ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2020;(1):234-241 // 10.5505/amj.2020.79553

THYROTROPHIN RECEPTOR ANTIBODY IS NOT ASSOCIATED WITH THYROID CANCER IN PATIENTS WITH TOXIC NODULAR AND MULTINODULAR GOITER

TOKSİK NODÜLER VE MULTİNODÜLER GUATRLI HASTALARDA TİROTROPİN RESEPTÖR ANTİKORU TİROİD KANSERİ İLE İLİŞKİLİ DEĞİLDİR

Cevdet Aydın[1], Husniye Baser[1], Neslihan Cuhaci[1], Didem Ozdemir[1], Abdussamed Yalcın[2], Elif Ozdemir[3], Reyhan Ersoy[1], Bekir Cakir[1]

[1]Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara

[2]Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of General Surgery, Ankara

[3]Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Nuclear Medicine, Ankara

Yazışma Adresi / Correspondence:
Hüsniye Başer (e-mail: drhusniyebaser@yahoo.com.tr)

Geliş Tarihi (Submitted): 25.07.2019 // Kabul Tarihi (Accepted): 18.11.2019

Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

ANKARA MEDICAL JOURNAL

Öz

Amaç: Graves hastalarında tiroid kanser sıklığı ve agresifliği ile yüksek tirotropin reseptör antikor (TRAb) düzeyleri arasında ilişki bildirilmiştir. Bu ilişki toksik nodüler guatr (TNG) ve toksik multinodüler guatrlı (TMNG) hastalarda araştırılmamıştır. Biz, TNG ve TMNG'li hastalarda, tiroid kanseri ile TRAb arasındaki ilişkiyi araştırmayı amaçladık.

Materyal ve Metot: TNG ve TMNG nedeniyle tiroidektomi olan hastalar retrospektif olarak değerlendirildi. Toplam 370 hastadan, TRAb düzeyi mevcut olan 191 TMNG ve 30 TNG hastası çalışmaya dahil edildi.

Bulgular: 221 TNG/TMNG'li hastanın 24'ünde (%10,86) TRAb pozitif bulundu. Histopatolojik değerlendirmede, 71 (%32,13) hasta malign, 150 (%67,87) hasta benigndi. 71 malign hastanın 7'sinde (%9,86) ve 150 benign hastanın 17'sinde (%11,33) TRAb pozitifti (p=0,742). Yaş, cinsiyet, serum tirotropin, serbest triiodotironin, serbest tiroksin düzeyleri, anti-tiroid peroksidaz ve anti-tiroglobulin antikor pozitifliği ile histopatolojik tümör tipi açısından TRAb pozitif ve negatif hastalar arasında fark yoktu (sırasıyla p=0,393, p=0,401, p=0,403, p=0,903, p=0,877, p=0,788, p=0,540 ve p=0,357). TRAb pozitif 7 (%29,17) hastada ve TRAb negatif 57 (%28,93) hastada papiller tiroid kanseri (PTK) saptandı (p=0,357). Klasik varyant PTK, TRAb pozitif 5 (%71,43) hastada ve TRAb negatif 50 (%87,72) hastada mevcuttu (p=0,242).

Sonuç: Bu çalışmada, TMNG/TNG'li hastalarda TRAb pozitifliğinin malignite riskini artırmadığı görüldü.

Anahtar Kelimeler: Tirotropin reseptör antikor, toksik nodüler guatr, toksik multinodüler guatr, tiroid kanseri.

Abstract

Objectives: Increased thyrotrophin receptor antibody (TRAb) was associated with thyroid cancer risk and aggressivity in patients with Graves disease. This relation was not investigated in patients with toxic nodular goiter (TNG) and toxic multinodular goiter (TMNG). We aimed to evaluate association between TRAb and thyroid cancer in patients with TNG and TMNG.

Materials and Methods: Patients who underwent thyroidectomy with a preoperative diagnosis of TNG and TMNG were reviewed retrospectively. Among 370 patients, TRAb was available in 191 TMNG and 30 TNG patients.

Results: TRAb was positive in 24 (10.86%) of 221 patients with TNG/TMNG. Histopathological result was malignant in 71 (32.13%) and benign in 150 (67.87%) patients. TRAb was positive in 7 (9.86%) of 71 malignant and 17 (11.33%) of 150 benign patients (p=0.742). Age, sex, serum thyrotrophin, free triiodothyronine, free thyroxine, anti-thyroid peroxidase and anti-thyroglobulin positivity, and histological tumor type did not differ between patients with positive and negative TRAb (p=0.393, p=0.401, p=0.403, p=0.903, p=0.877, p=0.788, p=0.540, and p=0.357, respectively). There was papillary thyroid cancer (PTC) in 7 (29.17%) patients with positive TRAb and 57 (28.93%) patients with negative TRAb (p=0.357). The variant of PTC was classical in 5 (71.43%) patients with positive and 50 (87.72%) patients with negative TRAb (p=0.242).

