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The role of preoperative serum thyroglobulin and thyroid auto-antibody levels before histopathological diagnosis of thyroid cancers

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Aim: If a frozen section pathological examination is not performed in unilateral thyroid nodule surgery and the postoperative pathological diagnosis is cancer, a second operation may be required. Therefore, it was studied whether serum thyroid auto-antibody levels are useful or not in determining preoperative malignancy in patients with thyroid disorders.

Materials and methods: It was investigated retrospectively whether there was a correlation between preoperative serum thyroglobulin (Tg), anti-thyroglobulin antibody (anti-Tg), and anti-thyroid peroxidase antibody (anti-TPO) levels and thyroid cancer in patients who had undergone thyroidectomy.

Results: Two hundred and eighty-seven patients who had undergone thyroid surgery and whose preoperative serum levels of Tg, anti-Tg, and anti-TPO had been recorded were included in this study. Only 54 (18.8%) of the patients had a malignant diagnosis in the postoperative histopathological examination. Sixteen of the patients who had a postoperative malignant thyroid disease diagnosis (29.6%) had high serum Tg, anti-TPO, and/or anti-Tg levels. The rate of high serum Tg levels was significant in patients with a benign pathology (49.4% vs. 31.5%, P = 0.018).

Conclusion: It appears that preoperative measurement of serum Tg, anti-TPO, and anti-Tg levels is not a useful method to predict malign thyroid diseases.

Key words: Thyroid cancers, anti-thyroid antibodies, thyroglobulin

Tiroid kanserlerinin histopatolojik tanı öncesinde serum tiroglobülin ve tiroid oto-antikorları seviyelerinin rolü

Amaç: Unilateral tiroid nodül cerrahisi sırasında frozen section işlemi yapılamadığı durumlarda, kanser olması durumunda, hastaların yeniden ameliyat olması gerekebilmektedir. Bu nedenle, tiroid nodüllerinde preoperatif malignitenin tesbitinde, serum tiroid otoantikor seviyelerinin yeri araştırıldı.

Yöntem ve gereç: Retrospektif olarak, tiroidektomi yapılmış olan hastaların preoperatif serum tiroglobulin (Tg), anti-tiroglobulin antikoru (anti-Tg) ve anti-tiroid peroksidaz antikoru (anti-TPO) düzeyleri ile tiroid kanserleri arasında bir ilişki olup olmadığını araştırıldı.

Bulgular: İki yıl içinde preoperatif serum Tg, anti-Tg ve anti-TPO seviyeleri bakılmış ve tiroid cerrahisi yapılmış 287 hasta çalışmaya alındı. Hastaların sadece 54 (% 18,8)'ünde postoperatif histopatolojik tiroid malignitesi tanısı aldı. Postoperatif tiroid kanseri saptanan bu hastaların 16 (% 29,6) 'inde serum Tg, anti-TPO ve/veya anti-Tg seviyeleri yüksek bulundu. Yüksek serum Tg düzeyi saptanma oranı benign grupta yüksekti (% 49,4 vs % 31,5 , P = 0,018).

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Sonuç: Malign tiroid hastalıklarını önceden tahmin etmede serum Tg, anti-TPO ve anti-Tg seviyelerinin ölçümü yardımcı bir yöntem değildir.

Anahtar sözcükler: Tiroid kanserleri, anti-tiroid antikorları, tiroglobulin

Introduction

Thyroid cancer accounts for about 1% of all cancer types and progresses slowly (1). It is the second most common endocrinological cancer type, following ovary cancer (2). The prevalence of thyroid cancer is closely related with environmental factors and geographical distribution. Although having a good prognosis differentiated thyroid cancer has the potential to rarely induce metastases. Though in the past hyperthyroidism was considered a protector against thyroid cancer, this approach has now changed. In the literature rates up to 21% for the combination of hyperthyroidism and cancer have been reported (3,4).

Different markers have been used to investigate residual tissue presence and tumour recurrence in patients who have undergone surgery for thyroid cancer. As an example the measurement of serum thyroglobulin or calcitonin levels can be presented. In the literature it was underlined that in patients who been operated on for thyroid cancer, serum thyroglobulin and thyroglobulin antibody values could only be more useful than thyroglobulin values in the examination of persistent and recurrent cancers (5). Moreover, the sensitivity and specificity of fine needle aspiration biopsy in the evaluation of thyroid nodules are around 70% (6-8).

Since frozen section examination is not used as an intra-operative pathological evaluation in many hospitals, unilateral lobectomy is performed, especially in patients with unilateral nodular goitre and without any findings of macroscopic pathology in the opposite thyroid lobe during an operation. When postoperative pathology results reveal malignancy the patients undergo a second operation or complementary thyroidectomy (9,10).

