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The Frequency of Synchronous Parathyroid Adenomas and Papillary Thyroid Carcinomas: Clinicopathological Evaluation

ABSTRACT

Objective: We aimed to evaluate the frequency and clinicopathological features of papillary thyroid carcinomas synchronized with parathyroid adenoma and to compare the "parathyroid adenoma with papillary thyroid carcinoma" and "parathyroid adenoma without papillary thyroid carcinoma" groups.

Methods: The study included 287 parathyroid adenoma cases that had concomitant thyroid surgery. Age, gender, parathyroid adenoma characteristics, diagnosis for thyroid materials, and clinicopathological prognostic parameters for papillary thyroid carcinomas were recorded from the pathology reports.

Results: Synchronous parathyroid adenoma and thyroid malignancy rate was 27.2%, and papillary thyroid carcinomas were 88.5% of the malignancies. Papillary thyroid carcinomas were mostly seen in female patients and in right thyroid lobe, the multifocality rate was 18.8%, the follicular variant being the most common, the majority were papillary microcarcinomas and pT1 tumors, extrathyroidal extension rate was 13%. "Parathyroid adenoma with papillary thyroid carcinoma" and "parathyroid adenoma without papillary thyroid carcinoma" groups were statistically similar in the patient and parathyroid adenoma characteristics. Intrathyroidal parathyroid adenomas and the right parathyroid gland involvement were more common in "parathyroid adenoma with papillary thyroid carcinoma" group, while multiple parathyroid adenomas and left parathyroid gland involvement were more common in "parathyroid adenoma without papillary thyroid carcinoma" group. Inferior parathyroid gland involvement was more common than the superior, and the mean parathyroid adenoma size was similar for both groups.

Conclusion: Synchronous parathyroid adenoma and papillary thyroid carcinoma cases are not uncommon, and detection of papillary thyroid carcinoma may change the surgical procedure. Therefore, all parathyroid adenoma cases should be thoroughly investigated for concomitant thyroid pathologies before surgery.

Keywords: Papillary thyroid carcinoma, parathyroid adenoma, surgical, synchronous, thyroid

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disease with a prevalence of 0.1%-0.4% in the general population.[1,2] Parathyroid adenomas (PAs) constitute the most common etiology of PHPT.[3-5] It was reported that 15%-75% of the PHPT patients had concomitant thyroid nodules.[6] The prevalence of papillary thyroid carcinomas (PTCs) with PHPT was reported as 1.3%-17.6% in several studies.[1,2,7,8]

The presence of PTC can change the surgical management in PHPT cases. It is important to identify PTC before the surgery to avoid complications due to additional surgical procedures and to minimize the cost.[1,4] Ultrasonography (USG), fine needle aspiration (FNA), and Technetium 99m-methoxyisobutylisonitrile (99mTc-MIBI) scanning are the most recommended diagnostic tools for thyroid nodules in cases with PHPT.[3,9]

Some features have been defined for PTCs with PHPT. Some authors reported that PTC cases with PHPT had more aggressive features compared to isolated PTCs.[1,2] In a study, it was reported that these patients were older than the isolated PTC cases.[2] Most of the PTC cases with PHPT have been reported to be papillary microcarcinomas.[1,10-12] Multifocality and extrathyroidal extension were reported higher in these cases compared to isolated PTCs.[2]

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In this study, we aimed to evaluate the frequency and clinicopathological features of synchronous PA and PTC cases, as well as to compare the "PA with PTC" and "PA without PTC" groups for the characteristics of the patients and PAs.

Materials and Methods

This study is in accordance with the Helsinki Declaration. The study protocol was accepted by Clinical Research Ethics Committee of Amasya University (Decision no: 35, Date: March 03, 2022). Since this is a retrospective archive study, informed consent was not obtained.

