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Evaluation of Nodular Goiter and Papillary Thyroid Cancer Coincidence in Patients with Primary Hyperparathyroidism

Primer Hiperparatiroidili Hastalarda Nodüler Guatr ve Papiller Tiroid Kanseri Birlikteliğinin Değerlendirilmesi

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ABSTRACT

Aim: Primary hyperparathyroidism and differentiated thyroid carcinoma are the most common endocrinological diseases. Since its first definition in the 1950s, nodular goiter and differentiated thyroid carcinoma in patients with primary hyperparathyroidism have been examined in many studies and an increase in cancer incidence has been found. In this study, we aimed to investigate the co-incidence of nodular goiter and differentiated thyroid cancer in patients with primary hyperparathyroidism.

Material and Methods: One hundred seventy-two patients who underwent parathyroid surgery in our hospital between 2012 and 2015 were included in this study. Demographic, clinic, and surgical data of the patients were reviewed retrospectively.

Results: The mean age of the patients was 54.3±11.3 years and 85.5% (n=147) of them were female. Nodular goiter was observed at a rate of 61.0% (n=105) in preoperative evaluation. Parathyroidectomy was performed in 125 (72.7%) and simultaneous total thyroidectomy was performed in 32 (18.6%) and lobectomy in 15 (8.7%) of the patients. Histopathologically, 94.8% (n=163) were interpreted as adenoma, 2.9% (n=5) as parathyroid hyperplasia, and 2.3% (n=4) as parathyroid carcinoma. Patients with papillary thyroid carcinoma (n=30) and benign (n=17) histopathologically were compared in terms of clinical and laboratory characteristics, and no significant difference was observed in any parameter.

Conclusion: There was no significant increase in thyroid nodularity, but a significant increase was found in differentiated thyroid carcinoma incidence in patients with primary hyperparathyroidism in this study in accordance with the literature. This finding highlights the importance of preoperative thyroid evaluation in this patient group.

Keywords: Primary hyperparathyroidism; nodular goiter; thyroid cancer.

ÖZ

Amaç: Primer hiperparatiroidi ve diferansiye tiroid karsinomu en sık görülen endokrinolojik hastalıklardır. İlk tanımlanmış olduğu 1950'li yıllardan bu yana primer hiperparatiroidili hastalarda nodüler guatr ve diferansiye tiroid karsinomu varlığı birçok çalışmada incelenmiş ve kanser insidansında bir artış olduğu saptanmıştır. Bu çalışmada, primer hiperparatiroidili hastalardaki nodüler guatr ve diferansiye tiroid kanseri birlikteliğinin araştırılması amaçlandı.

Gereç ve Yöntemler: Bu çalışmaya hastanemizde 2012 ve 2015 yılları arasında paratiroid cerrahisi yapılmış olan toplam 172 hasta dahil edildi. Hastaların demografik, klinik ve cerrahi verileri geriye dönük olarak incelendi.

Bulgular: Hastaların yaş ortalaması 54,3±11,3 yıl olup %85,5'i (n=147) kadın idi. Hastaların preoperatif değerlendirmesinde %61,0 (n=105) oranında nodüler guatr izlenmiştir. Hastaların 125'ine (%72,7) sadece paratiroidektomi uygulanırken 32'sine (%18,6) eş zamanlı total tiroidektomi ve 15'ine (%8,7) ise eş zamanlı lobektomi uygulanmıştır. Histopatolojik olarak değerlendirilen paratiroid dokularının %94,8'i (n=163) adenom olarak yorumlanırken, %2,9'u (n=5) paratiroid hiperplazisi ve %2,3'ü (n=4) paratiroid karsinomu olarak yorumlanmıştır. Histopatolojik olarak tiroid karsinomu saptanan (n=30) hastalar ile benign saptanan (n=17) hastalar klinik ve laboratuvar özellikleri yönünden karşılaştırılmış olup hiçbir parametrede anlamlı bir farklılık izlenmemiştir.