If parameters used in the identification of postoperative residual tumour and recurrent tumour can also be used to determine the postoperative malignancy risk, it will be possible to perform the most suitable surgical intervention in only one session in patients with high risk of thyroid malignancy and thereby to avoid the risk of complications related with the second surgical operation. Therefore, we planned this retrospective study to investigate whether preoperative serum thyroid auto-antibody levels (anti-TG, anti-TPO, and TG) had predictive value for preoperative malignancy in patients with thyroid diseases in the many hospitals where preoperative frozen-section examination is not performed.

Materials and methods

Our study had a retrospective clinical study design. It included 287 consecutive patients who had undergone thyroidectomy in a single centre between January 2007 and December 2008 and whose preoperative serum Tg, anti-Tg, and anti-TPO levels had been measured. Surgical indications of the patients were giant nodules in 27 patients (9.4%), follicular carcinoma in 2 patients (0.69%), Graves' disease in 9 patients (3.13%), Hürthle-cell adenoma in 6 patients (2.09%), congenital hypothyroidism in 5 patients (1.74%), multinodular goitre in 52 patients (18.11%), suspicious nodules in 44 patients (15.33%), papillary carcinoma in 18 patients (6.27%), toxic diffuse goitre in 61 patients (21.25%), and toxic multinodular goitre in 63 patients (21.95%). After the pathological examination, preoperative serum Tg, anti-Tg, and anti-TPO levels of 54 patients with malign and 233 patients with benign nodules were assessed.

Serum auto-antibody levels were measured with an Immulite 2000 device and using the chemiluminesence immunometric assay method. Reference values for Tg were 0-55 ng/mL, for anti-Tg 0-40 IU/mL, and for anti-TPO 0-35 IU/mL.

For statistical analysis of the results obtained in this study, SPSS (Statistical Package for the Social Sciences) for Windows 16.0 was used. Mean, standard deviation, minimum and maximum values,

when necessary 95% confidence intervals, and for categorical variables numerical and percentage values were used to summarise the parameter values. In multiple comparisons ANOVA (one way analysis of variance) and for the comparison of 2 values Student's t test (independent sample t test) was used to determine the distribution of all variable groups. Cross tabulation statistics were used to compare categorical variables (chi-square, Fisher).

Results

Patient characteristics

In the study, 215 of the patients were (74.9%) female and 72 (25.1%) were male and the mean age was 45.21 ± 13.06 years (range, 17-79 years) (Table 1).

Postoperative histopathologic diagnosis

Postoperative pathologic examination results are given in Table 1. The results revealed benign diseases in 230 patients (81.2%) and malignant pathologies in 54 patients (18.8%). According to the postoperative pathological diagnoses, the elevation frequencies in diagnosis preoperative serum Tg, anti-Tg, and anti-TPO levels are shown in Table 2.

Serum anti-TPO, Tg, and anti-Tg levels and their relationship with the histopathologic examination results are given in Table 3. There were no significant differences between patients with nodules classified as benign and malignant patients according to the histological findings in terms of age or gender. In 115 patients (49.4%) among 233 with benign histopathological features high levels of serum Tg were identified, while in 17 patients (31.5%) among 54 with malignant histopathologic features high levels of serum were observed (P = 0.018). Seventy-three (31.3%) patients in the benign pathology cohort and 15 (27.8%) patients in the malign pathology cohort had elevated serum anti-TPO levels (P = 0.610). Sixty-two patients with a benign pathology (26.6%) had elevated serum anti-Tg levels compared with 14 patients with a malign pathology (25.9%) who had elevated serum anti-Tg levels (P = 0.918).

Discussion

Since widespread access to healthcare and technological advancements have contributed to the diagnoses of certain diseases, thyroid cancer is diagnosed more frequently and more extensive

Table 1. Patient characteristics by histopathological diagnosis.