This is a descriptive study. Data were collected using the pathology archive retrospectively. The study included 287 cases which were diagnosed as PA by the pathology department of a university hospital between 2000 and 2021 and which had also concomitant thyroid surgery. Patient's age and gender; the number, localization, and size of each PA, the surgery type and the pathological diagnosis including both benign and malignant lesions for each thyroidectomy material were recorded from the pathology reports. Frequencies of benign thyroid diseases (BTDs), all thyroid malignancies, and PTCs synchronized with PA were evaluated.

Pathological prognostic parameters including histological subtype, localization, tumor size, multifocality, bilaterality, extrathyroidal extension, tumoral stage, lymph node metastasis, and distant metastasis were recorded for each PTC and the frequency of these parameters was calculated. World Health Organization 2017 classifications were used for histological typing of the tumors.[13] When there was more than 1 PTC focus in the same lobe, the tumor was considered as multifocal. The prognostic parameters were determined according to tumor focus which had the largest size. AJCC/TNM 8th edition was used to determine the tumor stage.[14]

The cases in which PTC was detected in the thyroid tissue were grouped as "PA with PTC" (Figure 1). The cases whose thyroid material was diagnosed as BTD and who had no accompanying PTC or non-PTC malignancy were grouped as "PA without PTC." The "PA with PTC" and "PA without PTC" groups were compared in terms of patient age, gender; number, localization, and the size of PA.

Statistical Analysis

Statistical analyses were performed by using IBM Statistical Package for Social Sciences Statistics for Windows, Version 21.0 (IBM Corp.; Armonk, NY, USA). Descriptive statistics were used to describe the data. Normal distribution was tested by Kolmogorov–Smirnov and Shapiro–Wilk test. Chi-square test was used for the categorical data, *t* test was used for the parametric data, and Mann Whitney *U* test was used for the non-parametric numerical data. $P < .05$ value was considered statistically significant.

MAIN POINTS

- The study included 287 parathyroid adenoma (PA) cases that had concomitant thyroid surgery: Synchronous PA and thyroid malignancy rate was 27.2% and papillary thyroid carcinomas (PTCs) accounted for 88.5% of the thyroid malignancies.
- Papillary thyroid carcinoma cases synchronized with PA were mostly seen in female patients and in right thyroid lobe, the multifocality rate was 18.8%, the follicular variant being the most common, the majority were papillary microcarcinomas and pT1 tumors, extrathyroidal extension rate was 13%.
- The "PA with PTC" and "PA without PTC" groups were statistically similar in the patient (age, gender) and PA (localization, number, and size) characteristics.

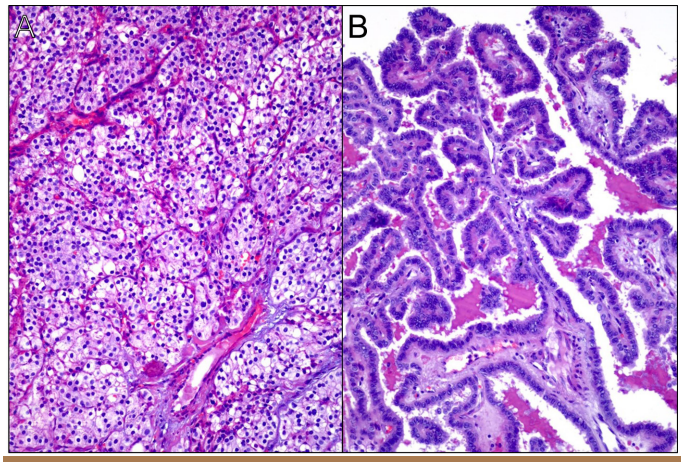

Figure 1. Microscopic view of the parathyroid adenoma (A) (H&E ×200). Classical variant papillary thyroid carcinoma in the same patient (B) (H&E ×200). H&E, hematoxylin and eosin.

Results

Patients

In a series of 287 PA cases, female : male ratio was approximately 6 : 1. The mean age was 56.3 ± 12.61 (14-90).

