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Original Research

An Analytical Comparison of Papillary Thyroid Carcinoma Patients Manifested with or without Graves' Disease

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Abstract

Objectives: There is still no clear relationship between the presence of Graves' disease (GD) and the development of papillary thyroid carcinoma. The aim of this study was to compare the clinicopathologic features of patients diagnosed with papillary thyroid carcinoma (PTC) with thyroid nodules and GD and patients with PTC with thyroid nodules but without autoimmune thyroid disease.

Methods: The study was designed in a retrospective manner and included a cohort of 239 patients with PTC who underwent total thyroidectomy. Age at diagnosis, disease stage, PTC subtypes, tumor size, radioactive iodine use, nodule ultrasonographic features, and risk of PTC recurrence were compared between patients with and without GD.

Results: Of 239 patients, 99 (41%) had GD, while 140 patients (without autoimmune thyroid disease) had only PTC. The tumor diameter was significantly smaller in the group with PTC + GD (1.45±1.28 cm vs. 1.81±1.34 cm, $p<0.05$). Significantly lower multifocal involvement rates were observed in the PTC + GD group compared to PTC-only group ($p<0.05$). The prevalence of the classic papillary thyroid carcinoma subtype was higher in patients without autoimmune thyroid disease (39% vs. 25.7%, $p<0.05$). Ultrasonographic features of nodules with GD and PTC do not have different characteristics from those of nodules with PTC without GD.

Conclusion: The risk of structural recurrence at the time of diagnosis appears to be similar when PTC is accompanied by GD as compared to PTC alone. Furthermore, the presence of smaller tumor sizes and less multifocality in GD-PTC coexistence may indicate a better prognosis.

Keywords: Graves' disease, papillary thyroid cancer, thyroid nodule

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Thyroid cancer, which is the most prevalent endocrine malignancy, has experienced a 300% increase in incidence worldwide over the last thirty years. In addition, the incidence rate among females is three times that of males.[1,2] Graves' disease (GD) is an autoimmune thyroid disease.[3] Patients with Graves' disease with certain characteristics may benefit more than surgical intervention, including goiters that cause significant compression, failure to remission with antithyroid drugs, significant side effects from antithyroid drugs or those with nodules with malignant potential.[4,5] Thyroid carcinomas can also be seen with GD. This condition may manifest itself clinically or may be accidentally detected. It is widely acknowledged that papillary thyroid carcinoma (PTC) is the most prevalent form of thyroid cancer with GD.[4] The prevalence of coincidental PTC in patients with Graves' disease can range from 0% to 10%. The risk of

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thyroid cancer is nearly five times higher in these patients compared to those with GD but without a thyroid nodule.[6-8] It is widely believed that Virchow discovered the relationship between inflammation and carcinogenesis in cancer tissues in 1863 and associated the two with the development of cancer.[7] The literature indicates contradictory information on the possible relationship between thyroid-stimulating hormone receptor antibodies and the progression of thyroid carcinoma in individuals with GD. However, the exact pathophysiological paths of this process remain mysterious. However, recent literature has not been able to establish a correlation between GD and a tendency for aggressive thyroid cancer.[6] Knowing the clinical difference between PTC that develops in the presence of GD and nodules and PTC that develops without GD will be an important guide for clinicians in terms of follow-up of patients. We aimed to analyze the differences between patients with Graves' disease who had thyroid nodules and papillary thyroid carcinomas and patients who had euthyroid and non-autoimmune thyroid nodules and papillary thyroid carcinomas.

