



The association between thyroid malignancy and chronic lymphocytic thyroiditis: should it alter the surgical approach?

Zależności między występowaniem nowotworów tarczycy a przewlekłym limfocytarnym zapaleniem tarczycy: zmiana zasad leczenia chirurgicznego?

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Abstract

Background: The relation between thyroid neoplasms and chronic lymphocytic thyroiditis (CLT) is controversial. While it is accepted that focal lymphocytic thyroiditis develops secondarily to malignancy, it is not clear whether diffuse lymphocytic thyroiditis has a tendency to develop into thyroid cancer. The aim of this study was to investigate the relation between CLT and malignant tumours of the thyroid and evaluate the surgical approach to CLT cases.

Material and methods: In this study, 917 patients operated on for thyroid diseases were investigated retrospectively. Seventy-seven (8.4%) patients histopathologically diagnosed as having CLT (either non-specific or Hashimoto's thyroiditis) were investigated for any concurrent malignant neoplasm. Fifteen patients in whom CLT and thyroid malignancy were coexisting were included in the study.

Results: In the pathological evaluation of 917 cases, malignancy in the thyroid was found in 97 (10.6%) cases. Seventy-seven cases were categorised as CLT. Of these 77, 16 (20.8%) were Hashimoto's thyroiditis (specific CLT) and the other 61 (79.2%) were non-specific CLT. In 15 cases, thyroid malignancy was found to be concurrent with CLT. Of the malignancies, nine (60%) were papillary carcinoma, three (20%) medullary carcinoma, one (6.6%) follicular carcinoma, one (6.6%) Hurthle cell carcinoma, and one (6.6%) lymphoma. In our series, the rate of the development of malignancy against the background of CLT was 19.48%, while the rate in the groups without CLT was 9.76%, with a statistically significant difference between the groups ($p = 0.008$).

Conclusions: CLT cases should be evaluated more carefully in terms of malignancy. If a nodule is detected on thyroiditis, the minimal surgical intervention should be lobectomy. Total thyroidectomy should be considered as preferable to subtotal thyroidectomy because of its many advantages such as controlling thyroiditis, removing the probability of reoperation, and hormonal stability.

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Key words: thyroid cancer, thyroiditis, surgery

Streszczenie

Wstęp: Istnieją kontrowersje na temat zależności między występowaniem nowotworów tarczycy a przewlekłym limfocytarnym zapaleniem tarczycy (CLT). Wykazano, że ogniskowe limfocytarne zapalenie tarczycy rozwija się wtórnie do zmian nowotworowych, jednak nadal nie wyjaśniono, czy osoby z rozsianą postacią limfocytarnego zapalenia tarczycy mają skłonność do zapadania na raka tarczycy. Celem badania było określenie zależności między CLT i złośliwymi nowotworami tarczycy oraz ocena chirurgicznego leczenia CLT.

Materiał i metody: Retrospektywnie analizowano dane 917 chorych operowanych z powodu chorób tarczycy. Siedemdziesiąt siedem (8,4%) osób z histopatologicznie zdiagnozowanym CLT (nieswoiste zapalenie tarczycy lub choroba Hashimoto) przebadano pod kątem nowotworów tarczycy. Do analizy włączono 15 chorych, u których stwierdzono współwystępowanie CLT i nowotworu tarczycy.

Wyniki: Ocena histopatologiczna 917 przypadków wykazała zmiany nowotworowe tarczycy u 97 (10,6%) chorych, natomiast u 77 osób stwierdzono CLT. U 16 (20,8%) osób z tej grupy rozpoznano chorobę Hashimoto (swoiste CLT), natomiast u 61 (79,2%) chorych — CLT. U 15 pacjentów nowotwór tarczycy współwystępował z CLT. Wśród stwierdzonych nowotworów odnotowano 9 przypadków (60%) raka brodawkowatego, 3 przypadki (20%) raka rdzeniastego, 1 przypadek (6,6%) raka pęcherzykowego, 1 przypadek (6,6%) raka z komórek Hurtle'a i 1 przypadek (6,6%) chłoniaka. W niniejszej analizie częstość rozwoju nowotworu na podłożu CLT wynosiła 19,48%; natomiast w grupie bez CLT nowotwór rozwinął się u 9,76%; różnica między grupami jest statystycznie istotna ($p = 0.008$).