Clinicopathological Features of Parathyroid Adenomas

When the cases of unknown localization were excluded, 199 of 250 (79.6%) PAs were originated from a single parathyroid gland (PTG). Considering the cases where the localization was known exactly, the left-inferior PTG involvement was the most common. Twenty of 250 (8%) cases had intrathyroidal PA (IT-PA) and 1 case had both a right-inferior PTG-localized PA and an IT-PA. Considering the larger size in the cases with multiple PAs, the mean PA size was 1.7 ± 0.85 (0.2-6) cm (Table 1).

Characteristics of Thyroidectomy Materials

The majority of the cases (281; 97.9%) were operated and diagnosed in the same university hospital: 192 bilateral total/subtotal, 76 unilateral total/subtotal, 13 complementary thyroidectomy materials (4 bilateral, 7 unilateral, and 2 unknown). Bilateral total/subtotal thyroidectomy materials of 6 (2.1%) cases were consulted from another center, and the diagnosis was made by evaluating the ready slides and paraffin blocks.

Diagnoses of the thyroidectomy materials were as follows: BTD in 209 (72.8%) and primary thyroid malignancy in 78 (27.2%) cases. Sixty-nine PA cases had synchronous PTC; they constitute 24% of all PA cases and 88.5% of the cases with thyroid malignancies. Pathological diagnoses of the thyroidectomy materials were summarized in Table 2.

Clinicopathological Features of Papillary Thyroid Carcinoma Cases Synchronized with Parathyroid Adenoma

Female : male ratio was 7.6:1 in 69 PTC cases. The mean age was 55.4 ± 11.9 (20-90). Papillary thyroid carcinomas were often localized in the right thyroid lobe. Bilaterality and multifocality rates were 14.5%

Table 1. Clinicopathological Features of PA Cases in the Study

	n	%
	Mean ± SD	
Age (years)	56.3 ± 12.61	
Gender		
Female	245	85.4
Male	42	14.6
Size of PA (cm)	1.7 ± 0.85	
Number of PA		
Single	**254**	**88.5**
Multiple	**33**	**11.5**
2	26	9.1
3	5	1.7
4	2	0.7
Localization of PA		
PTG	**229**	**79.8**
Single adenoma		
Left inferior	61	21.3
Right inferior	47	16.4
Left superior	29	10.1
Right superior	22	7.7
Right unknown	20	7.0
Left unknown	19	6.6
Unknown inferior	1	0.3
Multiple adenomas		
More than one PTG	27	9.4
Right inferior	1	0.3
Left inferior	1	0.3
Left unknown	1	0.3
IT-PA	**20**	**7.0**
Single adenoma	18	6.3
Multiple adenomas	2	0.7
PTG and IT-PA	**1**	**0.3**
Unknown	**37**	**12.9**
Total	**287**	**100**

IT-PA, intrathyroidal PA; PA, parathyroid adenoma; PTG, parathyroid gland; SD, standard deviation.

Table 2. Diagnosis of the Thyroidectomy Materials in Cases with PA

	n	%
Benign thyroid disease	**209**	**72.8**
Nodular hyperplasia	164	57.1
FA*	21	7.3
Chronic lymphocytic thyroiditis (Hashimoto)	16	5.6
Grave's disease	3	1.0
Diffuse hyperplasia	3	1.0
Non-specific lymphocytic thyroiditis	2	0.7
Malignant thyroid disease	**78**	**27.2**
PTC	63	22.0
PTC + FA	4	1.4
Medullary carcinoma	4	1.4
FC	3	1.0
PTC + FC	1	0.3
PTC + FC + FA	1	0.3
FC + FA	1	0.3
Anaplastic carcinoma + FA	1	0.3
Total	**287**	**100**

FA, follicular adenoma; FC, follicular carcinoma; PA, parathyroid adenoma; PTC, papillary thyroid carcinoma; SD, standard deviation. *Follicular adenomas accompanying carcinomas were not included in this group.

and 18.8%, respectively. Considering the larger size in bilateral and multifocal tumors, the mean PTC size was 0.8 ± 0.64 (0.08-3.5) cm. In 54 (78.3%) cases, the tumor size was ≤1 cm (papillary microcarcinoma): 30 follicular and 24 classical patterns. In all PTC series, follicular variant was the most common subtype with a rate of 53.6%. Extrathyroidal extension was present in only 9 (13%) cases. The most common tumoral stage was pT1. When we considered the cases which had sufficient clinical data, we saw that there were lymph node metastasis in 2 cases and no cases had distant metastasis. The clinicopathological features of PTCs synchronized with PA were summarized in Table 3.

