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Is Thyrotropin Receptor Antibody Positivity Associated with Cytology and Histopathology Results in Patients with Graves' Disease?

ABSTRACT

Objective: The effect of thyrotropin receptor antibody positivity on the cytology and histopathology of nodules developing on the basis of Graves' disease is unknown. The objective of this study was to evaluate the relationship between thyrotropin receptor antibody positivity and cytological and histopathological results in Graves' disease patients.

Methods: A total of 598 patients who underwent thyroidectomy due to Graves' disease and had preoperative thyrotropin receptor antibody levels were evaluated retrospectively. The study population was divided into 2 groups as thyrotropin receptor antibody-positive and -negative. Thyroid nodule cytology, histopathology results, and tumor characteristics in cases with thyroid cancer were compared between the groups.

Results: Thyrotropin receptor antibody was found as negative in 239 (40%) patients and positive in 359 (60%) patients. Cytological results were available in 363 nodules in the thyrotropin receptor antibody-negative and 185 nodules in the thyrotropin receptor antibody-positive group, and there was no significant difference between the groups in terms of cytology results ($P > .05$, all). Malignancy was detected in 13.4% of patients in the thyrotropin receptor antibody-positive group and in 13.8% patients in the thyrotropin receptor antibody-negative group ($P = .878$). There was no difference between the groups in terms of the incidence of papillary thyroid carcinoma ($P = .299$). The incidences of incidental carcinoma and microcarcinoma were similar in the groups ($P = .521$ and $P = .613$). There was no case with lymph node metastasis in both groups. Capsular invasion, vascular invasion, and extrathyroidal extension rates were similar between the groups ($P > .05$, all).

Conclusion: Contrary to the literature, we found that thyrotropin receptor antibody positivity did not increase the incidence of malignancy and did not affect cytology and histopathology results in Graves' disease patients.

Keywords: Cytology, Graves' disease, histopathology, thyrotropin receptor antibody

Introduction

Differentiated thyroid carcinoma (DTC) that originates from follicular thyroid cells is the most common endocrine malignancy. It accounts for 90% of all malignant thyroid lesions and the histological type is papillary thyroid carcinoma (PTC) in approximately 85% of cases.[1] The prevalence of DTC is increasing worldwide in recent years probably in relation with the widespread use of ultrasonography (US) and increased use of fine-needle aspiration biopsy (FNAB) which respectively can diagnose micronodules and microcarcinomas.[2-5]

Graves' disease (GD) is the most common cause of thyrotoxicosis.[6] There are controversies with regard to the rate and clinical course of DTC in patients with GD. It was previously reported that suppressed thyroid-stimulating hormone (TSH) in hyperthyroidism can be protective against thyroid cancer.[7] In addition, some clinicians even believed that the risk of thyroid cancer can be omitted in patients with hyperthyroidism.[8] Subsequent studies in the literature reported that thyroid cancer and hyperthyroidism could coexist, resulting in publication of more studies on the coexistence of these 2 diseases.[8-10]

Many studies have reported that the rate and aggressiveness of incidentally detected malignant thyroid lesions increase in GD. There are also reports that show local or distant metastasis of these small tumors in such patients.[10-12] In a study, patients with GD had a 3 times higher estimated risk for metastasis.[13] In addition, mortality was higher independent from primary tumor size.[10,11,14] Thyrotropin receptor antibodies (TRAbs) bind to the TSH receptor of the thyroid follicle cell and stimulate angiogenesis by increasing vascular endothelial growth

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factor, causing mitogenic and antiapoptotic effects. Some authors have proposed that thyroid-stimulating antibodies are related to the stimulation of malignant lesion and more aggressive behavior in thyroid carcinoma.[15,16] Despite all these studies, some studies have suggested that clinical features of DTC does not change in patients with and without GD.[17,18]

The previous literature examining the effect of TRAb on malignant thyroid lesions in patients with GD is limited. It is also unclear whether TRAb affects the nodule cytology in these patients. In this study, we aimed to evaluate the possible effect of TRAb positivity on the frequency of malignancy, FNAB and pathological findings, and tumor characteristics in patients with GD.