Wnioski: Należy z większą uwagą oceniać chorych z CLT ze względu na możliwość procesów rozrostowych. W przypadku wykrycia guzka u chorego z zapaleniem tarczycy minimalna interwencja chirurgiczna powinna obejmować lobektomię. Totalna tyroidektomia jest lepszym rozwiązaniem niż subtotalna tyroidektomia, ponieważ wiąże się z większymi korzyściami, do których należą kontrola zapalenia tarczycy, eliminacja ryzyka reoperacji i stabilizacja zaburzeń hormonalnych. (Endokrynol Pol 2011; 62 (4): 303-308)

Słowa kluczowe: nowotwór tarczycy, zapalenie tarczycy, leczenie chirurgiczne



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Introduction

Chronic lymphocytic thyroiditis (CLT, Hashimoto's thyroiditis, chronic autoimmune thyroiditis, lymphadenoid goitre) is an autoimmune inflammatory disease characterised by diffuse lymphoplasmocytic infiltration with occasional germinal centres, oncocytic metaplasia, interlobular fibrosis and parenchymal atrophy of thyroid tissue [1, 2]. Studies have found that CLT coexists with many other autoimmune diseases and malignant diseases of the thyroid gland [1–3]. It has been reported that Hashimoto's thyroiditis, the specific form of CLT, increases the tendency to the development of primary thyroid lymphoma, which is quite a rare disease, by 80 times [4]. Its causal relation with tumours of the thyroid which are of epithelial origin (especially papillary thyroid cancer), remains unclear.

Rudolf Virchow drew attention to the leukocytes in neoplastic tissues in 1863 and proposed that "lymphoreticular infiltration" in chronic inflammation regions is the origin of cancer. Recent studies into the relationship between tumour tissues and inflammation have supported Virchow's suggestion and opened up new horizons in preventing and treating cancer [5]. In inflammation, immune response develops as a consequence of the activation of chemokines, cytokines and growth factors, and damage occurs in stromal cells. In chronic inflammation, the cycle of repeated injury and healing provokes reactive alterations of stromal components which may lead to neoplastic transformation in epithelial cells.

The damage to stromal elements due to chronic inflammation does not contribute to neoplastic transformation, but chronic inflammation provokes in thyroid epithelial cells reactive alterations which may lead to neoplastic transformation.

The present study investigated the relationship between CLT and thyroid malignities, and evaluated the surgical approach to CLT.

Material and methods

In the present study, 917 patients operated on for thyroid diseases in I. General Surgery Clinic of Yıldırım Beyazıt Training and Investigation Hospital between 1999 and 2006 were investigated retrospectively. Seventy-seven (8.4%) patients who were pathologically diagnosed with CLT (either non-specific or Hashimoto's thyroiditis) were investigated in terms of concurrent thyroid malignancies in the I. Pathology Clinic at the same institution (*). Fifteen patients in whom chronic lymphocytic thyroiditis and thyroid malignancy were coexistent were included in the study.

Patients were evaluated with regard to age, sex, preoperative symptoms, preoperative anti-thyroid drugs

or levothyroxin use, plasma Anti-TPO (TPO Ab, Anti M), Anti-Tg (TgAb, Anti-T), thyroglobulin levels, Tc99m thyroid scintigraphy and thyroid ultrasonography, fine needle aspiration biopsy (FNAB), surgical intervention and postoperative complications.

CLT was diagnosed in the presence of stringent morphological criteria such as diffuse lymphoplasmocytic infiltration, lymph follicles, accentuation of lobulation, interlobular fibrosis and oncocytic metaplasia. Cases with focal lymphocytic thyroiditis were excluded from the study.

Data analysis was conducted using statistical software (SPSS Graduate Pack 14.0; SPSS Inc., Chicago, IL, USA). In analysis of this data, χ^2 test was used. With regard to the results, statistical significance was defined as $p \leq 0.05$.

Results

Of 917 patients treated surgically for thyroid diseases, 743 (81%) were female and 174 (19%) male. Female/male ratio was 4.27. In the examination of pathology specimens, malignancy was established in 97 patients. The mean age of all malignant cases was 47 ± 26.3 years and the female/male ratio was 4.1.

Of 77 (8.4%) patients with CLT, 66 (85.7%) were female with a female/male ratio of 6. Sixty-one patients were reported to have non-specific diffuse CLT, and 16 (20.7%) were reported to have Hashimoto's thyroiditis. In 15 (19.4%) patients, thyroid malignancy coexisting with CLT was found. Of these 15 patients, 13 (86.6%) were female, mean age 45 ± 7.77 years. Of the 15 patients, nine (60%) had papillary carcinoma, three (20%) medullary carcinoma, one (6.6%) follicular carcinoma, one (6.6%) Hurthle cell carcinoma and one (6.6%) lymphoma (Table I).