Conclusion: In this study, we showed that TRAb positivity did not increase the risk of malignancy in patients with TNG/TMNG.

Keywords: Thyrotrophin receptor antibody, toxic nodular goiter, toxic multinodular goiter, thyroid cancer.

Introduction

Hyperthyroidism is a common endocrine disorder that can be seen due to many different causes. The most common cause of hyperthyroidism is Graves disease in regions with high iodine intake, while toxic multinodular goiter (TMNG) is also an important cause in regions with moderate or severe iodine deficiency.[1] Graves disease is an autoimmune disease in which thyrotrophin (TSH) receptor stimulating antibodies are the primary cause of hyperthyroidism.[2] In low iodine intake populations, TMNG is suggested to develop from nontoxic nodular disease with time. As hormonal secretion from the autonomous nodule increases, hyperthyroidism ensues. However, it was reported that some autonomous nodules are monoclonal and develop secondary to activating point mutations in TSH receptor coding genes.[3,4]

Thyroid cancer incidence has increased in recent years all over the world.[5] Exposure to ionizing radiation, iodine excess or deficiency, increased use of imaging methods and early diagnosis of microcarcinomas (≤1 cm) all contribute to this increased incidence.[6,7] Approximately, 75-80% of thyroid cancers are papillary thyroid cancer (PTC).[8,9] In the literature, there are reports suggesting an association between serum TSH and PTC. The risk of PTC was shown to be low in patients with low TSH and high in patients with high TSH.[10] In addition to TSH, thyrotrophin receptor antibody (TRAb) was also reported to play role in the stimulation of angiogenesis and growth and invasiveness of thyroid cancer by increasing vascular endothelial growth factor, placental growth factor and upregulating the receptors of these growth factors.[11,12] The association between thyroid cancer and TRAb in patients with Graves disease was investigated in some previous studies.[13] However, to our knowledge, the literature does not include any study that evaluated this association in patients with TMNG or toxic nodular goiter (TNG). In this study, our aim was to evaluate the possible relation between TRAb and thyroid malignancy in patients with TMNG and TNG.

Materials and Methods

Medical records of 370 patients who had TMNG or TNG and underwent total thyroidectomy between 2007 and 2014 in our center were retrospectively reviewed for the study. TRAb was measured preoperatively in 191 patients with TMNG and 30 with TNG. The demographical characteristics, laboratory findings, thyroid autoantibodies, TRAb levels and histopathological results of the patients were recorded.

Serum TSH, free triiodothyronine (fT3), free thyroxine (fT4), antithyroid peroxidase antibody (anti-TPO) and antithyroglobulin antibody (anti-Tg) were measured by chemiluminescence method (Immulite 2000, Diagnostic Products Corp., Los Angeles, CA, USA ve UniCel DXI 800, Beckman Coulter, Brea, CA). The normal levels were 0.4-4.0 μIU/mL for serum TSH, 1.57-4.71 pg/mL for fT3, 0.61-1.12 ng/dL for fT4, < 10 U/mL for

antiTPO and <30 U/mL for antiTg. TRAb was measured by radioimmunoassay method using a gamma counter and levels above the reference range was defined as positive.

Esaote color doppler ultrasonography (US) (796FDII model; MAG Technology Co.Ltd., Yung-Ho City, Taipei, Taiwan) and a superficial probe (LA 523 13-4 model, 5.5-12.5 mHz) were used for thyroid US. The diameter, localization, echogenicity, structure, presence of microcalcification, macrocalcification and peripheral halo, and marginal regularity of nodules were determined.

Thyroid scintigraphy was performed with a gamma camera and a pinhole collimator using 185 MBq (5 mCi) Tc-99m pertechnetate. Anterior and left/right anterior oblique images were evaluated. The distance between the pinhole collimator and the neck of the patient was 10 centimeters. Variation of the function of different areas of the thyroid was evaluated and focal areas of increased and decreased function were compared with background thyroid activity. The localization of nodules in US was matched with uptake in scintigraphy. When the uptake in the nodule was lower than the normal surrounding thyroid tissue, it was defined as hypoactive and when it was higher, it was defined as hyperactive. Nodules with similar radioactivity as the other parts of the thyroid were considered as normoactive. In a patient with hyperthyroidism, when there was a hyperactive nodule and suppressed thyroid gland, TNG was diagnosed. When there was increased uptake in more than one nodule as well as hypoactive areas, TMNG was diagnosed.