Methods

The study included a cohort of 99 patients who underwent total thyroidectomy and were identified as having papillary thyroid cancer with Graves' disease and nodules. Of the 140 patients who underwent total thyroidectomy and were diagnosed with PTC and had non-GD non-autoimmune euthyroid suspicious nodules were also included. A retrospective analysis was conducted on the clinicopathological characteristics of the patients both before and after the surgery. Patients older than 18 years with nodules associated with Graves' disease who underwent total thyroidectomy with a pathology diagnosis of papillary thyroid carcinoma and patients who underwent surgery for euthyroid non-autoimmune multinodular goiter with a pathology diagnosis of papillary thyroid carcinoma were included in the study. Patients younger than 18 years of age, those with a history of previous radiotherapy to the neck region, and those who had been previously followed up for another cancer were excluded from the study. The following patient characteristics were documented: age, sex, pathological diagnosis and subtype, radioactive iodine treatment and dose, status of post-ablative screening, preoperative and 1-, 6-, and 12-month postoperative TSH, T4, thyroglobulin, and antithyroglobulin levels. Four criteria were used to establish the diagnosis of Graves' disease: pathological specimen diagnosis as diffuse hyperfunctioning thyroid tissue and TSH receptor antibody (TSHRab) positivity and diffuse thyroiditis ultrasonographic features and thyroid scintigraphy findings of GD.[9] We assessed the prognostic parameters, including tumor diameter, number of nodules, presence or absence of nodules, focality (multifocal or unifocal), lymph node metastasis (yes or no), invasion of the thyroid capsule, and extrathyroidal invasion. Furthermore, we noted the subtypes of PTC (microcarcinoma, follicular, classic, tall cell, oncocytic, trabecular, diffuse sclerosing, Warthin-like subtype), as well as the results of post-ablative 6th month screening. The study was approved by Gaziantep University Clinical Research Ethics Committee According to the decision dated 17/11/2021 and numbered 2021/349. Informed consents were obtained. The study design was organized in accordance with the Declaration of Helsinki.

Statistical Analysis

The Shapiro-Wilk test was employed to assess the numerical variables' adherence to the normal distribution. A non-parametric statistical instrument was utilized to compare the data of two distinct groups, the Mann-Whitney U test. To compare variables with normal distributions between the two groups, the U-test was applied. The variables were analyzed using two-way repeated-measures analysis of variance across multiple time intervals and groups. In order to examine the relationships between categorical variables, the chi-squared test was applied. The statistical software SPSS 22.0 for Windows (Armonk, New York: IBM Corp.) was employed to analyze the data. A level of significance of $p<0.05$ was deemed suitable.

Results

The characteristics of the patients are detailed in Table 1. There was no statistically significant difference observed between the two groups regarding nodule size, nodule echogenicity, nodule margin irregularity, or the presence of microcalcification in ultrasound ($p>0.05$), as shown in Table 2. Regarding PTC subtypes, the classical subtype ex-

Table 1. General characteristics of the patients

	Groups		
	GD+PTC Mean	PTC Mean	p
Age (Year)	51.12±12.62	52.14±13.35	0.366
Gender			
Male	15(14.4)	37(26.1)	0.003*
Female	84(85.6)	103(73.9)	
TSH (mU/mL)	1.86±1.81 (202)	2.1±7.71 (200)	0.026*
fT4(µg/dl)	1.02±0.28 (202)	0.99±0.25 (200)	0.802
Tumor diameter (cm)	1.45±1.28 (202)	1.81±1.34 (198)	0.001*
Nodule count	2.69±2.01 (99)	3.12±2.45 (140)	0.223
Nodule diameter (cm)	27.2±13.62 (99)	31.86±17.48 (140)	0.039*

p<0.05, *Mann Whitney U test; GD: Graves' disease; fT4: Free Thyroxine; TSH: Thyroid stimulating hormone; PTC: Papillary thyroid carcinoma.