In our series, the rate of the development of malignancy against the background of CLT was 19.48%; in the group without CLT it was 9.76%, with a statistically significant difference between the groups ($p = 0.008$) (Table II). According to the presence of CLT with between types of thyroid cancer were not statistically significant differences. The difference of the presence of CLT with between medullary cancer was found $p = 0.07$.

The commonest complaints in patients with CLT associated malignancy were nervousness in ten patients (66%); pressure-related symptoms: five patients (33.3%) such as feeling suffocated, dyspnea, and dysphagia; and hyperthyroidism-related symptoms 5 (33.3%) such as palpitations and sweating. A family history of cancer or exposure to radiation was established in none of the patients. Of the 15 patients, five (33.3%) underwent an operation one month after receiving anti-thyroid drug treatment due to hyperthyroidism and becoming

Table I. Distribution of malignant cases between groups (n = 97)

Tabela I. Częstość nowotworów w zależności od obecności CLT (n = 97)

	Malignancy (n = 97)	CLT (+) Malignancy (n = 15)	CLT (-) Malignancy (n = 82)
Mean age	47 ± 26.3	45.2 ± 7.77	46.8 ± 26.2
Female/male ratio	4.1 (78/19)	6.5 (13/2)	5.58 (65/17)
Histopathology			
Papillary carcinoma	61 (62%)	9 (60%)	52 (63.4%)
Follicular carcinoma	12 (12.3%)	1 (6.6%)	11 (13.4%)
Hurthle cell carcinoma	10 (10.3%)	1 (6.6%)	9 (10.9%)
Medullary carcinoma	7 (7.2%)	3 (20%)	4 (4.9%)
Anaplastic carcinoma	6 (6.1%)	(-)	6 (7.3%)
Lymphoma	1 (1%)	1 (6.6%)	(-)

Table II. Malignancy according to the presence or absence

Tabela II. Występowanie nowotworów w zależności od obecności CLT

	Malignancy (+)		Malignancy (-)		Total	
	n	%	n	%	n	%
CLT (+)	15	19.4	62	80.5	77	8.4
CLT (-)	82	9.8	758	90.2	840	91.6
Total	97	10.6	820	89.4	917	100.0

$\chi^2 = 7.043$; $p = 0.008$

euthyroid. No patient underwent thyroid hormone replacement preoperatively.

In serologic examination of ten patients, in six (60%) Anti-TPO and in four (40%) Anti-Tg was found to be high. Thyroglobulin levels were high in all ten patients, and were over 300ng/ml in four (40%) of them.

In eight patients who underwent thyroid scintigraphy, heterogenous appearance consistent with thyroiditis was observed. While in one patient a single hyperactive nodule was seen, in five patients multiple hypoactive nodules were present.

Nodular hyperplasia was reported in 14 (94.4%) of the patients who underwent thyroid ultrasonography. A solitary nodule was present in nine (64.3%) patients and multiple nodules in five (35.7%) patients. Calcification was reported in two patients with a solitary nodule and in one patient with multiple nodules. In one patient, diffuse hyperplasia was observed by USG.

In FNAB evaluation of the ten patients with thyroid nodules in the preoperative period, cytological findings consistent with malignancy were reported in three patients (one was consistent with medullary cancer and two with papillary cancer). In five patients

(two with colloid nodule, two with nodular hyperplasia, and one with non-suspected cytological picture) benign findings were reported, and in two patients findings compatible with CLT were reported. When compared to postoperative pathology results, it was established that a correct diagnosis had been made in two patients, and in another two, although malignancy had been missed, a diagnosis of thyroiditis had been correctly made. The clinical characteristics of the patients are shown in Table III.

The indications for surgical intervention and the operations made are shown in Table IV. Six patients (40%) underwent completion thyroidectomy after the first operation, five due to papillary carcinoma and one due to medullary carcinoma. Preoperative cytological examination was reported as "benign" in three of these patients. In one patient in whom perijugular multiple lymph nodes were found on the side of the lesion, completion thyroidectomy and left functional neck dissection was performed. Central neck dissection was carried out on one patient with peritracheal lymph nodes and another with medullary carcinoma. Fifty-five patients underwent a total of 18 operations. Overall, six patients,

Table III. Clinical features of malignant cases coexisting with CLT (n = 15)**Tabela III.** Cechy kliniczne nowotworów złośliwych współwystępujących z CLT (n = 15)