Sonuç: Primer hiperparatiroidili hastalarda tiroid nodülaritesinde anlamlı bir artış olmamakla birlikte, bu çalışmada literatürle uyumlu şekilde diferansiye tiroid kanseri insidansında anlamlı bir artış saptanmıştır. Bu bulgu da bu hasta grubunda preoperatif olarak yapılan tiroid dokusu değerlendirmesinin önemini vurgulamaktadır.

Anahtar kelimeler: Primer hiperparatiroidi; nodüler guatr; tiroid kanseri.

INTRODUCTION

Primary hyperparathyroidism is one of the most common endocrinological diseases currently. Its frequency in the population varies between 0.1-0.4%. The frequency increases with age and is most commonly detected in the fifth decade, and much more common in females than males. The cause is a single adenoma in 80-85% of patients and its treatment is surgical excision (1-4).

In the past, more invasive explorative surgeries were preferred as surgical approaches. However, nowadays, minimally invasive approaches have come to the fore, as the rate of single adenoma is significantly higher, the incidence of parathyroid cancer is very rare, and adenomas can be detected at a much higher rate with the development of preoperative imaging techniques. Therefore, the most common method preferred in parathyroid surgery today is minimally invasive parathyroid surgery. With the minimally invasive approach, the rates of neurological complications such as loss of voice have been greatly reduced (5-7).

One of the foremost and widely used imaging methods in preoperative evaluation is neck ultrasound (US). Neck US performed in experienced hands is very sufficient to accurately detect the localization of parathyroid pathologies, it can also detect accompanying thyroid pathologies early and accurately (8,9).

The rate of concomitant thyroid nodularity in primary hyperparathyroidism varies between 15-75% according to the literature (3,10). This frequency rate is similar to the nodular goiter seen in the normal population. Today, with the widespread use of neck US, the rate of nodule detection in the thyroid has increased to 70% (11). However, according to studies the incidence of thyroid malignancy in primary hyperparathyroidism is between 2-29.8% and it's higher than the normal population (3,10,12). There is a known association between primary hyperparathyroidism and medullary thyroid cancer in Multiple Endocrine Neoplasia-2 (MEN-2) Syndrome. However, the most common thyroid malignancy in patients with sporadic primary hyperparathyroidism is differentiated thyroid cancer (12).

Differentiated thyroid carcinoma is one of the most common malignancies and about 80-85% of the cases consist of papillary thyroid carcinoma (PTC). In recent years, with the increase in the accessibility and quality of neck US and other imaging modalities, there has been an increase in the rate of diagnosis of occult thyroid carcinoma, but also there has been a parallel increase in the general incidence and mortality of thyroid cancer (11,13,14).

The association of primary hyperparathyroidism and differentiated thyroid cancer was first described by Ogburn and Black in 1956 (15). Since then, many studies have been conducted on primary hyperparathyroidism and differentiated thyroid carcinoma, and in these studies, it has been found that primary hyperparathyroidism changes the frequency and characteristics of differentiated thyroid cancer.

In this study, we aimed to investigate the rates of concomitant benign and malignant thyroid nodules and differentiated thyroid carcinoma in our patients with primary hyperparathyroidism who underwent parathyroid surgery in our center.

MATERIAL AND METHODS

Patients with primary hyperparathyroidism, over the age of 18, who underwent surgery in our center between January 2012 and 2015 were included in the study. The data of the patients were scanned retrospectively from the online data system of our center. The diagnosis of primary hyperparathyroidism was made by high serum calcium (Ca) values accompanied by high or inappropriately normal parathyroid hormone (PTH) levels. After scanning the demographic data, routine laboratory tests and imaging required by their diseases were performed. Fine-needle aspiration biopsy (FNAB) was performed on appropriate nodules from patients with thyroid nodularity according to neck US results. In line with the examination and FNAB results, the patients with parathyroid surgery indications were evaluated and subjected to a surgical procedure suitable for accompanying thyroid pathologies.

Patients with any syndromic condition such as MEN-2 syndrome that will affect the frequency of thyroid nodules or cancer, with a history of radiotherapy to the neck, a familial history of thyroid carcinoma, chronic renal failure, and active thyroid cancer or any other active malignancy and pregnant women were excluded from the study.

