newly diagnosed thyroiditis (40.3

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± 12.2 years, males/females 9/160) and 53 healthy subjects (35.5 ± 8.9 years, males/females 6/47) were included in the study. For the control group, we selected 53 healthy subjects with no clinical, laboratory (thyroid stimulating hormone (TSH), TPOAb, TgAb, leukocyte count, C-reactive protein, and erythrocyte sedimentation rate) and ultrasonographic evidence of thyroid diseases or other neck diseases. All patients underwent US examination of the thyroid and paratracheal regions (Figure). All patients underwent thyroid function tests, TPOAb, and antithyroglobulin antibody (TgAb). Diagnosis of CAT was based upon the presence of parenchymal hypoechogenicity (compared to adjacent muscle structures) in conjunction with elevated levels of TPOAb and/or TgAb. Patients who had a thyroid nodule, clinical evidence of nonthyroidal benign diseases of the neck and head, or a positive history of other autoimmune systemic or other systemic diseases involving lymphoid tissue were excluded. Previous amiodarone, interferon, IL-2 therapy was added as a criterion for exclusion.

To examine the effect of PLN presence on CAT course, 84 patients out of 97 euthyroid patients at diagnosis were reevaluated 5 years later and they underwent US examination of the thyroid and paratracheal regions, and thyroid function tests were repeated.

2.1. Ultrasonography

Thyroid US was performed and interpreted by the same experienced physicians (GA, SI), using the same equipment with an 11 MHz linear transducer (Logiq 3 Pro, GE Medical Systems, Milwaukee, WI, USA). The subjects were examined in the supine position with hyperextended neck. Images were obtained in the transverse and longitudinal planes. The sizes of each lobe were measured, and the volume was calculated by the mean of the elliptical shape volume formula ($\pi/6 \times$ length $\times$ width $\times$ depth). The paratracheal region is limited laterally by the carotid vessels, posteriorly by the cervical musculature on the right and the esophagus on the left, anteriorly by the strap muscles, and inferiorly by the arterial and venous brachiocephalic trunks. For each PLN we recorded the following: long-axis diameter (expressed in mm); short-axis diameter (defined as the widest diameter of the node in the axial plane perpendicular to the long-axis diameter; expressed in mm); long-axis diameter/short-axis diameter ratio (L/S ratio).

2.2. Laboratory tests

Serum TSH level was evaluated using an Abbott ARCHITECT 2000 device and the chemiluminescence microparticle immunoassay (CMIA). Serum TgAb and TPOAb values were evaluated by immunoradiometric assay (IRMA) methods (ICN Pharmaceuticals, USA). Normal ranges in our laboratory are as follows: TSH 0.35–4.94 μIU/mL; TgAb < 50 IU/mL and TPOAb < 10 IU/mL). Patients with TSH > 4.94 were considered hypothyroid.

2.3. Statistical analysis

Data analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Whether the

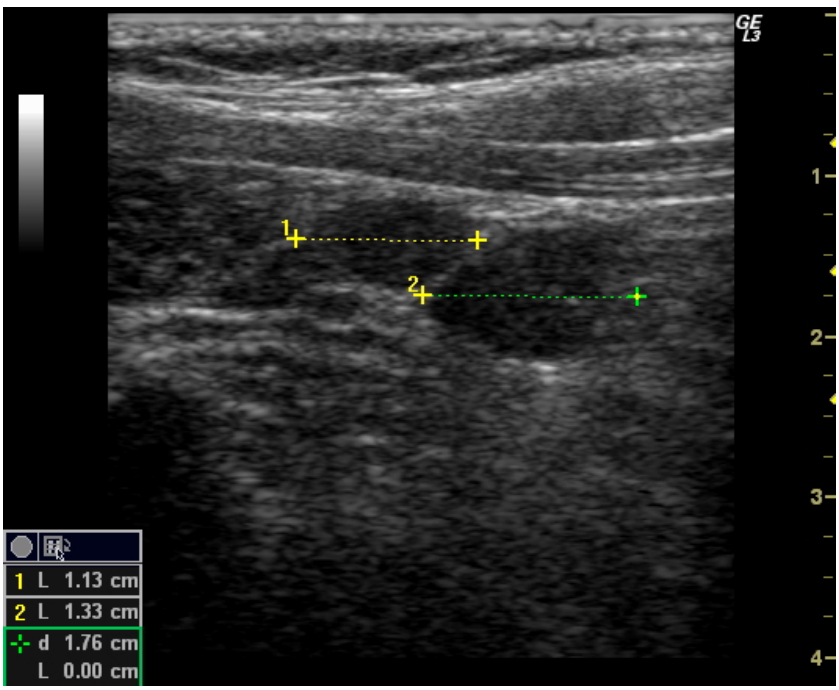

Figure. Ultrasonographic imaging of thyroid and paratracheal region.

distributions of continuous variables were normal or not was determined by Kolmogorov–Smirnov test. Data were shown as mean ± SD or number of cases and percentages, where applicable.