Complaints	n (%)
Nervousness	10 (66)
Symptoms of pressure	5 (33.3)
Palpitations and sweating	5 (33.3)
Rapid growth	1 (6.6)
Hoarseness	1 (6.6)
Hormonal status	
Hyperthyroidism	5 (33.3)
Euthyroid	10 (66.6)
Serology (n = 10)	
Anti-TPO (> 20 IU/ml)	6/10
Anti-TgAb (> 20 IU/ml)	4/10
Thyroglobulin (> 300 ng/ml)	4/10
Thyroid scintigraphy (n = 8)	
Heterogeneity	6
Hypoactive nodule	5
Hyperactive nodule	1
Thyroid ultrasonography (n = 15)	
Diffuse hyperplasia	1 (6.6)
Nodular hyperplasia	14 (94.4)
Solitary	9 (64.3)
Multiple	5 (35.7)
Cervical lymphadenopathy	1 (6.6)
FNAB (n = 10)	
CLT	2
Benign	5
Malignant	3

three of whom had undergone first operations at different centres, underwent a completion thyroidectomy. One patient, who underwent completion thyroidectomy and a central neck dissection, developed permanent hypoparathyroidism. In another patient, hoarseness, which improved after four months, developed.

The pathological characteristics of patients are shown in Table V. Four patients had coexistent lymphocytic thyroiditis and multifocal papillary cancer. All patients were alive and disease-free after between four and ten years of follow-up.

Discussion

The relationship between CLT and thyroid malignancies was first suggested by the study of Dailey et al. in 1955

[6]. The prevalence of malignancy concurrent with CLT has been reported either by FNAB carried out in patients with high thyroid autoantibody titration [7, 8] or by examination of specimens from patients who underwent thyroidectomy [9–15]. In various series, the incidence of thyroid cancer developing against the background of CLT has been reported to be between 0.5% and 23% [7–14]. The meta-analysis by Singh et al. [11] reported that the prevalence of thyroid cancer was significantly higher in patients with Hashimoto's thyroiditis than in those without thyroiditis (odds ratio of 1.89). Repplinger et al. [15] reported that in Hashimoto's thyroiditis the prevalence of papillary cancer was significantly higher (9% vs. 36%, $p < 0.001$). In our series, the rate of malignancy development against the background of CLT was found to be 19.48%, but 9.76% in the group without CLT ($p = 0.008$). This result agrees with those of studies reporting malignancies concurrent with CLT in thyroidectomy specimens. In the series presented, the two-fold increase in malignancy prevalence suggests that CLT cases should be evaluated more carefully in terms of malignancy.

Although histopathologic criteria were used in the studies reporting high prevalence of malignancy in pathology specimens, the terms non-specific CLT and Hashimoto's thyroiditis were used interchangeably or without being distinguished, which may be related to the fact that these studies were carried out mostly by surgeons. Incidence studies carried out with FNAB are far from reflecting actual prevalence because pathologic correlation is not present. Establishing the real prevalence is quite difficult and can only be done through large prospective studies including clinical, radiological, serological, cytological and pathological evaluations.

The malignancy that most frequently coexists with CLT is papillary cancer [9–15]. In the series presented, papillary carcinoma was established in nine patients and medullary carcinoma in three patients. Total thyroidectomy and central neck dissection was carried out in one patient with medullary cancer after FNAB, and another patient whose subtotal thyroidectomy specimen disclosed medullary cancer. Few studies have investigated the relationship between CLT and medullary cancer. In some studies, medullary cancer cases concurrent with CLT have been reported [9, 10, 13, 16]. In our study, the difference of between the CLT with medullary cancer is not a statistically significant ($p = 0.07$). The number of patients with medullary cancer seems to be too small to find any difference. This difference may be significant in larger series.

In our series, CLT occurred six times more frequently in women. The prevalence of the disease increased in the fourth and fifth decades. The number of coexistent

Table IV. Indications for operation and surgical interventions

Tabela IV. Wskazania do leczenia chirurgicznego

Indications for operation	n (%)	
Hyperthyroidism	5 (33.3)	
Symptoms of pressure	5 (33.3)	
Malignancy or its suspicion	5 (33.3)	
Operation (no. of patients = 15)	First operation	Second operation
Total thyroidectomy	6	
Total thyroidectomy + central neck dissection	1	
Unilateral lobectomy*	2	
Unilateral lobectomy + isthmusectomy*	1	
Bilateral subtotal lobectomy**	3	
Near total thyroidectomy	2	
Completion thyroidectomy		4
Completion thyroidectomy + functional neck dissection		1
Completion thyroidectomy + central neck dissection		1