Pathological diagnosis	Age	Gender	
	Year ± SD (range)	Female n (%)	Male n (%)
MNG	46.62 ± 13.16 (17-72)	111 (74.0)	39 (26.0)
HT	45.88 ± 13.16 (24-70)	28 (84.9)	5 (15.1)
FA	37.36 ± 14.29 (19-61)	12 (85.7)	2 (14.3)
DH	38.90 ± 12.19 (18-59)	13 (65.0)	7 (35.0)
TDG	39.7 ± 11.33 (26-55)	5 (55.6)	4 (44.4)
HHA	44.67 ± 13.44 (33-70)	5 (83.3)	1 (16.7)
GT	54 (54-54)	0 (0.0)	1 (100.0)
PTC	45.90 ± 12.14 (18-79)	37 (74.0)	13 (26.0)
FTC	40.00 ± 2.83 (38-42)	2 (100.0)	0 (0.0)
MTC	57.00 ± 9.90 (50-64)	2 (100.0)	0 (0.0)
P - value	**0.6**	**0.377**	

SD-standard deviation, MNG-multinodular goitre, HT-Hashimoto's thyroiditis, FA-follicular adenoma, DH-diffuse hyperplasia, TDG-toxic diffuse goitre, HHA-Hürthle cells adenoma, GT-granulomatous thyroiditis, PTC-papillary thyroid carcinoma, FTC-follicular thyroid carcinoma, MTC- medullary carcinoma.

Table 2. Normal or elevated serum anti-TPO, Tg, and anti-Tg levels according to histopathological diagnosis.

Pathological diagnosis	Anti-TPO, n (%)		Tg, n (%)		Anti-Tg, n(%)	
	Normal	Elevated	Normal	Elevated	Normal	Elevated
MNG	131 (87.3)	19 (12.7)	67 (44.7)	83 (55.3)	127 (84.7)	23 (15.3)
HT	6 (18.2)	27 (81.8)	25 (75.8)	8 (24.2)	10 (30.3)	23 (69.7)
FA	9 (64.3)	5 (35.7)	7 (50.0)	7 (50.0)	12 (85.7)	2 (14.3)
DH	8 (40.0)	12 (60.0)	13 (65.0)	7 (35.0)	12 (60.0)	8 (40.0)
TDG	1 (11.1)	8 (89.9)	4 (44.4)	5 (55.6)	5 (55.6)	4 (44.4)
HHA	4 (66.7)	2 (33.3)	2 (33.3)	4 (66.7)	4 (66.7)	2 (33.3)
GT	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)
PTC	36 (72.0)	14 (28.0)	36 (72.0)	14 (28.0)	36 (72.0)	14 (28.0)
FTC	2 (100.0)	0 (0.0)	1 (50.0)	1 (50.0)	2 (100.0)	0 (0.0)
MTC	1 (50.0)	1 (50.0)	0 (0.0)	2 (100.0)	2 (100.0)	0 (0,0)
P - value	**P = 0.000**		**P = 0.04**		**P = 0.000**	

MNG-multinodular goitre, HT-Hashimoto's thyroiditis, FA-follicular adenoma, DH-diffuse hyperplasia, TDG-toxic diffuse goitre, HHA-Hürthle cells adenoma, GT-granulomatous thyroiditis, PTC-papillary thyroid carcinoma, FTC-follicular thyroid carcinoma, MTC-medullary thyroid carcinoma.

Table 3. Comparison of elevated serum anti-TPO, Tg, and anti-Tg levels in benign (n = 233) and malignant (n = 54) pathology groups.

	Benign pathology	Malignant pathology	P - value
Age, mean ± SD	45.01 ± 13.30 (17-72)	46.09 ± 12.02 (18-79)	0.59
Gender (M/F)	174/59	41/13	0.849
Elevated anti-TPO, n (%)	73 (31.3)	15 (27.8)	0.610
Elevated Tg, n (%)	115 (49.4)	17 (31.5)	0.018
Elevated anti-Tg, n (%)	62 (26.6)	14 (25.9)	0.918

SD- standard deviation.

and higher numbers of surgical interventions are performed (2).

In cases where risk of preoperative malignancy is not well established, adequate surgical resection cannot be conducted, especially when an intraoperative frozen-section examination is not possible in patients scheduled for thyroidectomy. In such cases if the postoperative pathological assessment reveals thyroid cancer it will be possible to perform a second operation in this patient. The most significant

complication observed following thyroidectomy operations is hypocalcemia secondary to recurrent laryngeal and parathyroid gland damage (5-10). The likelihood of developing such complications is higher after the second operation. Therefore, it is advised to provide adequate surgical intervention in the first operation. New techniques that will help to predict the risk of thyroid malignancy in a more accurate way are required to avoid such undesirable conditions.

In Turkey in recent years thyroid cancer has been diagnosed more frequently and more extensive and higher numbers of surgical operations have been performed (9). Overall, treatment options to be used in thyroid diseases are surgery, medical treatment, and radioactive I-131 therapy. Suspicion of malignancy, pressure symptoms, hyperthyroidism, retrosternal goitre, and cosmetic reasons are among indications for thyroidectomy. Among them suspicion of malignancy is the most frequent indication in clinical practice (10-16).