Laboratory Analysis and Imaging

Blood was taken from the patients by venous route in the morning after an overnight fast for laboratory analysis. Ca and phosphorus (P) levels were studied with the colorimetric method, thyroid stimulating hormone (TSH) and anti-thyroid peroxidase (anti-TPO) levels were studied with chemiluminescence microparticle immunological method, PTH levels were studied with intact chemiluminescence immunoassay method and 25-OH-D3 levels were studied with radioimmunoassay method in Abbott Architect I 2000 SR® device. Twenty-four-hour urinary Ca levels were studied and recorded by atomic absorption spectrophotometry method.

Neck US was performed by experienced Endocrinology and Metabolic Diseases Specialists with a 13 mHz linear probe B Mode High-Resolution USG device (Logic 9, General Electric USA®). In ultrasonographic evaluation; the number of parathyroid adenoma, its detailed location, and dimensions in all three planes, borders, echogenicity, Doppler blood supply, and relationship with surrounding tissues were defined. In addition; the size, echogenicity, Doppler blood supply of the thyroid tissue in all three planes, detailed location, diameters, borders, echogenicity, and ultrasonographic features (cystic content, spongioform appearance, microcalcification, macrocalcification foci, etc.) and Doppler blood supply of the nodules were specified. Planar images of 99mTc-MIBI sestamibi (methoxy-isobutyl-isonitrile) were obtained using a single-headed Siemens E-Cam gamma camera with a low-energy high-resolution collimator positioned as close to the neck region as possible. Early images were taken 15 minutes after MIBI application from anterior, left, and right anterior oblique angles (Thyroidal phase). Late images were obtained between 90-120 minutes (Parathyroidal phase). Cases that could not be visualized with the two basic imaging methods were referred to further imaging methods.

Fine-Needle Aspiration Biopsy and Surgical Procedure

Indications for performing FNAB were determined according to the American Thyroid Association's 2015 guidelines and the pathologic evaluations and classifications

were made according to the Bethesda system (11,16). Surgical procedures were performed by our experienced surgeons in the General Surgery Department of our center. Parathyroid surgery indication was determined according to the Fourth International Workshop 2014 Endocrine Society Guidelines criteria (17).

Video-assisted minimally invasive parathyroid surgery was applied as a standard procedure to the patients whose adenoma was localized preoperatively and no additional thyroid pathology that would require surgery was detected. Simultaneous thyroid surgery together with parathyroid surgery was planned for the patients with thyroid nodularity detected in preoperative imaging and FNAB results with Bethesda class III and above, those with nodules that are unsuitable for sampling but may be risky for malignancy, and those with plunging and retrosternal goiter. Lobectomy with adenomectomy was performed in unilateral suspicious nodules, and total thyroidectomy with adenomectomy procedure was performed in patients with bilateral multinodular goiter.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics software, Version 22. The normality of the distribution of continuous variables was determined using the Kolmogorov-Smirnov test. Categorical variables were described as frequencies and percentages. Categorical features and relationships between groups were assessed using an appropriate chi-square test. The continuous variables were expressed as mean and standard deviation or median, interquartile range, and minimum-maximum, depending on the normality of their distribution. The Mann-Whitney U test was used to compare the variables that were not normally distributed. On the other hand, the Student's t test was used to compare the variables with normal distribution. To determine if predictor factors, such as particular test results and demographic information, substantially predicted thyroid cancer, logistic regression was used. The statistically significant two-tailed p-value was considered as <0.05.

RESULTS

A total of 172 patients, all of whom underwent parathyroidectomy were included in the study. The mean age was 54.3±11.3 years and 147 (85.5%) of the patients were female. It was observed that parathyroid adenoma was located most frequently in the lower right (n=71, 41.3%) and lower left (n=68, 39.5%) locations, respectively. According to the preoperative US, goiter was observed in 105 (61.0%) of the patients, and the mean thyroid volume was found to be 14.4±10.5 cm^3. Mean serum Ca and P levels were 11.1±0.7 mg/dL, and 2.6±0.5 mg/dL, and the median PTH level was 179 pg/dL, respectively (Table 1).