Comparison of "Parathyroid Adenoma with Papillary Thyroid Carcinoma" and "Parathyroid Adenoma without Papillary Thyroid Carcinoma" Groups

Two groups were statistically similar for age and gender. Female was the predominant gender for both groups. Multiple PAs were more frequent in "PA without PTC" whereas IT-PA rate was higher in "PA with PTC" group; both of these results were not statistically significant. The groups were similar for the mean PA size. Inferior PTG involvement was more common than superior one for both groups. While the left PTG involvement was more frequent for "PA without PTC" group, the right side was more frequently involved for "PA with PTC" group. However, there was no statistically significant difference between the 2 groups in terms of PA localization (Table 4).

Discussion

Parathyroid adenoma is the most common etiology for PHPT with a rate of 80%, the other etiologies are multiple gland disease in approximately 20% and parathyroid carcinomas in 0.5% of the cases.[4] Thyroid diseases with PHPT, particularly PTC, are not uncommon and have been studied several times.[1,2,7,8]

The frequency of BTD with PHPT was reported as 17%-66%.[5,7,8] In our study, the diagnosis of thyroid material was BTD in 72.8% of the cases with PA. As consistent with the literature, nodular hyperplasia was the most common disease in this group with a rate of 78.5%.[15] Isolated follicular adenomas constituted 10% (21/209) of all BTD cases.

The prevalence of PTC with PHPT was reported as 1.3%-17.6% in several studies.[1,2,7,8] The broad spectrum of the reported rates may be due to the differences in the geographical regions where the studies were conducted and the methods used. In this study, we used the pathology archive data to determine the frequency of synchronous PA and PTC cases and included the cases with PA diagnosis that had concomitant thyroid surgery. In this way, we found the rate of PA with thyroid malignancy to be 27.2%, and PTC composed of 88.5% of the malignant group. Parathyroid adenomas with PTC rate was 24% in all PA series. In our study, higher rates of thyroid malignancies with PA may be due to our study group included only the patients who underwent surgery. In our center, we always take large numbers

Table 3. Clinicopathological Features of PTC Cases Synchronized with PA

	n	%
	Mean ± SD	
Age (years)	55.4 ± 11.9	
Age		
≤50 years	25	36.2
>50 years	44	63.8
Gender		
Female	61	88.4
Male	8	11.6
Multifocality		
Present	13	18.8
Absent	56	81.2
Bilaterality		
Present	10	14.5
Absent	59	85.5
Localization		
Right lobe	30	43.5
Left lobe	25	36.2
Isthmus	9	13.0
Right and left lobes	2	2.9
Right lobe, left lobe, and isthmus	1	1.4
Unknown	2	2.9
PTC size (cm)	0.8 ± 0.64	
PTC size		
≤1 cm	54	78.3
>1 cm	15	21.7
Histological type		
Papillary microcarcinoma (follicular)	30	43.5
Papillary microcarcinoma (classical)	24	34.8
Follicular variant PTC	7	10.1
Classical variant PTC	5	7.2
Oncocytic variant PTC	2	2.9
Warthin-like variant PTC	1	1.4
Extrathyroidal extension		
Present	9	13.0
Absent	60	87.0
Tumoral stage		
pT1	65	94.2
pT2	2	2.9
pT3	2	2.9
Lymph node metastasis		
Present	2	2.9
Absent	3	4.3
Unknown	64	92.8
Distant metastasis		
Present	0	0
Absent	3	4.3
Unknown	66	95.7
Total	**69**	**100**

PA, parathyroid adenoma; PTC, papillary thyroid carcinoma.

of samples from thyroidectomy materials, even if they have a non-tumoral indication, which increases our incidence of incidentally detected microcarcinomas.

