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Coexistence of Primary Hyperparathyroidism and Differentiated Thyroid Carcinoma: Is It a Coincidence?

ABSTRACT

Objective: Coexistence of primary hyperparathyroidism and differentiated thyroid carcinoma has been reported from time to time. However, the clinical features and risk factors of this association are unclear. In this study, we aimed to evaluate the relationship between primary hyperparathyroidism and differentiated thyroid carcinoma.

Methods: The files of patients who were diagnosed with parathyroid adenoma and underwent parathyroid surgery in the endocrinology outpatient clinic between January 2015 and June 2021 were reviewed retrospectively. The clinical signs, biochemical abnormalities, and histological features of the patients were analyzed.

Results: This study included 255 patients who were operated on with the diagnosis of parathyroid adenoma. When the ultrasonography reports of the patients were evaluated, thyroid nodules were detected in 100/255 (39.2%) patients. When the postoperative histology of the patients was evaluated, differentiated thyroid carcinoma was detected in 35/255 (13.7%) patients. Parathormone and calcium levels were found to be significantly lower in patients with differentiated thyroid carcinoma compared to patients with benign thyroid nodules ($P < .05$). In logistic regression analysis, there was a significant correlation between the presence of differentiated thyroid carcinoma and low serum calcium level (odds ratio: 0.031; 95% CI: 0.001-0.654; $P = .035$). In the receiver operating characteristic curve analysis, we found that serum calcium level <11.05 mg/dL in patients with parathyroid adenoma has good capacity to differentiate differentiated thyroid carcinoma from benign thyroid nodule (area under the curve: 0.648, $P = .032$, 71.4% sensitivity, and 72.7% specificity).

Conclusion: We can say that the incidence of thyroid nodules increases in parathyroid adenoma compared to the general population and the probability of differentiated thyroid carcinoma increases as the calcium level decreases in these nodules.

Keywords: Calcium, parathyroid adenoma, thyroid cancer

Introduction

Primary hyperparathyroidism (PHPT) is present in 0.04%-0.1% of the general population, and parathyroid adenoma occurs in 75%-85% of PHPT patients.[1,2] Although the pathological association between parathyroid and thyroid diseases is common, the combination of parathyroid adenoma and differentiated thyroid carcinoma (DTC) is rare.[3] Differentiated thyroid carcinoma with PHPT has been reported in 2%-18% of patients who undergone surgery for PHPT.[2] On the other hand, previous reports mostly consist of small series and case reports.[4] The coexistence of PHPT and DTC is rare, and PHPT was usually considered as the primary pathology and was diagnosed before the identification of the thyroid carcinoma that was usually diagnosed in a pathology specimen as an incidental finding after parathyroid surgery. Such a phenomenon would further complicate the management process, especially with the need for a second surgery[2]; therefore, a good preoperative diagnostic method will be required. It is controversial whether the relationship between parathyroid adenoma and DTC is coincidental (genetic factors, head and neck region irradiation, parathormone, and calcium may play a role in the pathogenic mechanism).[5-7] The aim of this study is to evaluate the relationship of parathyroid adenoma with DTC.

Materials and Methods

The study protocol was prepared according to the Declaration of Helsinki, and ethical approval received from the ethical committee of Erzurum Regional Training and Research hospital (2021/21-272). Our study is a retrospective, cross-sectional study. The files of patients

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who were diagnosed with parathyroid adenoma in the endocrinology outpatient clinic between January 2015 and June 2021 were reviewed retrospectively. Patients diagnosed with parathyroid adenoma and undergoing parathyroid surgery were included in the study.

Age, gender, serum calcium, 24-hour urine calcium, serum phosphorus, parathyroid hormone (PTH), 25-hydroxy vitamin D (VD), alkaline phosphatase (ALP), thyroid peroxidase antibody (anti-TPO), free thyroxine (FT4), thyroid-stimulating hormone (TSH), bone densitometers, thyroid ultrasonography, fine-needle aspiration biopsy results from sonographically risky nodules in thyroid ultrasonography, and postoperative histology were evaluated. All patients included in the study had hyperparathyroidism and hypercalcemia due to primary hyperparathyroidism. Evaluation of 24-hour urinary calcium levels of all patients was done, and cases with familial hypocalciuric hypercalcemia were excluded from the study.