Postoperative histopathological results were classified as benign and malignant. Thyroid malignancies were classified as PTC, follicular thyroid cancer (FTC), poorly differentiated thyroid cancer (PDTC), medullary thyroid cancer (MTC) and thyroid tumors of uncertain malignant potential (TT-UMP).

The institutional review board approved the study (Approval date: 23.12.2015, number: 26379996-278) in accordance with the ethical standards of Helsinki declaration.

Statistical analysis

All data were analyzed by SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). Kolmogorov Smirnov test was used to test the distribution of continuous variables. Continuous variables were expressed as median (minimum-maximum). The number (%) of categorical variables were determined. The comparisons between groups were performed by Mann-Whitney U test. Pearson chi-square test was performed to compare categorical variables. Statistical significance was defined as a p value <0.05.

Results

The mean age of 221 patients with TNG/TMNG was 54.00 (23.00-79.00) years. There were 149 (67.42%) female and 72 (32.58%) male patients. Anti-TPO and anti-Tg were positive in 15 (8.43%) and 17 (9.09%) patients, respectively. TRAb positivity was observed in 24 (10.86%) patients. Histopathological diagnosis was malignant in 71 (32.13%) and benign in 150 (67.87%) patients. TRAb was positive in 7 (9.86%) of malignant patients and 17 (11.33%) of benign patients (p=0.742).

Table 1. Comparison of patients with positive and negative thyrotrophin receptor antibody in toxic nodular/multinodular goiter

	TRAb positive (n=24)	**TRAb negative (n=197)**	**P**
Age (year) [Median (min-max)]	54.00 (35.00-72.00)	54.00 (23.00-79.00)	0.393
Sex [n (%)] **Male** **Female**	 6 (25) 18 (75)	 66 (33.50) 131 (66.49)	0.401
TSH (µIU/mL) [Median (min-max)]	0.02 (0.00-0.70)	0.01 (0.00-0.73)	0.403
fT3 (pg/mL) [Median (min-max)]	4.21 (3.02-14.25)	4.36 (2.04-16.20)	0.903
fT4 (ng/dL) [Median (min-max)]	1.65 (0.93-3.99)	1.50 (1.05-5.16)	0.877
Anti-TPO positivity* [n (%)]	2 (10)	13 (8.23)	0.788
Anti-Tg positivity [n (%)]**	1 (5.26)	16 (9.52)	0.540
Malignant histopathology	**n=7**	**n=64**	
PTC [n (%)]	7 (100)	57 (89.06)	0.357
FTC [n (%)]	0	5 (7.81)	-
PDTC [n (%)]	0	1 (1.56)	-
TT-UMP [n (%)]	0	1 (1.56)	-
Lymph node metastasis	0	3 (4.69)	-

TRAb: thyrotropin receptor antibody, TSH: thyrotrophin, fT4: free thyroxine, fT3: free triiodothyronine, anti-TPO: anti-thyroid peroxidase antibody, anti-Tg: anti-thyroglobulin antibody, PTC: papillary thyroid cancer, FTC: follicular thyroid cancer, PDTC: poorly differentiated thyroid cancer, TT-UMP: thyroid tumors of uncertain malignant potential

*n=20 for TRAb positive, n=158 for TRAb negative

** n=19 for TRAb positive, n=168 for TRAb negative

Table 2. Variants of papillary thyroid cancer in patients with positive and negative thyrotrophin receptor antibody in toxic nodular/multinodular goiter

Papillary thyroid cancer	TRAb positive (n=7) (%)	TRAb negative (n=57) (%)	p
Classical	5 (71.43)	50 (87.72)	0.242
Follicular	0	6 (10.53)	-
Oncocytic	1 (14.29)	1 (1.75)	0.072
Tall cell	1 (14.29)	0	-

TRAb: thyrotropin receptor antibody

Clinical and histopathological characteristics of TNG/TMNG patients with positive and negative TRAb were compared in Table 1. The mean age was 54.00 (35.00-72.00) years in TRAb positive and 54.00 (23.00-79.00) years in TRAb negative patients (p=0.393). Serum TSH, fT3 and fT4 levels did not differ in two groups (p=0.403, p=0.903 and p=0.877, respectively). Anti-TPO and anti-Tg positivities were similar in two groups (p=0.788 and p=0.540, respectively). 7 (29.17%) patients with positive TRAb had malignant histopathology and all were PTC. Among patients with negative TRAb, malignant histopathology was observed in 64 (32.49 %) patients and 57 (89.06%) of these had PTC, 5 (7.81%) had FTC, 1 (1.56%) had PDTC and 1 (1.56%) had TT-UMP. There was no significant difference in the rate of PTC between patients with positive and negative TRAb (p=0.357). 3 (4.69%) patients with negative TRAb had lymph node metastasis.