However, since a preoperative frozen section examination is not performed in the majority of Turkey's hospitals, a second surgical operation can be performed based on the postoperative pathologic findings. Furthermore, patients are inevitably re-exposed to the risks associated with general anaesthesia, postoperative complications, cosmetic problems secondary to incision scar, hypocalcaemia risk, incision site infection, and such complications as recurrent laryngeal and superior laryngeal nerve damage.

Several methods are used to predict malignancy risk. Fine needle aspiration biopsy (FNAB) of the thyroid and ultrasonography (US) are the primary methods. Serum calcitonin levels are also an important marker for medullary thyroid cancer (17). In addition, serum calcitonin and carcinoembryonic antigen levels are used in the diagnosis of recurrent disease. A standard biochemical marker used in patients who have undergone thyroidectomy and been diagnosed with differentiated thyroid cancer in the pathological findings is serum thyroglobulin level (18).

In our study there was no significant difference in elevated preoperative serum anti-Tg and anti-TPO levels in patients with postoperative pathological benign and malignancy findings. The frequency of elevated serum Tg levels was significantly higher in patients diagnosed with benign nodules (49.4% vs. 31.5%, P = 0.018). In the literature there are some trials investigating the importance of serum anti-Tg levels in the monitoring of differentiated thyroid cancers. When a total tumour ablation was performed in differentiated thyroid cancer with elevated serum anti-Tg level, serum antibody levels were found to be markedly decreases in 6 months. However, it was shown that the interval for serum anti-Tg levels to restore in normal range could be prolonged. Therefore, the importance of the tendency of antibody levels to decrease over time was underlined in intermittent serial serum anti-Tg follow-up rather than the level of serum anti-Tg (19). In the monitoring of recurrent and residual diseases in differentiated thyroid malignancy, it is more meaningful to take into account the serum Tg and anti-Tg levels compared with serum Tg monitoring alone (5,18).

When serum Tg levels are not elevated, it was shown that the determination of permanently high serum anti-Tg levels can be utilised in diagnosing recurrent and residual differentiated thyroid carcinomas (20). Similarly, in the monitoring of a papillary thyroid cancer patient, even though serum Tg levels were too low to measure, high thyroid auto-antibody levels and TgmRNA (thyroglobulin m-RNA) presence in serum were confirmed and in the subsequent follow-up examinations it was reported that lymph node metastases had developed in this patient (21).

It was shown that incidence of elevated serum thyroid auto-antibody levels is significantly higher in Hashimoto's thyroiditis, Graves' disease, and subacute thyroiditis relative to other thyroid diseases (22). There have been some studies examining the relation between thyroid malignancy and thyroid autoimmunity. In the study by Fiore et al., although no difference was observed between patients with benign thyroid nodular disease and patients with papillary thyroid cancer, it was established that serum levels increased with increasing severity of lymphatic infiltrations in papillary thyroid cancer (23). These data support the idea that increased invasion level and increased immune response can co-exist in papillary thyroid cancer. In pathologically diagnosed

malignancies in our investigations, excluding the assessment of invasion parameters of tumours such as lymphatic infiltration level was considered the most important limiting aspect of the study.

In another study investigating the association between thyroid autoimmunity and thyroid malignancy, serum thyroid autoantibody levels in 570 patients who had undergone thyroidectomy, the presence of thyroid hypoechogenicity, and histological lymphatic infiltration on ultrasound were studied and it was reported that none of these parameters was related with malignancy. While thyroid auto-antibody was determined in 32/135 patients (23.7%) with thyroid cancer, autoantibody was observed in 90/435 patients (20.6%) with benign lesions and this difference was not significant (24). In other retrospective studies among patients with solitary thyroid nodules, the results of 197 patients with positive thyroid autoantibody and 393 patients with negative autoantibody obtained with ultrasound-guided FNAB were evaluated. FNAB findings were divided into 3 groups as benign, intermediate risk, and suspicious. The percentage of patients with malignant nodules was higher in the group with positive thyroid autoantibody (18.8% vs. 9.2%, $P < 0.001$). In this study a significant association between thyroid cancer and thyroid autoimmunity was established (25). In our study such an association was not observed.

In conclusion, no diagnostic value of preoperative serum Tg and thyroid autoantibody levels among patients with thyroid cancer was established and pathological assessment with intraoperative frozen-section analysis remains valuable. Prospective studies with new technological imaging or molecular marker identification techniques are required to obtain accurate preoperative diagnoses in thyroid cancers.

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