All ultrasonography was performed by a single physician. Nodules, number, diameter, location, marginal arrangement, echogenicity, and blood supply characteristics were evaluated. Fine-needle aspiration biopsies and postoperative histology were evaluated by 2 experienced pathologists.

The patients had no risk factors for thyroid cancer according to the American Thyroid Association 2015 guidelines (exposure to head and neck radiation, family history of thyroid cancer, and history of thyroid cancer).[8]

Patients with medullary thyroid cancer in the postoperative histological examination were excluded from the study (1 patient had medullary thyroid cancer and 1 patient had c-cell hyperplasia, and these patients were excluded from the study).

Statistical Analysis

We performed all statistical analyses using Statistical Package for the Social Sciences software for Windows version 22.0 (IBM Corp.; Armonk, NY, USA). All categorical variables were presented as frequencies and percentiles. All continuous variables were presented as mean ± standard deviation, except for data that did not have a normal distribution, which were expressed as medians (interquartile ranges). All categorical variables were presented as proportions. Comparisons of the means and proportions were performed with independent samples *t*-test and the chi-square test. Multivariate logistic regression analyses were used to investigate the association between DTC and parathyroid adenoma. A receiver operating characteristic (ROC) analysis was conducted to determine the capacity of the clinical and biochemistry markers to predict DTC in PHPT patients with thyroid nodules. $P < .05$ was considered statistically significant.

Results

A total of 255 patients (214 female and 41 male) who were operated on with the diagnosis of parathyroid adenoma were included in the study. The mean age of the patients was 51.98 ± 15.32 years. Demographic and laboratory findings of the patients are given in Table 1.

Table 1. Demographic and Laboratory Findings of the Patients

Demographic and Laboratory Parameters	Range	Findings
N		255
Age (year ± SD)		51.98 ± 15.3
Gender, n (%)		
Female		214 (83.9%)
Male		41 (16.1%)
Parathormone	18.5-88 pg/mL	342.12 ± 310.73 pg/mL
Calcium	8.7-10.4 mg/dL	11.82 ± 0.84 mg/dL
Phosphorus	2.4-5.1 mg/dL	2.44 ± 0.52 mg/dL
Alkaline phosphatase	46-116 U/L	147.27 ± 82.88 U/L
24-hour urine calcium	100-300 mg/24 h	359.21 ± 141.21 mg/24 h
25-hydroxy vitamin D	30-100 ng/mL	11.08 ± 6.12 ng/mL
Creatinine	0.55-1.02 mg/dL	0.66 ± 0.14 mg/dL
TSH	0.55-4.78 IU/mL	1.49 ± 0.81 IU/mL
FT4	0.83-1.43 ng/dL	1.04 ± 0.13 ng/dL
Anti-TPO	0-60 U/mL	22.18 ± 14.75 U/mL
Thyroid ultrasonography		No nodules, 155 (60.8%)
		Single nodule, 25 (9.8%)
		Multiple nodules, 75 (29.4%)
Localization of parathyroid adenoma		Right, 140 (54.9%)
		Left, 115 (45.1%)

SD, standard deviation; TSH, thyroid-stimulating hormone; FT4, free thyroxine; anti-TPO, thyroid peroxidase antibody.

When the preoperative thyroid ultrasonography reports of the patients were evaluated, thyroid nodule was not detected in 155 (60.7%) patients and was detected in 100 (39.2%) patients [single nodule in 25 (9.8%) and multiple nodule in 75 (29.4%)]. Of the 155 patients in whom the nodule was detected, 84 were women and 16 were men, and the mean age was 62.4 ± 10.21 years. In the results of fine-needle aspiration biopsy made from these nodules, benign cytology was detected in 63 (63%) patients, malignant cytology in 33(33%), and atypia of undetermined significance in 4(4%) (Table 2). The malignant cytology rate was 20%[5] in a single thyroid nodule,

Table 2. Findings of Ultrasonography and Fine-Needle Aspiration Biopsy of the Patients

Thyroid Ultrasonography	Cases [n = 255]	Fine-Needle Aspiration Biopsy
No thyroid nodule	155 (60.8%)	
Single nodule	25 (9.8%)	Benign, n = 20
		Malign, n = 5
Multiple nodules	75 (29.4%)	Benign, n = 43
		Malign, n = 28
		AUS, n = 4

AUS, atypia of undetermined significance.