The variants of PTC were determined in patients with TNG/TMNG (Table 2). In TRAb positive group, 5 (71.43%) patients had classical, 1 (14.29%) had oncocytic and 1 (14.29%) had tall cell variant PTC. In TRAb negative group, the variants of PTC were classical in 50 (87.72%), follicular in 6 (10.53%) and oncocytic in 1 (1.75%) patient. Rates of classical and oncocytic variant PTC were similar in TRAb positive and negative patients (p= 0.242 and p= 0.072, respectively)

Discussion

The risk of thyroid cancer was reported to increase with increased TSH in patients with nodular thyroid disease. In addition, it is known that TSH stimulation plays an important role in the progression of PTC.[14-16] It was suggested by some authors that low TSH secondary to thyroid autonomy might prevent the ability of mutated oncogenes to cause cancer.[17] This led to the hypothesis that low TSH in patients with TMNG/TNG might decrease the risk of incidental thyroid cancer.[18] However, a metanalysis showed that the incidences of thyroid cancer were 5.9% in 2150 patients with TMNG and 4.8% in 873 patients with TNG, which were similar to the incidences in nontoxic patients with multinodular and nodular goiter.[18] In the present study, because we included TNG/TMNG patients with available TRAb levels, the malignancy rate can not represent all patients with TNG/TMNG. However, in a previous study from our center, the malignancy rate in TNG and TMNG patients was 24.7%.[19]

The number of studies evaluating TRAb in patients with TMNG is limited. Pederson et al found positive TRAb in 97 of 106 patients with Graves, 15 of 94 with TMNG and 1 of 100 healthy subjects. There was not any patient with positive TRAb and nontoxic goiter. Thyroid volume and nodule number were similar in TMNG patients with positive and negative TRAb, while fT3, fT4, anti-TPO and anti-Tg positivities were higher in patients with positive TRAb.[20] In another study of 100 patients with TMNG, TRAb was positive in 12.0% of patients and complications after radioactive iodine therapy was higher in these patients.[21] In the present study, TRAb positivity in surgically treated TNG/TMNG patients was 10.9% and TSH, fT3, fT4 levels and anti-TPO and anti-Tg positivities were similar in patients with positive and negative TRAb.

Although differentiated thyroid cancer (DTC) has a favorable prognosis, persistent or recurrent disease can be seen in a limited number of patients. Thus, it is important to determine patients who require more aggressive treatment. To date, very few studies have investigated the relationship between TRAb and thyroid malignancy. Ergin et al reported that TRAb levels were not useful to predict micropapillary thyroid cancer in patients with Graves disease.[13] To our knowledge, there is not any previous study that evaluated the association between TRAb and malignancy in patients with TNG/TMNG. We found similar malignancy rates in TNG/TMNG patients with positive and negative TRAb. Although the difference was not statistically significant, classical variant PTC was lower in patients with positive TRAb. Xie et al showed that PTC patients with lymph node metastasis had higher TRAb compared to patients without lymph node metastasis and suggested that TRAb positivity was one of the risk factors for lymph node metastasis.[22] However, in our study, there were 3 patients with lymph node metastasis and all had negative TRAb levels.

TMNG occurs due to increased secretion of thyroid hormones from multiple hyperfunctioning nodules. In a patient with multinodular goiter, Graves disease may also develop. In this situation, it is difficult to distinguish Graves from TMNG. High prevalence of multinodular goiter in countries with moderate-low iodine intake may be problematic in this context. Pederson et al reported that TMNG patients with positive TRAb had more serious hyperthyroidism than patients with negative TRAb. They suggested that patients diagnosed with TMNG and positive TRAb probably had concomitant Graves disease and functional or nonfunctional thyroid nodules.[20] This study concluded that measurement of TRAb in patients with newly diagnosed hyperthyroidism might help to differentiate and identify TMNG patients with a different clinical course, particularly in low iodine intake regions.[20]

The main limitation of our study was its retrospective design and TRAb was not available in all patients with TNG/TMNG. This study included TNG/TMNG patients who underwent thyroidectomy and it is known that radioactive iodine is one of the treatment approaches in these patients. TRAb levels in patients who received RAI therapy and possible effects of TRAb on the effectiveness and complications of this treatment modality are not known.