While the differences in normally distributed data between the CAT and control groups were evaluated by Student's t-test, the Mann–Whitney U test was applied for the comparisons of not normally distributed variables. Nominal data were analyzed by Pearson's chi-square or Fisher's exact test, where appropriate. Whether the differences between baseline and final thyroid volume, number and volume of PLNs within CAT group were statistically significant or not was evaluated by Wilcoxon's signed rank test. Degrees of association between continuous variables were analyzed by Spearman's rank correlation test.

A P value less than 0.05 was considered statistically significant.

3. Results

3.1. Results of baseline characteristics

Characteristics of the patients and controls are provided in Table 1. TSH, TPOAb, and TgAb were significantly higher in the CAT group compared to the controls (P < 0.001 for all). At the time of diagnosis, thyroid volume was higher in the CAT group compared to the controls but did not differ significantly (P = 0.201).

PLNs were significantly more common in the CAT group compared to the controls (75.1% vs. 30.1%, P < 0.001) (Table 2). Numbers of PLNs were comparable between the subjects in the control and CAT groups in whom LNs were detected (P = 0.072), and the CAT group had significantly higher PLN volume compared to the controls (P = 0.022).

Although both long and short LN sizes were greater in the CAT group compared to the controls (9.6 ± 5.3 mm vs. 6.6 ± 3.0 mm, P = 0.010; 5.0 ± 1.4 mm vs. 3.9 ± 1.3 mm, P = 0.046), the ratio of long versus short sizes was statistically comparable between the groups (P = 0.455) (Table 2).

The TSH, TPOAb, and TgAb levels were similar at the time of diagnosis between the PLN positive and negative CAT patients [respectively 3.5 ± 2.2 vs. 3.5 ± 2.3, P = 0.888; 141.7 (0.04–1087) vs. 46.4 (0–910), P = 0.104; and 88.5 (0.1–4000) vs. 26.6 (0–620), P = 0.06].

There was a statistically significant positive correlation between TPOAb level and the number of PLNs (r = 0.256 and P < 0.001), whereas no statistically significant correlation was found between the TgAb level and the number of PLNs (r = 0.040 and P = 0.660). There was no significant correlation between TSH and PLN numbers (r = –0.104 and P = 0.245). No correlation was found between PLN volumes and TSH, TPOAb, and TgAb levels (respectively r = 0.07, P = 0.309; r = 0.04, P = 0.491; and r = –0.009, P = 0.890).

PLN volume at diagnosis ≥0.085 cm^3 predicts CAT diagnosis with 82.3% sensitivity and 75.0% specificity (AUC = 0.779, 95% CI = 0.590–0.969).

Initially, 97 patients were euthyroid and 72 patients were hypothyroid. PLN was positive in 73.5% of the euthyroid patients and PLN was present in 82% of the hypothyroid patients, respectively, and were similar between the 2 groups (P = 0.250).

3.2. Results of analyses 5 years after diagnosis

There was a statistically significant reduction in thyroid volume from baseline at year 5 in the CAT group (P < 0.001) (Table 3). Five years after the diagnosis there was no statistically significant difference in the number of PLNs (P = 0.673) but statistically a significant decrease was found in PLN volume (P < 0.001) in the CAT group.

Sixty-nine of the 84 euthyroid subjects that were able to be reevaluated in the fifth year were still euthyroid while 15 developed hypothyroidism. In all patients, PLN presence

Table 1. Clinical and biochemical characteristics of chronic autoimmune thyroiditis and control groups.

Variables	CAT (n = 169) (mean ± SD)	Control (n = 53) (mean ± SD)	P-value
Age (year)	40.3 ± 12.2	35.5 ± 8.9	0.077†
Sex (male/female)	9 (5.3%)/160 (94.7%)	6 (11.3%)/47 (88.7%)	0.257
TSH (μIU/mL)	3.2 ± 2.3	1.91 ± 1.1	<0.001¶
TPOAb (IU/L)	196.78 ± 265.29	2.90 ± 2.38	<0.001¶
TgAb (IU/L)	210.15 ± 511.21	2.83 ± 2.55	<0.001¶
Thyroid volume (cm^3)	13.4 ± 9.03	11.6 ± 2.50	0.451¶

† Student's t-test, ‡ Fisher's exact test, ¶ Mann–Whitney U test.
CAT, chronic autoimmune thyroiditis; TSH, thyrotropin; TPOAb, antithyroperoxidase antibodies; TgAb, antithyroglobulin antibodies; NS, not significant; SD, standard deviation.