MAIN POINTS

- Study aims to evaluate the relationship between primary hyperparathyroidism and differentiated thyroid carcinoma.
- It's been found that the frequency of thyroid nodules increased in patients with parathyroid adenoma and possibility of malignancy development in these nodules increased.

Table 3. Laboratory Data of Patients Without Thyroid Nodules and Patients with Thyroid Nodules

	Ranges	Without Thyroid Nodules (n = 155)	With Thyroid Nodules (n = 100)	*P*
Age		**45.26 ± 14.37**	**62.40 ± 10.2**	**<.001**
Gender		F = 130 (83.8%)	F = 84 (84%)	.545
		M = 25 (16.2%)	M = 16 (16%)	.541
Parathormone	**18.5-88 pg/mL**	**293.16 ± 46.48**	**418 ± 71.4**	**.045**
Calcium	8.7-10.4 mg/dL	11.73 ± 0.81	11.95 ± 0.89	.364
Phosphorus	2.4-5.1 mg/dL	2.41 ± 0.58	2.49 ± 0.44	.127
Alkaline phosphatase	46-116 U/L	133.0.6 ± 71.77	169.70 ± 95.74	.129
24-hour urine calcium	100-300 mg/24 h	338.61 ± 131.82	391.15 ± 153.7	.199
25-hydroxy vitamin D	**30-100 ng/mL**	**12.13 ± 7.01**	**9.45 ± 4.03**	**.043**
TSH	0.55-4.78 IU/mL	1.48 ± 0.71	1.24 ± 0.94	.302
FT4	0.83-1.43 ng/dL	1.02 ± 0.12	1.09 ± 0.94	.069
Anti-TPO	0-60 U/mL	20.50 ± 14.5	24.79 ± 14.91	.317

The bold values in the table are significant that are statistically special. TSH, thyroid-stimulating hormone; FT4, free thyroxine; anti-TPO, thyroid peroxidase antibody.

Table 4. Laboratory Data of Patients Without DTC and Patients With DTC in PHPT Patients

	Ranges	Patients Without DTC (N = 220)	Patients With DTC (N = 35)	*P*
Age		50.93 ± 15.71	58.57 ± 11.35	.204
Gender		F = 184 (83.6%)	F = 30 (85.7%)	.551
		M = 36 (16.4%)	M = 5 (14.3%)	.542
Parathormone	**18.5-88 pg/mL**	**352.64 ± 50.06**	**276 ± 34.68**	**.042**
Calcium	8.7-10.4 mg/dL	**11.83 ± 0.87**	**11.01 ± 0.64**	**.032**
Phosphorus	2.4-5.1 mg/dL	2.40 ± 0.52	2.69 ± 0.52	.173
Alkaline phosphatase	46-116 U/L	144.88 ± 87.1	162.38 ± 69.1	.179
24-hour urine calcium	100-300 mg/24 h	355.61 ± 146.82	381.28 ± 43.5	.434
25-hydroxy vitamin D	**30-100 ng/mL**	**11.48 ± 7.01**	**8.52 ± 2.11**	**.028**
TSH	0.55-4.78 IU/mL	1.44 ± 0.81	1.01 ± 0.591	.155
FT4	0.83-1.43 ng/dL	1.02 ± 0.12	1.18 ± 0.156	.144
Anti-TPO	0-60 U/mL	20.50 ± 14.5	27.8 ± 12.1	.283

The bold values in the table are significant that are statistically special. TSH, thyroid-stimulating hormone; FT4, free thyroxine; anti-TPO, thyroid peroxidase antibody.

while the malignant cytology rate was 37% (28) in multiple nodules. In patients with parathyroid adenoma, the malignancy rate of single thyroid nodules was not different from the malignancy rate of multiple thyroid nodules ($P > .005$).