Table 2. Comparison of thyroid nodules' characteristics

	GD+PTC, n (%)	PTC, n (%)	p
Nodule diameter			
<2 cm	33 (33.7)	38 (27.1)	0.316
2-4 cm	43 (43.9)	59 (42.1)	
>4 cm	23 (22.4)	43 (30.7)	
Nodule echogenicity			
Hypoechoic	33 (33.7)	39 (27.9)	0.333
Hyperechoic	12 (12.2)	10 (7.1)	
Mixechoic	45 (45.9)	77 (55)	
Isoechoic	8 (8.2)	14 (10)	
Nodule margin irregularity	33 (33.7)	42 (30)	0.548
Microcalcification	24 (24.5)	31 (22.1)	0.672

p<0.05, * chi-square test; GD: Graves' Disease; n: Number of parameters; PTC: Papillary thyroid carcinoma.

hibited the most pronounced distinction between the two groups, as its prevalence was significantly higher in the PTC group (p=0.009). On all patients, total thyroidectomy was performed. In the GD+PTC group, 87.52% of patients underwent radioactive iodine therapy during the postoperative period, compared to 98% in the PTC group (p>0.05). A total of 93% of patients in the GD+PTC group did not exhibit any activity involvement during the 6-month postoperative screening. Activity involvement was not detected in 97.8% of the PTC group patients. There was no statistically significant difference observed in the 6-month postoperative screening results between the two groups (p>0.05). No statistically significant difference was observed between the two cohorts regarding extrathyroidal involvement, vascular invasion, or lymph node invasion (p>0.05). Significantly less multifocal involvement was observed in the GD+PTC group compared to the PTC group (p=0.008). When tumor size was compared between the two groups, the GD+PTC group exhibited a significantly smaller tumor size (p=0.001) (Table 3).

Discussion

The prognostic significance of the correlation between thyroid cancer and Graves' disease remains uncertain. The correlation between thyroid cancer and Graves' disease can be obvious or incidentally identified. Estimated occurrence rate of Graves' disease and thyroid cancer has divergent rates in various studies. Boutzios et al. reported a PTC incidence rate of 33.7% in patients who underwent total thyroidectomy for Graves' disease. Ergin et al. found a slightly lower incidence rate of 29.2%, while Pazaitou-Panayiotou et al. reported an incidence rate of 21.1%.[10-12] Given these rates, it appears likely that physicians specializing in thyroidology may frequently encounter this association in their daily clinical practice. It is still unclear how the prognostic features of patients with GD with thyroid nodules and PTC after surgery differ from those of patients with PTC without GD. It is believed that thyroid receptor antibodies, known to boost thyroid cell proliferation and activity in response to TSH-like signals, contribute to the development of GD in patients.[13] However, it is not clearly known whether these antibodies cause thyroid malignancy or lead to a different prognosis in patients with PTC. However, in the literature, there are reports that the presence of focal or diffuse lymphoid infiltration in Graves' disease increases the risk of developing PTC.[14] In the presence of GD, there is an increased risk of PTC multifocality, according to a 2019 meta-analysis. While some research has indicated that GD-associated PTC with favorable characteristics may still display aggressive behavior, another study contends that this correlation should only be discussed when PTC is at least 1 cm.[15] According to the results of this study, the cohort with GD and PTC together had lower multifocality and smaller tumor size compared to the cohort with PTC alone. A potential positive prognostic indicator for patients diagnosed with papillary carcinoma and Graves' disease is the observation of reduced multifocality and smaller tumor size. This could be since Graves' disease exhibits more pronounced symptoms during its early stages, necessitating clinicians to conduct an ultrasound examination earlier. Furthermore, the increased frequency of routine ultrasound examinations in patients with Graves' disease may have made it possible to detect PTC at smaller sizes. The frequency of the tall cell subtype, which possesses aggressive biological behavior among the PTC subtypes, did not differ significantly. Recently, there have been numerous revisions to the diagnostic criteria pertaining to the follicular subtype of PTC.[16] In this study, patients diagnosed with noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and invasive encapsulated follicular variant PTC were excluded due to different categorizations in the WHO 5th edition. There is a lack of consensus in the literature regarding the differences in ultrasonographic characteristics between nodules with papillary thyroid carcinoma (PTC) that coexist with Graves' disease (GD) and nodules with PTC without GD. Chung et al.[17] compared the USG characteristics of thyroid cancers in patients with GD to those of patients without GD who had thyroid cancer. It was revealed that thyroid cancer nodules in GD presented greater hypervascularity and lower hypoechogenicity in comparison to nodules with cancer not in GD. In a multicenter study of 15,259 patients, no difference was found in terms of ultrasonographic features.[18] In this study, there were no significant differences ob-