Materials and Methods

This study was designed as a retrospective cross-sectional study. The medical records of 598 patients who underwent thyroidectomy between January 2009 and December 2018 due to GD and had preoperative TRAb levels were screened retrospectively. Patients' preoperative data, TRAb levels, cytology, and final histopathology outcomes were recorded. In addition, histopathological type, microcarcinoma and incidentality rates, tumor characteristics (size, capsule and vascular invasion, extrathyroidal extension, and lymph node metastasis) were recorded in patients with thyroid cancer. Patients with TRAb levels above the reference value were classified as TRAb-positive and those below the reference value as TRAb-negative. The cytology, histopathology results, and tumor characteristics of the groups were compared. The study was approved by the medical ethics committee of Yıldırım Beyazıt University Faculty of Medicine (approval date and number: 2021/41) and in accordance with ethical standarts of Helsinki declaration.

Graves' disease was diagnosed when a patient had clinical findings supportive of hyperthyroidism and had suppressed TSH, elevated free triiodothyronine (fT4) or free thyroxine (fT3), and diffusely increased activity in the gland during scintigraphical examination. Thyrotropin receptor antibody positivity was not considered as essential for the diagnosis. Patients with a history of head and neck malignancy or radiation, patients who were under the age 18 years, and patients who were pregnanct were excluded. Surgical indications were hyperthyroidism refractory to medical treatment, development of side effects with antithyroid drugs, suspicious or malignant cytology results, compression symptoms related to enlarged goiters, presence of ophthalmopathy, and patient's preference.

Chemiluminescence methods (Immulite 2000, Diagnostic Products Corp., Los Angeles, Calif, USA and UniCel DXI 800, Beckman Coulter, Brea, Calif, USA) were used for the measurement of TSH, fT3, and fT4 levels. Thyrotropin receptor antibody was measured by radioimmunoassay method using a gamma counter.

An Esaote color Doppler US (Model 796FDII; MAG Technology Co. Ltd., Yung-Ho City, Taipei, Taiwan) and a superficial probe (Model LA523 13–4, 5.5–12.5 MHz) were used for thyroid US. Fine-needle aspiration biopsy was performed with a 27-gauge needle and 20-mL syringe under US guidance by experienced endocrinologists. Fine-needle aspiration biopsy indications were diameter >1 cm or presence of any suspicious US feature in nodules ≤1 cm. Suspicious features were determined as taller-than-wide shape, hypoechoic appearence, presence of irregular margins, and presence of microcalcification. All patients were informed about the FNAB procedure and informed consent was obtained. Fine-needle aspiration biopsy specimens were classified according to the Bethesda classification: non-diagnostic (ND), benign, atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS), follicular neoplasm (FN)/suspicious for follicular neoplasm (SFN), suspicious for malignancy (SM), and malignant.

Histopathological results were classified as benign and malignant. Thyroid cancer was categorized as follows: PTC, follicular thyroid cancer (FTC), hurthle cell thyroid cancer (HCTC), medullary thyroid cancer (MTC), anaplastic thyroid cancer (ATC), and thyroid tumors of uncertain malignant potential (TT-UMP).

Statistical Analysis

Statistical Package for the Social Sciences version 21.0 for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Whether continuous variables were distributed normally or not was examined by Shapiro–Wilk's test. Median (minimum-maximum) values were given since there were non-normally distributed variables. Number and percent of categorical variables were presented. The difference between groups was examined by Pearson's chi-square test and Fisher's exact test for the categorical variables and Mann–Whitney U test for the continuous variables. Statistical significance was accepted when $P < .05$.

Results

Data of 598 patients were analyzed. Thyrotropin receptor antibody was negative in 239 (40%) and positive in 359 (60%) patients. There were 62 males and 177 female patients in TRAb-negative group, and 127 male and 232 female patients in TRAb-positive group. The median ages of TRAb-negative and TRAb-positive groups were 45 (18-80) years and 41 (18-76) years, respectively ($P = .015$ and $P < .001$). Thyroid-stimulating hormone level was significantly lower and fT3 was significantly higher in the TRAb-positive compared to the TRAb-negative group ($P = .018$ and $P = .001$), while the mean fT4 level was similar ($P = .137$).