In order to analyze the risk factors for thyroid nodules in patients with parathyroid adenoma, 100 patients with thyroid nodules and 155 patients without thyroid nodules were divided into 2 subgroups (Table 3). While the mean age of those without thyroid nodules was 45.26, the mean age of those with thyroid nodules was 62.40, the difference was statistically significant ($P < .001$). When patients with thyroid nodules were compared to patients without thyroid nodules, PTH values were higher and VD levels were lower, the difference was statistically significant ($P = .045$). There was no statistically significant difference in gender, calcium, phosphorus, ALP, 24-hour urine calcium, TSH, FT4, and anti-TPO between both the groups.

When the postoperative histology of the patients was evaluated, DTC (26 papillary thyroid carcinoma, 4 papillary microcarcinoma, and 5 follicular thyroid carcinoma) was detected in 35/255 (13.7%) patients (Table 4). To analyze DTC risk factors in patients with parathyroid adenoma, patients with DTC (35/255) and patients without DTC (220/255) were compared. Parathyroid hormone, calcium, and VD levels were found to be lower in patients with DTC, and the difference was statistically significant ($P < .05$). All other parameters were similar between the 2 subgroups, and the difference was not statistically significant.

According to the pathological report of patients with thyroid nodules, it was examined in 2 subgroups; as malignant thyroid nodule (35/100) and benign thyroid nodule (65/100) (Table 5). When patients with benign thyroid nodules and patients with malignant thyroid nodules were compared, PTH and calcium levels were found to be low in patients with malignant nodules, and the difference was statistically significant ($P < .05$). All other parameters were not statistically significant between the 2 subgroups.

Multivariate logistic regression analyses were used to further explore the relationship of DTC with parathyroid adenoma. A correlation was found between serum calcium level in the presence of DTC (odds ratio: 0.031; 95% CI: 0.001-0.654; $P = .035$). In ROC analysis, serum calcium levels <11.05 mg/dL had a good capacity to differentiate patients with DTC from patients with benign thyroid nodules, area under the curve (AUC): 0.648 ($P = .032$). This cutoff point for serum calcium level was 71.4% sensitive and 72.7% specific in predicting DTC.

Discussion

In our study, we found that the frequency of thyroid nodules increased in patients with parathyroid adenoma and possibility of malignancy development in these nodules increased. In addition, in the presence of thyroid nodule in parathyroid adenoma, we found that when the serum calcium cutoff value is <11.05 mg/dL, it has a good capacity to diagnose DTC.

Table 5. Data of Patients with Benign Thyroid Nodules and Patients with Malignant Nodules in PHPT Patients

		Benign Nodule	Malign Nodule	
	Ranges	**n = 65**	**n = 35**	***P***
Age		64.46 ± 9.35	58.57 ± 11.35	.228
Gender		F = 54 (83.1%)	F = 30 (85.7%)	.553
		M = 11 (16.9%)	M = 5 (14.3%)	.543
Parathormone	**18.5-88 pg/mL**	**494.46 ± 123.12**	**276 ± 34.68**	**.006**
Calcium	8.7-10.4 mg/dL	**12.08 ± 1.01**	**11.01 ± 0.64**	**.026**
Phosphorus	2.4-5.1 mg/dL	2.38 ± 0.37	2.69 ± 0.52	.555
Alkaline phosphatase	46-116 U/L	173.07 ± 31.73	162.38 ± 69.1	.474
24-hour urine calcium	100-300 mg/24 h	396.46 ± 48.58	381.28 ± 43.5	.262
25-hydroxy vitamin D	**30-100 ng/mL**	9.92 ± 4.77	8.52 ± 2.11	.099
TSH	0.55-4.78 IU/mL	1.34 ± 0.36	1.01 ± 0.591	.248
FT4	0.83-1.43 ng/dL	1.02 ± 0.69	1.18 ± 0.156	.117
Anti-TPO	0-60 U/mL	23.16 ± 16.4	27.8 ± 12.1	.386
Nodule diameter		19.69 ± 8.59	23.71 ± 8.69	.555

The bold values in the table are significant that are statistically special.
TSH, thyroid-stimulating hormone; FT4, free thyroxine; anti-TPO, thyroid peroxidase antibody.

Primary hyperparathyroidism is a common endocrine disease in the population with a prevalence of 0.1%-0.2% and is the most common cause of asymptomatic hypercalcemia.[9] Primary hyperparathyroidism develops due to 80% parotid adenoma, 15%-20% parathyroid hyperplasia, and <0.5% parathyroid carcinoma.[9] Parathyroid adenomas are more common in female than male, and more than half of the cases are over the age of 50.[9] In our study, consistent with the literature, the majority of patients with parathyroid adenoma were female (83.9%), with a mean age of 51.98 years.