In the present study, TRAb positivity was similar in benign and malignant patients with TNG/TMNG. The distribution of thyroid cancer type did not differ in TRAb positive and negative patients. Future prospective studies will help to clarify the possible relation between TRAb and malignant thyroid diseases in patients with TNG/TMNG.

Conflicting interest/financial disclosure: The authors declare that they have no conflict of interest.

References

1. Laurberg P, Pedersen KM, Vestergaard H, Sigurdsson G. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area vs. high incidence of Graves' disease in the young in a high iodine intake area: Comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. J Intern Med 1991;229:415-20.
2. Rees Smith B, Rickards CR, Davies Jones E, et al. The thyrotropin receptor and its role in Graves' disease. J Endocrinol Invest 1985;8:175-82.
3. Paschke R, Tonacchera M, Van Sande J, Parma J, Vassart G. Identification and functional characterization of two new somatic mutations causing constitutive activation of the thyrotropin receptor in hyperfunctioning autonomous adenomas of the thyroid. J Clin Endocrinol Metab 1994;79:1785-9.
4. Tonacchera M, Agretti P, Chiovato L, et al. Activating thyrotropin receptormutations are present in nonadenomatous hyperfunctioning nodules of toxic or autonomous multinodular goiter. J Clin Endocrinol Metab 2000;85:2270-4.
5. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014;140:317-22.
6. Davies L, Morris LG, Haymart M, et al; AACE Endocrine Surgery Scientific Committee. American Association of Clinical Endocrinologists and American College of Endocrinology disease state clinical review: the increasing incidence of thyroid cancer. Endocr Pract 2015;21:686-96.
7. He LZ, Zeng TS, Pu L, Pan SX, Xia WF, Chen LL. Thyroid hormones, autoantibodies, ultrasonography, and clinical parameters for predicting thyroid cancer. Int J Endocrinol 2016; 2016:8215834.
8. Mazzaferri EL, Young RL. Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. Am J Med 1981;70:511–8.
9. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995. Cancer 1998;83:2638–48.

10. Fiore E, Vitti P. Serum TSH and risk of papillary thyroid cancer in nodular thyroid disease. J Clin Endocrinol Metab 2012;97:1134-45.
11. Belfiore A, Garofalo MR, Giuffrida D, et al. Increased aggressiveness of thyroid cancer in patients with Graves' disease. J Clin Endocrinol Metab 1990;70:830-5.
12. Filetti S, Belfiore A, Amir SM, et al. The role of thyroid-stimulating antibodies of Graves' disease in differentiated thyroid cancer. N Engl J Med 1988;318:753-9.
13. Ergin AB, Saralaya S, Olansky L. Incidental papillary thyroid carcinoma: clinical characteristics and prognostic factors among patients with Graves' disease and euthyroid goiter, Cleveland Clinic experience. Am J Otolaryngol 2014;35:784-90.
14. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab 2006;91:4295-301.
15. Kim SS, Lee BJ, Lee JC, et al. Preoperative serum thyroid stimulating hormone levels in well-differentiated thyroid carcinoma is a predictive factor for lateral lymph node metastasis as well as extrathyroidal extension in Korean patients: a single-center experience. Endocrine 2011;39:259-65.
16. Gerschpacher M, Göbl C, Anderwald C, Gessl A, Krebs M. Thyrotropin serum concentrations in patients with papillary thyroid microcancers. Thyroid 2010;20:389-92.
17. Fiore E, Rago T, Provenzale MA, et al. Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role. Endocr Relat Cancer 2009;16:1251-60.
18. Negro R, Valcavi R, Toulis KA. Incidental thyroid cancer in toxic and nontoxic goiter: Is TSH associated with malignanCy rate? Results of a meta-analysis. Endocr Pract 2013;19: 212-8.
19. Dirikoç A, Fakı S, Başer H, et al. Thyroid malignancy risk in different clinical thyroid diseases. Turk J Med Sci 2017;47:1509-19.
20. Pedersen IB, Knudsen N, Perrild H, Ovesen L, Laurberg P. TSH-receptor antibody measurement for differentiation of hyperthyroidism into Graves' disease and multinodular toxic goitre: a comparison of two competitive binding assays. Clin Endocrinol (Oxf) 2001; 55:381-90.
21. Nygaard B, Faber J, Vejle A, HegeduEs L, Hansen JM. Transition of nodular toxic goiter to autoimmune hyperthyroidism triggered by 131 I therapy. Thyroid 1999;9:477-81.
22. Xie Y, Liu YW, Wang MY, et al. Risk factors of lymph node metastasis in patients with thyroid papillary carcinoma associated with Graves disease. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2016;38:554-8.