Table 4. Comparison of "PA with PTC" and "PA without PTC" Groups

	PA without PTC		PA with PTC		
	Mean ± SD		Mean ± SD		
	n	%	n	%	*P**
Age (years)					
Mean ± SD	56.6 ± 12.8		55.4 ± 11.9		.514
Age					
≤50 years	64	30.6	25	36.2	.386
>50 years	145	69.4	44	63.8	
Gender					
Female	179	85.6	61	88.4	.563
Male	30	14.4	8	11.6	
Size of PA (cm)					
Mean ± SD	1.7 ± 0.9		1.6 ± 0.6		.163
Number of PA					
Single	181	86.6	65	94.2	.086
Multiple	28	13.4	4	5.8	
Origin of PA**					
PTG	169	93.9	54	87.0	.102
IT-PA	11	6.1	8	12.9	
Superior/inferior localization of PA***					
Superior PTG	37	30.6	16	35.6	.541
Inferior PTG	84	69.4	29	64.4	
Right/left localization of PA******					
Right PTG	64	42.1	28	54.9	.112
Left PTG	88	57.9	23	45.1	
Total	**209**	**100**	**69**	**100**	**278**

IT-PA, intrathyroidal PA; PA, parathyroid adenoma; PTC, papillary thyroid carcinoma; PTG, parathyroid gland.
* $P < .05$ was considered statistically significant.
**One case who had a PA located in right-inferior PTG and also an IT-PA, and 35 cases with no available data about PA origin were excluded during the statistical analysis.
***18 cases who had both superior and inferior PTG involvement, 20 cases with IT-PA, 74 cases with no available data about the localization were excluded during the statistical analysis.
****18 cases who had both right and left PTG involvement, 20 cases with IT-PA, 37 cases with no available data about the localization were excluded during the statistical analysis.

Medullary thyroid carcinoma with PHPT due to genetic relationship was well documented in multiple endocrine neoplasia type I and IIa.[5,10] However, the mechanisms underlying the relationship between PHPT and PTC are unclear. Some authors suggest a possible hypothesis based on shared embryological origin and genes, high parathyroid hormone (PTH), low 1.25-hydroxy vitamin D as well as hypercalcemia.[5] High levels of PTH, low 1.25-hydroxy vitamin D, and hypercalcemia result in mitogenesis and neovascularization by stimulating angiogenic growth factors and fibroblast growth factors, so these factors can stimulate tumor growth.[5,16] Some authors suggested that low-dose head and neck radiation therapy could be a risk factor for inducing 2 entities.[3,9] Since this is a retrospective archive study, head and neck radiation history was unknown for our patients, and we could not make an assessment on this subject.

Minimal invasive parathyroidectomy is a widely accepted procedure for PA cases.[4,17] However, if a thyroid nodule requires thyroidectomy, simultaneous parathyroidectomy and thyroidectomy should be preferred. Otherwise, performing the second surgical

procedure may cause some complications such as increased recurrent nerve damage, hoarseness and permanent hypocalcemia, and also increase the cost.[1,4,17]

In PHPT cases, USG and 99mTc-MIBI are routinely performed.[17] 99mTc-MIBI has been reported as the most sensitive diagnostic method to determine the PA localization and can also identify ectopic tissues.[9] Combined use of 99mTc-MIBI scanning, USG, and USG-guided FNA is the most recommended method for the diagnosis of thyroid nodules in cases with PA.[3,9]

Both PHPT and PTC with PHPT cases were reported as more frequent in females.[2,5,10-12] Primary hyperparathyroidism incidence increases with age.[5] Lehwald et al[11] found that 71.4% of 35 PTC cases with PHPT were between 50 and 70 years old. In a study, it was found that PTC cases with PHPT were older than isolated PTC cases.[2] Çelik et al compared 21 BTD and 20 PTC cases with PHPT which had PA diagnosis in 26. They found no difference between the 2 groups in terms of age and gender.[15]

In our study, 85.4% of all PA cases and 88.4% of PA with PTC cases were female, as consistent with the literature. The mean age for all PA cases was 56.3, and it was statistically similar in "PA without PTC" and "PA with PTC" groups (56.6 and 55.4, respectively).