Minimally invasive parathyroidectomy was performed in 125 (72.7%) of the patients. However simultaneous parathyroidectomy and total thyroidectomy were performed in 32 (18.6%) and simultaneous parathyroidectomy and unilateral lobectomy were performed in 15 (8.7%) patients. Histopathologically 94.8% (n=163) were interpreted as parathyroid adenoma, 2.9% (n=5) as parathyroid hyperplasia, and 2.3% (n=4) as parathyroid carcinoma. PTC was detected in 30 (63.8%) of 47 patients who underwent thyroidectomy, corresponding to 17.4% of the total patient group (Table 2).

According to tumor localizations, it was determined that 46.7% (n=14) was single-focus left lobe, 23.3% (n=7) single-focus right lobe, 20.0% (n=6) bilateral, 6.7% (n=2) multifocal right lobe, and 3.3 % (n=1) multifocal left lobe. All of the corresponding nodules (100%) were of solid hypoechoic nature in the preoperative US in the cases with thyroid carcinoma. In FNAB, 22.2% (n=6) of the nodules were reported as malignant cytology, 18.5% (n=5) were benign, 48.2% (n=13) were atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), and 3.7% (n=1) were as follicular neoplasia (Table 3).

Table 1. Baseline clinical and laboratory characteristics of the patients (n=172)

Age (years)	54.3±11.3
Gender, n (%)	
Female	147 (85.5)
Male	25 (14.5)
Body mass index (kg/m^2)	30.8±6.5
Smoking, n (%)	30 (17.4)
Tumor localization, n (%)	
Right superior	7 (4.1)
Right inferior	71 (41.3)
Left superior	12 (7.0)
Left inferior	68 (39.5)
Double adenoma	4 (2.3)
Others (Ectopic)	10 (5.8)
Goiter, n (%)	105 (61.0)
Thyroid volume (cm^3)	14.4±10.5
Adenoma volume (cm^3)	0.49 (0.24-0.98) [0.03-17.70]
TSH (mIU/L)	1.84±1.24
Anti-TPO positivity, n (%)	28 (16.3)
Serum creatinine (mg/dL)	0.7 (0.6-0.8) [0.5-1.5]
Albumin (gr/L)	4.5±0.3
Preoperative serum iPTH (pg/dL)	179 (126-252) [68-1727]
Corrected calcium (mg/dL)	11.1±0.7
Urinary calcium (mg/24-hour)	370±188
Phosphorus (mg/dL)	2.6±0.5
25-hydroxy vitamin D3 (ng/ml)	10 (6-17) [4-150]
Renal stone, n (%)	58 (33.7)
Osteoporosis, n (%)	82 (47.7)

TSH: thyroid stimulating hormone, Anti-TPO: anti-thyroid peroxidase, iPTH: intact parathyroid hormone, descriptive statistics for continuous variables were expressed as mean±standard deviation or as median (interquartile range, 25^{th}-75^{th} percentile) [minimum-maximum] depending on the normality of their distribution

Table 2. Surgery and histological results (n=172)

Surgery, n (%)	
Parathyroidectomy	125 (72.7)
Parathyroidectomy+total thyroidectomy	32 (18.6)
Parathyroidectomy+lobectomy	15 (8.7)
Histopathological findings for thyroid, n (%)	
Benign	142 (82.6)
Malignant	30 (17.4)
Histopathological findings for parathyroid, n (%)	
Adenoma	163 (94.8)
Hyperplasia	5 (2.9)
Carcinoma	4 (2.3)

Table 3. Preoperative fine needle aspiration results of cases with malignant pathology results (n=27)

Fine needle aspiration, n (%)	
Nondiagnostic	2 (7.4)
Benign	5 (18.5)
AUS/FLUS	13 (48.2)
Follicular neoplasm or suspicious	1 (3.7)
Malignant	6 (22.2)

AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance

Patients with thyroid carcinoma (n=30) and benign pathology (n=17) were compared in terms of clinical and laboratory characteristics, and no significant difference was observed in any of the parameters (Table 4). Age, gender, thyroid volume, parathyroid adenoma volume, urinary Ca level, serum Ca, and serum 25-OH-D3 levels which may have an impact on the development of thyroid cancer in patients with parathyroid adenoma, were analyzed by univariate regression analysis. It was determined that only thyroid volume had a significant effect (OR: 1.06, 95% CI: 1.016-1.101, p=0.006).