In the preoperative US evaluation, 352 patients had no nodule, 74 patients had 1 nodule, and 172 patients had ≥2 nodules. Fine-needle aspiration biopsy outcome was available in 363 nodules in the TRAb-negative and 185 nodules in the TRAb-positive group. The cytology results of the 2 groups were given in Table 1 ($P > .05$).

The histopathology of 81 (13.6%) of 598 patients was malignant. In the TRAb-negative group, the histopathology results of 206 (86.2%) patients were benign and 33 (13.8%) patients were malignant; in the TRAb-positive group, 311 (86.6%) patients were benign and 48 (13.4%) patients were malignant, and the difference was not

MAIN POINTS

- The effect of thyrotropin receptor antibody positivity on malignant thyroid lesions in patients with Graves' disease is limited.
- It is not known whether thyrotropin receptor antibodies affect thyroid nodule cytology and aggressive behavior in thyroid carcinoma.
- In this article, we found that thyrotropin receptor antibody positivity did not affect cytology and histopathology results and was not associated with aggressive tumor behavior in patients with Graves' disease.

Table 1. Comparison of Demographic Characteristics, Laboratory Findings, and Cytology Results of Graves' Disease Patients with Positive and Negative Thyrotropin Receptor Antibodies

	TRAb-Negative	TRAb-Positive	
	n = 239	n = 359	*P*
Age (years)	45 (18-80)	41 (18-76)	**<.001**
Gender (male/female) (n)	62/177	127/232	**.015**
TSH (μIU/mL)	0.17 (0.001-21.00)	0.050 (0.001-38.00)	**.018**
fT3 (pg/mL)	3.40 (1.19-18.60)	3.66 (1.64-32.00)	**.001**
fT4 (ng/dL)	1.23 (0.27-4.43)	1.14(0.07-6.93)	.137
Nodules with FNAB	**n = 363**	**n = 185**	
Cytology (n,%)			
ND	81 (22.31)	52 (28.10)	.135
Benign	258 (71.07)	113 (61.08)	.068
AUS/FLUS	19 (5.23)	13 (7.02)	.513
FN/SFN	1 (0.27)	1 (0.54)	1.000
SM	3 (0,82)	4 (2,16)	.233
Malignant	1 (0,27)	2 (1,08)	.265

TRAb, thyrotropin receptor antibody; TSH, thyroid-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; FNAB, fine-needle aspiration biopsy; ND, non-diagnostic; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for follicular neoplasm; SM, suspicious for malignancy.

statistically significant ($P = .878$). Papillary thyroid carcinoma was found in 30 patients, FTC in 2 patients, and TT-UMP in 1 patient in the TRAb-negative group, while PTC was found in 47 patients, and HCTC in 1 patient in the TRAb-positive group ($P = .299$ for PTC). There were no patients with MTC or ATC. The median tumor diameter was measured as 8 mm and 5.5 mm in the TRAb-negative and -positive groups, respectively ($P = .238$). The groups had similar rates of incidentality and microcarcinoma ($P = .521$ and $P = .613$). In addition, the rates of capsular invasion, vascular invasion, and extrathyroidal extension did not change significantly between groups (for all $P > .05$). There was no patient with lymph node metastasis in the groups (Table 2).