Nodular thyroid disease is observed at a rate of 30%-40% in patients with PHPT.[10,11] In our study, thyroid nodules were detected in 39.3% of patients with parathyroid adenoma, consistent with the literature. The association of parathyroid adenoma and DTC was first described by Ogburn and Black12 in 1956.

The combination of parathyroid adenoma and DTC is encountered at a rate of 2%-18%.[12] In our study, we found the association of parathyroid adenoma and DTC (30 papillary thyroid cancers and 5 follicular thyroid cancers) at a rate of 13.7%. The mean age of parathyroid adenoma and DTC has been reported as 52, 53, and 58 years.[4,12,13] In our study, we found the mean age to be 58.5 years. In our study, in accordance with the literature, 85.7% of the cases with parathyroid adenoma with DTC were found to be women.[4,12,13]

Differentiated thyroid cancers constitute 80%-90% of all thyroid cancers and are subdivided into papillary, follicular, and poorly differentiated thyroid cancers.[8] While the incidence of differentiated thyroid cancer in the general population is 4.8-14.9/100 000,[8] this rate is higher in patients with parathyroid adenoma.[14] In our study, we found a 35% malignancy rate of nodules in the coexistence of parathyroid adenoma and thyroid nodule. Considering that the malignancy rate of thyroid nodules in the general population is between 5% and 15%,[15] we can say that the possibility of malignancy of thyroid nodules in parathyroid adenomas increases.

There are studies showing that genetic factors and head and neck radiotherapy cause DTC development in hyperparathyroidism.[6] However, when the history of the patients in our study was evaluated, there was no history of exposure to head and neck radiation, no family history of thyroid cancer, and no history of thyroid cancer

The increase in parathormone levels causes immune dysfunction, T cell sensitivity and B cell dysfunction, and an increase in cancer incidence by affecting phagocytosis.[16,17] Many studies have shown that hyperparathyroidism causes breast cancer and thyroid cancer.[18,19] In our study, the PTH levels of those with thyroid nodules were found to be higher than those without thyroid nodules and statistically significant ($P = .045$). But when the benign thyroid nodule is compared with the malignant thyroid nodule, PTH levels were found to be significantly higher in benign nodules ($P = .006$). We found that higher PTH increased benign thyroid nodules but not malignant thyroid nodules.

Apart from its major role in calcium homeostasis, VD can directly or indirectly regulate multiple signaling pathways related to cellular proliferation, differentiation, apoptosis, and angiogenesis. VD deficiency has the potential to affect cancer development and growth.[20] There are studies showing that the risk of developing thyroid nodules and cancer increases in VD deficiency.[21] As the level of VD deficiency increases in patients with parathyroid adenoma, we found that it causes an increased risk of developing thyroid nodule ($P = .043$) and DTC ($P = .028$).

There are many studies examining the relationship between serum calcium level and cancer. For example, both serum ionized calcium and total serum calcium were found to be lower in colorectal cancers compared to the control group.[22] In another study, serum calcium levels were found to be lower in women with esophagus cancers and colon cancers.[23] Serum calcium level was also found to be lower in prostate cancer.[24] The relationship between thyroid cancer and serum calcium levels is unclear. In our study, serum calcium levels were found to be lower in patients with DTC compared to patients with benign thyroid nodules.

It was performed in a single center and a limited number of patients were included. We observed an increase in the frequency of DTC if calcium <11.05 mg/dL in patients with parathyroid adenoma, but we do not know what the underlying histopathological mechanism is.

Conclusions

Our results show that the frequency of thyroid nodules increases in the presence of parathyroid adenoma and the risk of developing DTC in these nodules is increased compared to the general population. In addition, we found that serum calcium level <11.05 mg/dL in patients with parathyroid adenoma has a good capacity to differentiate DTC from benign thyroid nodule.

Ethics Committee Approval: The study was approved by the medical ethics committee of Erzurum Regional Training and Research hospital (2021/21-272).

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

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors declare that they have no competing interest.

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