Table 2. Baseline US characteristics of paratracheal lymph nodes in chronic autoimmune thyroiditis and control groups.

US characteristics	CAT (n = 169) (mean ± SD)	Control (n = 53) (mean ± SD)	P-value
Patients with PLNs	127 (75.1%)	16 (30.1%)	<0.001†
Number of PLNs	2.90 ± 2.36	1.50 ± 0.76	0.072‡
Volume of PLNs (cm^3)	0.23 ± 0.45	0.07 ± 0.08	0.022‡
Long-axis diameter of PLNs (mm)	9.63 ± 5.27	6.56 ± 3.02	0.010‡
Short-axis diameter of PLNs (mm)	4.96 ± 1.35	3.87 ± 1.33	0.046‡
L/S ratio	1.95 ± 0.60	1.80 ± 0.77	0.455‡

† Pearson's chi-square test, ‡ Mann–Whitney U test.
PLNs, Paratracheal lymph nodes; US, ultrasonography; L/S ratio, long-axis diameter/short-axis diameter ratio.

Table 3. Comparison of the thyroid and paratracheal lymph node characteristics of the patients with chronic autoimmune thyroiditis who were euthyroid at the time of diagnosis and 5 years after the time of diagnosis (n = 84).

Variables	Baseline (mean ± SD)	After 5 years (mean ± SD)	P-value †
Thyroid volume (cm^3)	5.62 ± 3.17	4.50 ± 3.46	<0.001
Number of PLNs	2.91 ± 1.71	3.19 ± 1.71	0.673
Volume of PLNs (cm^3)	0.19 ± 0.12	0.06 ± 0.05	<0.001

† Wilcoxon's signed rank test.
PLNs, Paratracheal lymph nodes

in those who developed hypothyroidism was significantly higher than in those who remained euthyroid (respectively 100% vs. 68%, P = 0.009) (Table 4). The volume of PLNs and TPOAb and TgAb titers at the time of diagnosis of patients who developed hypothyroidism at the end of year 5 was higher compared to the group of patients who remained euthyroid, although the groups differed significantly only in TgAb (P = 0.181, P = 0.430, and P = 0.014, respectively). The proportion of patients who remained euthyroid at the end of year 5 did not differ significantly compared to those who developed hypothyroidism at post-5 year examinations of the number of PLNs (3.2 ± 2.1 vs. 2.5 ± 1.5, P = 0.106).

In regression analysis, when variables affecting hypothyroidism development among CAT patients at 5 years were examined, age, TSH levels, and PLN volume were found to be statistically significant (Table 5).

Age ≥ 42 years was found to predict hypothyroidism with 61.5% and 58.5% sensitivity and specificity, while TSH value ≥ 2.36 was found to predict hypothyroidism with 61.5% sensitivity and 43.9% specificity, respectively.

4. Discussion

It is now known that not only the thyroid gland but also the peripheral LNs contain lymphoid follicles in autoimmune thyroid diseases (5–7). Recent studies showed that LNs observed in CAT patients had inflammatory character (8,9).

In our study, PLN was more common in the CAT group than in the control group and the long PLNs and short PLNs, as well as their volumes, were greater in the CAT group. Similar to the results of our study, a study demonstrated more common PLN among CAT patients compared to controls and the authors noted that they considered these LNs to be of inflammatory nature although they did not describe the long/short axis of the LNs. The authors described that the optimal cutoff for predicting CAT was the presence of more than 2 PLNs larger than 7 mm (8). In our study PLN volume ≥ 0.085 cm^3 was predictive of CAT with 82.3% sensitivity and 75.0% specificity.

The titer of TPOAb correlates well with the number of autoreactive lymphocytes infiltrating the thyroid (10) and

Table 4. Comparison of baseline diagnostic ultrasound and laboratory characteristics of patients who were euthyroid with their thyroid function after 5 years.