Table 3. Clinicopathological and prognostic variables comparison of the goups

	Groups		
	GD+PTC, n (%)	PTC, n (%)	p
Nodule diameter	27.2±13.62 (99)	31,86±17.48 (140)	0.039*
Tumor diameter			
<2 cm	144 (71.29)	119 (59.50)	0.035*
2-4 cm	46 (22.77)	60 (30.0)	
>4 cm	12 (5.94)	21 (10.50)	
Multifocality	123 (60.9)	146 (73.4)	0.008*
Capsule Invasion			
Yes	84 (41.6)	88 (44.4)	0.563
No	118 (58.4)	110 (55.6)	
Extrathyroidal Invasion			
Yes	15 (7.4)	13 (6.5)	0.726
No	187 (92.6)	186 (93.5)	
Lymph node invasion			
Yes	29 (14.36)	23 (11.50)	0.394
No	173 (85.64)	177 (88.50)	
Distant Metastasis			
Yes	0 (0.0)	0 (0.0)	1.000
No	202 (100.0)	200 (100.0)	
Vascular Invasion			
Yes	2 (0.99)	0 (0,0)	0.159
No	200 (99.01)	200 (100.0)	
ATA structural recurrence risk**			
Low risk	98	90	0.566
Intermediate risk	20	34	
High risk	29	23	
Subgroup of PTC			
Classic	52 (25.74)	78 (39)	0.009*
Infiltrative Follicular	29 (14.36)	26 (13)	
Tall cell	20 (9.9)	24 (12)	
Diffuse sclerosing	1 (0.5)	1 (0.5)	
Trabecular(solid)	4 (1.98)	10 (5)	
Oncocytic	5 (2.48)	4 (2)	
Warthin-like	4 (1.98)	0 (0)	
Postablative 6th month screening			
No activity in screening	147 (93)	136 (97.8)	0.126
T Stages			
T1-T2	178 (88.12)	164 (82.0)	0.086
T3-T4	24 (11.88)	36 (18.0)	
N Stages			
N0	175 (86.63)	176 (88.0)	0.681
N1	27 (13.37)	24 (12.0)	
M Stages			
M0	202 (100.0)	200 (100.0)	1.000
M1	0 (0.0)	0 (0.0)	

p<0,05. * chi-square test ** 2015 American Thyroid Association Management Guidelines, Papillary thyroid carcinoma; GD: Graves' disease, PTC: Papillary thyroid carcinoma n: number.

served among the groups in terms of microcalcification characteristics, nodule diameter, echogenicity, or marginal irregularity. Retrospective design and representing patients in a single center are the limitations of the study.

Conclusion

In conclusion, ultrasonographic features of nodules with GD and PTC do not have different characteristics from those of nodules with PTC without GD. The risk of structural

recurrence at the time of diagnosis appears to be similar when PTC is accompanied by GD as compared to the presence of PTC alone. PTC patients with Graves' disease had lower tumor sizes and less multifocality at the time of diagnosis as compared to PTC patients with euthyroid and non-autoimmune thyroid nodules. Therefore, the GD-PTC association may be a harbinger of a more favorable prognosis.

Disclosures

Patient Informed Consent: This study has the informed consents of the all patients

Ethics Committee Approval: The study was approved by Gaziantep University Clinical Research Ethics Committee (Number: 2021/349, Date: 17.11.2021).

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