Table 2. Comparison of the Histopathology Results and Tumor Characteristics of the Groups

	TRAb-Negative	TRAb-Positive	
	n = 239	n = 359	*P*
Histopathology (n,%)			
Benign	206 (86.19)	311 (86.62)	.878
Malignant	33 (13.80)	48 (13.37)	
Tumor type (n,%)			
PTC	30 (90.90)	47 (97.91)	.299
FTC	2 (6.06)	-	NA
HCTC	-	1 (2.08)	NA
TT-UMP	1 (3.03)	-	NA
Tumor size (mm)	8 (1-37)	5.5(1-25)	.238
Incidental (n,%)	20 (60.60)	31 (64.58)	.521
Microcarcinoma (n,%)	19 (57.27)	28 (58.33)	.613
Capsular invasion (n,%)	3 (9.09)	5 (10.41)	.490
Vascular invasion (n,%)	1 (3.03)	1 (2.08)	.495
Extrathyroidal extension (n,%)	2 (6.06)	3 (6.25)	.395
Lymph node metastasis (n,%)	-	-	-

TRAb, thyrotropin receptor antibody; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; HCTC, hurthle cell thyroid cancer; TT-UMP, thyroid tumors of uncertain malignant potential; NA, not applicable.

Table 3. Comparison of PTC Variants Between Groups

	TRAb-Negative	TRAb-Positive	
	(n = 30)	(n = 47)	*P*
PTC variant (n,%)			
Classical	24 (80)	37 (78.72)	.908
Follicular	1 (3.33)	4 (8.51)	.389
Oncocytic	3 (10)	3 (6.38)	.690
Tall cell	0	1 (2.12)	NA
Encapsulated follicular	2 (6.66)	1 (2.12)	.568
Encapsulated oncocytic	0	1 (2.12)	NA

TRAb, thyrotropin receptor antibody; PTC, papillary thyroid cancer; NA, not applicable.

The classical PTC was the most common variant in both groups (80% vs 78.7%) and the distribution of PTC variants was similar in both groups. While there was 1 patient with tall cell variant in the TRAb-positive group, no patient had tall cell variant in the TRAb-negative group (Table 3).

Discussion

There are conflicting results regarding the prevalence, aggressiveness, and long-term outcomes of DTC in patients with GD.[12,19] While some studies report that the prevalence, aggressiveness, and mortality of DTC are increased in patients with GD, others report that the prevalence and clinical course of DTC in patients with and without GD are similar.[12,17,20,21] Thyrotropin receptor antibody has been suggested to play role in the development of thyroid cancer based on in vitro studies, which have been supported by some clinical studies but not others.[16,17,19,22,23] Due to conflicting findings in the literature, we evaluated the effect of TRAb positivity on cytology, histopathology, and tumor characteristics in patients with GD and found that TRAb-positive and -negative patients had similar features.

Ultrasonography is the gold standard method used for the evaluation of thyroid gland and detection of thyroid nodules.[1,24] Shi et al[25] identified thyroid nodules with US in 39% of 233 GD patients who underwent thyroidectomy and reported that these nodules were benign in 41%, AUS in 31%, SFN or suspicious for hurthle cell neoplasm in 13%, SM in 6%, and malignant in 9% of these patients.[25] In another study involving 66 GD patients with thyroidectomy, the incidence of thyroid nodules was determined as 77%, and it was determined that 27% of the patients had a solitary nodule and 50% multiple nodules. In the same study, it was found that most of the cytological outcomes of 47 nodules subjected to FNAB were benign or in the AUS/FLUS categories.[26] Premoli et al[27] reported that preoperative thyroid volumes were higher and palpable nodule rates and number of FNABs were lower in DTC patients with GD compared to those without GD (72.5% vs 41.1%; 89.1% vs 51.8%, respectively). In our study, while 58.9% of our patient group had no nodules on US,

solitary nodules were detected in 12.4% and ≥2 nodules in 28.8% of the patients. Fine-needle aspiration biopsy was performed on a total of 548 nodules and cytology results were determined as ND in 24.3%, benign in 67.7%, AUS/FLUS in 5.8%, FN/SFN in 0.4%, SM in 1.3%, and malignant in 0.6% of these nodules. There was no significant difference between cytology outcomes of TRAb-positive and -negative patients.