Variables	Euthyroid (n = 69)	Hypothyroid (n = 15)	P-value
PLNs (n, %)	47 (68)	15 (100)	0.009
Volume of PLNs (cm^3)	0.13 ± 0.06	0.18 ± 0.15	0.181
TPOAb (IU/L)	158.70 ± 245.73	211.07 ± 163.62	0.430
TgAb (IU/L)	128.2 ± 323.2	479.5 ± 1033.3	0.014

Table 5. Effect of baseline laboratory and US features on hypothyroidism development at the end of 5 years in the CAT group

Coefficients[a]						
Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. error	Beta		
	Constant	4.452	0.965		4.615	0.001
	Age (years)	–0.028	0.010	–0.758	–2.781	0.019
	TSH (μIU/mL)	–0.246	0.068	–0.749	–3.620	0.005
	sT3 (pg/mL)	–0.144	0.164	–0.248	–0.877	0.401
	sT4 (ng/dL)	0.415	0.356	0.222	1.164	0.272
	Number of PLNs	–0.067	0.084	–0.235	–0.797	0.444
	Volume of PLNs (cm^3)	–2.841	1.359	–0.444	–2.090	0.043
	TPOAb (IU/L)	–0.495	0.349	–0.443	–1.419	0.186
	TgAb (IU/L)	0.261	0.426	0.196	0.611	0.555

the degree of sonographic hypoechogenicity, heterogeneity, and pseudonodular hypoechoic infiltration (11). TPOAb has been established to represent the current activity of CAT and subsequent thyroid destruction because the TPO-antigen is closely involved with cell-mediated cytotoxicity, whereas the TgAb is not (12). Multiple antigen configurations of thyroglobulin are produced when it becomes iodinated, resulting in functionally active but immunologically distinct molecules (13). The studies failed to demonstrate a relation between sonographic heterogeneity and TgAb levels (11,14). In our study, there was no relationship between TgAb level and PLN number. With the previously proven correlation with disease activity and inflammatory response, TPOAb level was positively correlated with the number of PLNs in our study. This result supports the relationship between PLNs and current inflammation of the thyroid tissue in CAT patients. However, TgAb titer at the time of diagnosis was more effective than TPOAb in predicting hypothyroidism development during the course of CAT.

A recent study has demonstrated that the number of cervical LNs with a long diameter of > 1 cm in levels II, III, and IV and the axis of lymph nodes in levels III and IV were higher in CAT patients compared to controls (9). The authors think that the LNs with benignant hyperplastic appearance detected mainly in levels II, III, and IV were characteristics of CAT patients. In that study, PLN was determined only in five CAT patients and statistical analysis was not performed due to the limited number of patients. In our study, we found that thyroid volume and PLNs were significantly reduced at the 5-year follow-up. PLN occurs in CAT when the inflammatory process is active, with PLNs reducing in size with lengthening disease duration and diminishing inflammation. Although the disease duration of the five patients with identified PLN was not reported, we are of the opinion that retrothyroidal LNs were not identified because the patients for whom PLNs were not identified had long disease durations.

All patients who were euthyroid at the time of diagnosis but developed hypothyroidism at the end of

year 5 were PLN-positive at the time of diagnosis. We think that PLNs detected in CAT patients might reflect not only the extent of current inflammation of the thyroid tissue but also subsequent destruction in CAT. TPOAb and TgAb titers at the time of diagnosis of patients who developed hypothyroidism at the end of year 5 were higher compared to patients who remained euthyroid while only the TgAb difference was statistically significant. TgAb-positive CAT patients may clinically present as euthyroid, subclinical, or with overt hypothyroidism. The role of TgAb in CAT progression is still not clear. Previous studies have demonstrated that immunological properties of TgAb such as immunoglobulin G subclasses (15), titers, and avidity (16) might be involved in CAT. Another study demonstrated that CAT patients with different thyroid functional status exhibit different Tg epitope recognition patterns (17). We found in our study that high TgAb titer, TSH, age, PLNs presence, and PLNs volume at the time of diagnosis were predictive of hypothyroidism development during the course of CAT. Similar to our results, a previous study has also reported that high titer of TgAb and advanced age could be a possible predictor of hypothyroidism in CAT (18).

Because healthy thyrocytes decrease over time, the risk of developing hypothyroidism at the end of 5 years is higher in CAT patients with high autoantibody levels, a marker of significant inflammation, and PLNs on the first examination. We are of the opinion that thyrocyte reserves were partially adequate in CAT patients with ongoing active inflammation, which we associated with the presence of PLNs persisting over a period of 5 years, and that these patients thus remained euthyroid after 5 years.

There are a limited number of publications on sonographic features of LNs in CAT. To the best of our knowledge, there is no study on the relationship of PLN presence and CAT course. In conclusion, CAT patients may present with inflammatory LNs, and PLNs might reflect not only the extent of current inflammation of the thyroid tissue but also subsequent destruction in CAT.

There were limitations to our study. Except for PLN size, features such as cortical thickness, type of vascularization, and contour of the lymph nodes were not evaluated. The development of hypothyroidism in a small number of patients in the 5th year is another limitation. Further studies of detailed sonographic features of PLNs with more patients are needed to clarify this subject.

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