*patients operated on in our clinic who underwent completion thyroidectomy; **patients operated on in another centre who underwent completion thyroidectomy

Table V. Pathological characteristics of malignant cases coexisting with CLT (*)

Tabela V. Charakterystyka histopatologiczna nowotworów złośliwych współwystępujących z CLT

	Multifocal disease	Under 45 years	45 years and older	Stage
Papillary carcinoma	4	T1N0M0 (4)	T1N0M0 (2)	Stage I (7)
		T2N1bM0 (1)	T2N0M0 (1)	Stage II (1)
			T4aN0M0 (1)	Stage IVa (1)
Follicular carcinoma			T1N0M0	Stage I (1)
Hurthle cell carcinoma			T1N0M0	Stage I (1)
Medullary carcinoma		T1N1aM0 (1)		Stage I (2)
		T1N0M0 (2)		Stage III (1)
Lymphoma		Diffuse large B-cell lymphoma		Stage II#

*Number of patients shown in parenthesis; #Ann Arbor Classification

malignities is also absolutely higher in women. This preponderance has also been observed in other studies [9, 11, 13, 15, 17, 18].

While lymphocytic infiltration associated with malignancy is considered to indicate a favourable prognosis in hepatocellular cancer, melanoma, non small-cell lung cancer and transitional cell cancers of the bladder, it is regarded as a sign of an aggressive tumour in breast and renal cell cancers. Thyroid malignities, particularly papillary carcinoma, may occur along with lymphocytic infiltration. Kebebe et al. reported that the presence of lymphocytic infiltration was not an independent prognostic factor, and was not associated with a lower recurrence rate or a lower frequency of distant metastasis [19].

Lymphocytic infiltration accompanying malignancy is observed around the tumour and focally, unlike that in CLT. In CLT, lymphocytic infiltration is of diffuse structure and associated with follicular hyperplasia.

In a diagnosis of CLT, there are difficulties in the evaluation of FNAB in terms of oncocyctic cell and lymphocytic infiltration [20, 21]. In the series presented, although the diagnosis of CLT was made correctly in two patients, malignancy could not be reported in seven patients. In three patients, even though the diagnosis of malignancy was made, it could not be related to CLT.

Thyroid USG is a reasonably efficient examination method in detecting nodules in the thyroid larger than 3mm, in determining whether the nodules are

solid or cystic, in the follow-up of nodules, in imaging pathological cervical lymph nodes, and in obtaining a biopsy. If sonographic features of nodule includes solid, hypoechogenicity, punctuate microcalcifications, irregular or microlobulated borders and intranodular central vascularity or nodule associated with pathological lymphadenopathy it is deemed risky in terms of malignancy. In these cases, the biopsy is required. Even if the results of the biopsy are benign, these findings warrant histological diagnosis. Therefore, surgical intervention should be a serious option.

In the medical treatment of CLT, the suppression of thyroid-stimulating hormone (TSH) plays an important part in the treatment of all autoimmune thyroiditis cases. With levothyroxin, the size of the thyroid gland and autoantibody levels decrease considerably within two years [22]. In the presence of hyperthyroidism, anti-thyroid drugs and beta-blocker drugs with long lasting effects should be used. Treatment with radioactive iodine is another option in patients who experience a relapse [23].

If there is neoplasia accompanying CLT, surgical intervention is indicated if:

- the dominant nodule does not regress in spite of TSH suppression treatment (although the suppression of thyroid nodules with T4 is not recommended under ATA guidelines, it is a treatment applied in many centres);
- the thyroid gland continues to be enlarged despite thyroid suppression;
- findings suggesting malignancy such as radiation history, hoarseness, dysphagia, tracheal pressure or cervical lymphadenopathy are present;
- hyperthyroidism is present;
- FNAB is not helpful in diagnosis;
- cosmetic deformity is present [12, 16–18, 24].

Conclusions

CLT cases should be appraised more carefully in terms of malignancy. If a solitary nodule is detected against the background of thyroiditis, the minimal surgical intervention should be lobectomy. After pathological examination, further surgical interventions should be planned. In the presence of multiple nodules, total thyroidectomy should be preferred in case multifocal malignancy develops. In addition, total thyroidectomy

should be considered as preferable to lobectomy or subtotal thyroidectomy because of its many advantages such as controlling thyroiditis, removing the need for reoperation, and hormonal stability.

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