There are some evidence that a malignant focus can be stimulated and a more aggressive behavior can be induced by the TRAb in thyroid cancer.[15,16] Thyrotropin receptor antibody was blamed for increased aggressiveness of DTC in patients with GD owing to the growth and angiogenesis-promoting effects of it.[28] There are studies reporting that the titers of thyroid-stimulating immunoglobulin (TSI) are similar between GD patients with and without PTC; however, the effect of TSI Ab in the proliferation of thyroid cells may be independent of its titers.[29] In our study, malignancy rates of TRAb-negative and TRAb-positive patients were found to be similar (13.8% vs 13.4%). In addition, the types of thyroid cancer did not change between the groups. Premoli et al[27] showed that histological findings were similar in DTC patients with and without GD, and the most common histological variant of PTC was classical in 2 groups. Similarly, the classical variant of PTC was observed the predominant variant in both TRAb-positive and TRAb-negative patients in our study. The distribution of PTC variants was similar in both groups. While tall cell variant was observed only in 1 patient in the TRAb-positive group, no tall cell variant was observed in the TRAb-negative group.

It is not rare to detect incidental carcinomas in patients with GD.[26] You et al[26] detected malignancy in 55% of patients who had thyroidectomy due to GD and reported that 30% of these tumors were incidental. Premoli et al[27] also reported that the incidences of incidental thyroid cancer and microcarcinoma were higher in those with GD than in those without (76% vs 37% and 60% vs 37%). In our study, 63% of thyroid cancer cases were incidental and 58% were microcarcinomas. It was determined that TRAb positivity did not affect the incidentality and frequency of microcarcinoma.

Premoli et al[27] reported that stages and extrathyroid extension rates were similar between DTC patients with and without GD. You et al[26] also reported that 14% of the study group had aggressive pathological features. Central lymph node metastasis was found in 12%, extrathyroidal extension in 6%, and diffuse sclerosing tumor variant in 1.5% of the patients. In another study, although the incidence of tall cell carcinoma and multifocality in GD patients was higher than those with euthyroid goiter, there was not any statistical significance and TNM stages were similar between euthyroid goiter with PTC and GD patients with PTC.[29] In our study, 9.9% of patients with thyroid carcinoma had capsular invasion, 2.5% had vascular invasion, and 6.2% had extrathyroidal extension. Lymph node metastasis was not observed in any of the patients. Due to our study design, these rates could not be compared with patients without GD. However, the effect of TRAb positivity on these rates was evaluated and no difference was observed between TRAb-negative and -positive groups.

This study has some limitations. Since our study aimed to evaluate the effect of TRAb positivity on cytology and histopathology in patients with GD, our study population consisted of only TRAb-positive or -negative GD patients who underwent thyroidectomy. Patients with euthyroid nodular/multinodular goiter were not included in the study. Although there are studies in the literature comparing malignancy rates in patients with euthyroid goiter and GD, TRAb levels were not measured in the euthyroid groups and the effects on malignancy were not investigated in these studies.[29,30] In 1 of these studies, incidences of micro-PTC were found in 28% of the euthyroid goiter group and in 26% of the GD group, whereas the TSI ab titer was measured only in the GD group and did not predict micro-PTC. Another limitation of our study is that long-term follow-up data of patients with malignancy could not be reached since our study was retrospective.

In conclusion, although the frequency of thyroid cancer in GD was evaluated previously, there are limited data on the effect of TRAb positivity on the frequency of thyroid carcinoma and preoperative cytological outcomes. In our study, the effect of TRAb positivity on both cytology and histopathology and tumor characteristics was evaluated in GD patients. It was determined that TRAb positivity did not affect the frequency of malignancy, cytology, and histopathology results. Although it has been reported that there may be a relationship between TRAb positivity and aggressive tumor characteristics, in our study, TRAb-positive and -negative groups had similar aggressive tumor variants and tumor characteristics such as capsular, vascular, and extrathyroidal invasion. In addition, no lymph node metastasis was detected in any patient with GD. Based on these findings, it could be said that TRAb positivity has no effect on cytology and histopathology results in GD patients. However, further extensive studies are needed on this subject.

Ethics Committee Approval: The study was approved by the medical ethics committee of Yıldırım Beyazıt University Faculty of Medicine (No: 2021/41).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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