The most PTCs with PHPT were reported as microcarcinoma.[1,10-12] In a study, it was found that PTC cases with PHPT had smaller tumor size (median 0.7 cm) than the isolated PTCs (median 1.5 cm).[2] Yazici et al[10] found that the mean size of 6 PTCs with PA was 0.81 (0.4-1.7) cm. In our study, 78.3% of 69 PTC cases were papillary microcarcinomas, similar to the literature. The mean PTC size was 0.8 (0.08-3.5) cm.

In the literature, the classical variant PTC was reported as the most common PTC subtype in cases with PA.[2,5] Unlike the literature, in our series, the most common histological type was the follicular variant for both microcarcinomas and the larger PTCs.

In a study, multifocality was found in 4 of 12 PTCs with PHPT.[5] Çetin et al[2] compared 31 PTC with PHPT cases and 186 isolated PTC cases, and they found that the multifocality was significantly higher (45.2%) in the former. In our study, the multifocality rate was 18.8% and lower than the other study results.

Çetin et al[2] found that the extrathyroidal extension was higher (16.1%) in PTC with the PHPT group than isolated PTC, but this result was not statistically significant. In another study, extrathyroidal extension was present in 11.4% of 35 PTC with PHPT cases.[11] Liu et al[16] found that extrathyroidal extension was more common in PTC with asymptomatic PHPT cases compared to symptomatic ones. In our study, extrathyroidal extension rate was 13%.

In a study including both the cases with primary and renal hyperparathyroidism (HPT), Tsai et al reported that PTC cases with HPT were usually diagnosed in the early stage. However, they reported that comorbidity due to HPT decreases long-term survival and the cardiovascular event may be considered as the major cause of death.[18] Beebeejaun et al[5] detected lymph node involvement in 3 of 12 PTC with PHPT cases. In another study, lymph node involvement was present in 8.6% of 35 cases.[11] In our study, the tumoral stage was mostly pT1 with a rate of 94.2%. The lymph node metastasis was present in 2 of 5 cases with sufficient information and there was no case with distant metastasis. Since this is a retrospective study, we could not evaluate the survival of the patients.

Unlike the other studies, we compared "PA with PTC" and "PA without PTC" groups for the patient and synchronous PA characteristics in this study. Two groups were statistically similar in terms of age and gender. Females were predominant in both. Multiple PA rate was more frequent in "PA without PTC" group and IT-PA rate was more frequent in "PA with PTC" group. However, these results were not statistically significant.

Yazici et al[10] evaluated 6 PTC with PA cases. They found that 5 of the PAs were located in inferior PTGs and all of them were located on the right side. They found the median PA size as 1.4 (0.5-3.8) cm. In another study including 8 cases of PA with PTC, the mean PA size was found as 2.1 (0.6-3.5) cm.[9] In our study, right side and inferior PTG involvements were more common in "PA with PTC" group. Mean PA size was 1.7 and 1.6 cm in "PA without PTC" and "PA with PTC" groups, respectively. In the statistical analysis, there was no difference between "PA with PTC" and "PA without PTC" groups in terms of PA localization and size.

Our study had some limitations. Firstly, it is based on only retrospective pathological data. However, preoperative thyroidectomy indications, radiological and biochemical laboratory data of cases are also necessary for further interpretation and discussion. In addition, since there was not enough data, no comment could be made on the survival of cases.

Conclusion

Cases with synchronous PA and PTC are not uncommon, and detection of PTC before surgery may change the surgical procedure. Therefore, all PA cases should be thoroughly investigated for concomitant thyroid pathologies before surgical treatment.

Ethics Committee Approval: The study protocol was accepted by Clinical Research Ethics Committee of Amasya University (Approval no: 35, Date: March 03, 2022).

Informed Consent: Since this is a retrospective archive study, informed consent was not obtained.

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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