DISCUSSION

Primary hyperparathyroidism is the third most common endocrinological disease after thyroid diseases and diabetes mellitus (1,12). Differentiated thyroid carcinoma is also one of the most common malignancies currently and the most common thyroid malignancy in patients with primary hyperparathyroidism is PTC (12). Given the worldwide high prevalence of both diseases, the possibility of one inducing the other and increasing its frequency is of interest.

In our study, 85.5% (n=147) of the patients who underwent parathyroidectomy were female and the mean age was 54.3±11.3 years. In our patient group, we found nodular goiter in 61.0% (n=105) and PTC in 17.4% (n=30).

The female/male ratio and mean age in our study are similar to the studies in the literature (3,12,18,19). Although differentiated thyroid carcinoma can be seen at younger ages, the age of occurrence of sporadic primary hyperparathyroidism is mostly in the fifth decade, and the average female-to-male ratio is around 7-8/1 (1,3). Our study is compatible with the literature in this respect.

Since its first definition in 1956, there have been numerous studies in the literature examining the frequency and characteristics of nodular thyroid disease and differentiated thyroid cancer in primary hyperparathyroidism. According to the general results of these studies, the incidence of nodular goiter in primary hyperparathyroidism was roughly the same as in the general population, while the frequency of PTC was found to be increased. In the study of Vargas-Ortega et al. (3) the rate of PTC in 59 patients who underwent simultaneous parathyroid and thyroid surgery was found to be 20.3%, similar to our study. Also in the study of Hu et al. (20), the PTC rate was found 22% compatible with our study. In the study of Liu et al. (12) the rate of nodular goiter in 304 patients with hyperparathyroidism was found to be 61.5%, similar to ours, but the rate of PTC was found to be 29.9%, slightly higher than ours. In two studies conducted in Türkiye, the rates of concomitant nodular goiter in patients with hyperparathyroidism were found to be 42% and 55.6%, and PTC rates of 11.3% and 10.2% (18,21). In another study, the nodularity rate was found to be 53.6%, and the PTC rate was 13.6% (2). In our study, the frequency of nodular goiter and papillary cancer in patients with primary hyperparathyroidism is consistent with the literature.

When we compared the patients with PTC with those who were with benign cytology, we found no difference in terms of demographic characteristics and clinical parameters. In three studies, two of which were conducted in Türkiye, no significant difference was found between benign and malignant groups in patients with hyperparathyroidism in terms of age, gender, preoperative PTH, Ca, P, 25-OH-D3, 24-hour urinary Ca levels (3,21,22) compatible to our study. In the study of Celik et al. (22) also anti-TPO levels were compared and no significant difference was found similar to our study. In

Table 4. Comparison of clinical and laboratory characteristics of patients with and without thyroid carcinoma

	Thyroid Carcinoma		**p**
	Yes (n=30)	**No (n=17)**	
Age (years)	54.5±10.2	58.5±12.2	0.227
Gender, female, n (%)	25 (83.3)	15 (88.2)	0.650
Smoking, n (%)	6 (20.0)	2 (11.8)	0.470
Body mass index (kg/m^2)	30.5±6.0	30.9±4.0	0.793
Thyroid volume (cm^3)	20.3±10.4	20.8±22.2	0.912
Adenoma volume (cm^3)	0.48 (0.28-0.81) [0.08-3.49]	0.57 (0.38-3.12) [0.04-8.21]	0.285
TSH (mIU/L)	1.65±1.12	1.27±0.86	0.239
Anti-TPO positivity, n (%)	4 (13.3)	1 (5.9)	0.426
Serum creatinine (mg/dL)	0.60 (0.57-0.80) [0.50-1.50]	0.70 (0.60-0.90) [0.50-1.40]	0.370
Preoperative serum iPTH (pg/dL)	195 (122-289) [74-830]	205 (130-420) [94-645]	0.580
Corrected calcium (mg/dL)	11.0±0.7	11.3±0.8	0.132
Urinary calcium (mg/24-hour)	339±175	366±138	0.609
25-hydroxy vitamin D3 (ng/ml)	8.5 (7.0-20.8) [4-63]	12.0 (6.5-17.0) [4-20]	0.764

TSH: thyroid stimulating hormone, Anti-TPO: anti-thyroid peroxidase, iPTH: intact parathyroid hormone, descriptive statistics for continuous variables were expressed as mean±standard deviation or as median (interquartile range, 25^{th}-75^{th} percentile) [minimum-maximum] depending on the normality of their distribution

the other two studies, lower preoperative Ca and PTH levels were found in the PTC group compared to the benign group (12,20). In a study conducted in Korea, 25-OH-D3 levels were found to be significantly lower in patients with hyperparathyroidism accompanied by PTC compared to those with only hyperparathyroidism (23).

In our study, the rate of patients who underwent simultaneous parathyroid-thyroid surgery was similar to other studies. Preoperative FNAB was performed in 57% of patients scheduled for simultaneous thyroid parathyroid surgery. Our preoperative FNAB and simultaneous thyroid surgery rates are similar to the study of Haciyanli et al (21). In this study, 26.3% of the patients were found with malignant cytology by preoperative FNAB, while this rate remained at 12.7% in our study. An average of 5% of thyroid nodules are malignant. Preoperative FNAB is the best method to detect differentiated thyroid cancer, but it is known in the literature that the false-negative rate can reach up to 40% in patients with primary hyperparathyroidism (19,21,24).

The rate of thyroid nodularity in patients with primary hyperparathyroidism was similar to the general population in the literature but it was observed that differentiated thyroid cancer rate is increased in these patients. Although it is thought that incidentally detected occult tumors may increase this frequency while imaging related to primary hyperparathyroidism is performed, some recent studies have also found an increase in invasiveness in PTC in patients with primary hyperparathyroidism (12,25,26).

The reason why the risk of differentiated thyroid cancer is increased in patients with primary hyperparathyroidism has not yet been fully clarified. Common embryological origin of the thyroid and parathyroid tissue and the commonly shared effect of numerous genes and transcription factors come to the fore. In addition, it is speculated that chronically high PTH and Ca, and low 25-OH-D3 levels increase the levels of many growth factors such as insulin-like growth factor-1 (IGF-1), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF), and thus have a mitogenic effect on thyroid follicular cells (18,25-29). Larger studies are needed to understand the definite effect of hyperparathyroidism on differentiated thyroid cancer.

Our study has some limitations. It is a retrospective and single-center study with a limited number of patients, and there is no separate PTC control group comparing papillary tumor characteristics. Nevertheless, in our study, we investigated the frequency of nodular goiter and differentiated thyroid cancer in our primary hyperparathyroidia patients operated in our tertiary center. In accordance with the literature, the rate of nodularity was found to be 61.0% and the rate of PTC was found to be 17.4%. As a tertiary center where selected patients are referred and operated on, we think that our study, together with a few studies from Türkiye, contributes to the literature.

CONCLUSION

Although there is no increased rate of thyroid nodularity in patients with primary hyperparathyroidism compared to the population, the frequency of differentiated thyroid cancer is defined as 2-29% in the literature. In our study, the nodularity rate was found to be close to the norm at 61.0%, but the frequency of papillary tumors was found to be 17.4%, more common than the normal population, but consistent with the literature. The pathogenetic mechanisms by which hyperparathyroidism increases the frequency of differentiated thyroid cancer are not yet certain, but it is now certain that it does. Therefore, it is important to make appropriate preoperative thyroid imaging and sampling in patients with hyperparathyroidism and to plan appropriate simultaneous thyroid surgeries correctly both in terms of early detection of thyroid cancer and in protecting the patient from unnecessary re-surgeries.

Ethics Committee Approval: The study was approved by the Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital (23.03.2015, 21/03).

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