

Incidental Finding of Papillary Thyroid Carcinoma in the Patients with Primary Hyperparathyroidism

Primer Hiperparatiroidi Hastalarında İnsidental Papiller Tiroid Karsinomu Riski

Pinar Yazici, Mehmet Mihmanli, Emre Bozdog, Nurcihan Aygun, Mehmet Uludag

Clinic of General Surgery, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Turkey

Abstract

Objective: The relationship between primary hyperparathyroidism (pHPT) and papillary thyroid cancer (PTC) still remains unclear. We aimed to investigate the incidence of the co-existence of pHPT and PTC.

Materials and Methods: Between 2010 and 2013, all patients with pHPT were retrospectively reviewed and those undergoing concomitant thyroid surgery were recorded. Of these, patients with a pathological result showing papillary or micro-papillary thyroid cancer were included into the study. A chart review of 228 patients who underwent surgery for pHPT revealed 86 (37.7%) patients with concurrent thyroid disease requiring surgical treatment.

Results: Thyroid cancer was noted in six female patients (6.9%) undergoing thyroid resection, and 2.6% of all patients with pHPT. Four patients underwent total thyroidectomy while lobectomy was applied in the remaining two. None of the cases with lobectomy required a completion thyroidectomy.

Conclusion: We demonstrated the concurrence of PTC and pHPT at a rate of 2.6% which appeared as a coincidental pathology; however, thyroid disorders, seen in one of three patients with pHPT, were not uncommon. Further research is still needed to develop a reliable explanation for relationship between pHPT and non-medullary thyroid cancer.

Keywords: Primary hyperparathyroidism, thyroid disorders, surgical treatment, papillary thyroid cancer

Özet

Amaç: Her ne kadar primer hiperparatiroidi (pHPT) ile medüller tiroid kanser ilişkisi bilinse de papiller tiroid kanseri ile ilişkisi halen net değildir. Biz bu çalışmada pHPT tanısı nedeniyle opere ettiğimiz hastalardaki papiller tiroid kanser sıklığını incelemeyi amaçladık.

Gereç ve Yöntem: Primer HPT tanısı ile 2010 ve 2013 yılları arasında eş zamanlı tiroid cerrahisi uygulanan hastalar retrospektif olarak incelendi. Bu hastalardan patoloji sonucunda papiller veya mikropapiller tiroid kanseri tanısı alan hastalar çalışmaya dahil edildi. Çalışma sürecinde pHPT tanısı ile cerrahi tedavi uygulanan 228 hastadan 86'sında (%37,7) ek tiroid cerrahisi uygulandığı saptandı.

Bulgular: Ek tiroid cerrahisi uygulanan 6 kadın hastada (%6,9)-pHPT hastalarının %2,6'sı tiroid kanseri saptandı. Dört hastada total tiroidektomi papiller diğer 2 hastada lobektomi yapıldı. Hastaların hiçbirinde tamamlayıcı tiroidektomiye ihtiyaç duyulmadı.

Sonuç: Primer HPT hastalarında %30 oranında tiroid patolojisi izlenmesine rağmen %2,6 gibi düşük bir orandaki tiroid kanser birlikteliği tesadüfi olarak ilişkilendirilebilir. Fakat medüller olmayan tiroid kanseri ile pHPT arasındaki bağa daha güvenilir bir açıklama getirebilmek için ileri çalışmalar gerekmektedir.

Anahtar Kelimeler: Primer hiperparatiroidi, tiroid bezi hastalıkları, cerrahi tedavi, papiller tiroid kanseri

Introduction

Although primary hyperparathyroidism (pHPT) and concomitant medullary thyroid disease is well described in the literature as a part of multiple endocrine neoplasia (MEN Type I and IIa), coexistence of pHPT and papillary thyroid cancer (PTC) has been documented in sporadic case reports and in some small series. In these reports, diagnosis of PTC is mostly incidentally while pHPT is usually the primary pathology [1, 2]. This incidental diagnosis can result in need for second neck surgery for the completion of thyroidectomy

that remains a debatable issue among surgeons. Therefore, evaluation of the thyroid glands prior to surgery allows the surgeon to plan optimal surgical approach and determine the extent of thyroidectomy.

In recent years, due to advanced methods for localization, there has been a considerable interest in performing minimally invasive procedure in pHPT patients [3]. This focused approach, compared to standard bilateral neck exploration, may be accompanied by an increase in the possibility of overlooked thyroid pathology. However, the clinical significance of these incidentally diagnosed thyroid tumours or whether

Received: November 14, 2014 / **Accepted:** February 12, 2015

Correspondence to: Pinar Yazici, Clinic of General Surgery, Şişli Etfal Training and Research Hospital, İstanbul, Turkey

Phone: +90 212 373 50 00 e-mail: drpinarayzici@gmail.com

©Copyright 2015 by the Atatürk University School of Medicine - Available online at www.eurasianjmed.com

DOI:10.5152/eurasianjmed.2015.119



they are really incidental in published reports is still unclear. In this report, we aimed to investigate the frequency of incidentally diagnosed papillary thyroid cancer in pHPT patients who underwent concomitant surgical treatment for thyroid disorders.

Materials and Methods

Between January 2010 and July 2013, 228 patients who underwent parathyroid surgery due to pHPT were reviewed retrospectively. All patients with concomitant thyroid disease requiring surgical treatment were analysed. Of these, patients whose final pathological examination revealed PTC were included into the study. Patients diagnosed with medullary or follicular thyroid cancer (n=3) were excluded. Demographic features, preoperative diagnostic methods, type of surgical treatment, postoperative period and pathological examination were recorded.

Diagnosis of thyroid disorder was based on information including clinical history, physical examination, thyroid hormone profile, ultrasound (US) and scintigraphy. Additionally, fine needle aspiration biopsy (FNAB) was performed in patients, whose US revealed questionable findings in thyroid gland. These are as follows: single hypoechoic lesion with irregular margins with or without punctate calcifications, solid nodules larger than 1 cm, solid nodules smaller than 1 cm in high-risk patients regarding US findings and increased risk for thyroid cancer (prior neck radiation, surgical history of thyroid lobectomy for cancer, history of MEN). All patients were consented for surgical intervention to thyroid gland in addition to parathyroid surgery. Surgical approaches [bilateral neck exploration or unilateral exploration (anterior or lateral)] were based on the location of the abnormal parathyroid glands and extension of thyroid disorder determined preoperatively. Continuous data are expressed as mean±standard deviation for normally distributed variables. Median was used for data, which were not normally distributed.

Results

All patients were women with a median age of 51 years (range: 45-79). Overall incidence of incidental PTC in pHPT patients was 2.6% (6/228). It was 6.9% (6/86) regarding the concomitant thyroid procedures, which were performed in 86 patients (37.7%). None of them had a history of previous head or neck irradiation. Laboratory findings showed elevated parathyroid hormone (median: 336 pg/mL, range: 147-2610 pg/mL) and calcium levels (11.6±0.7 mg/dL) in all patients. Ultrasound results revealed suspected right-sided parathyroid adenoma in three patients while concomitant thyroid pathology was reported in all. Of those with thyroid pathology, four cases had nodules in both lobes. Tc-99m MIBI scintigraphy revealed findings consistent with a parathyroid adenoma in four patients.

Table 1. Demographic and operative features of the patients

Parameters	
Age (years, median, range)	51±11.9 (45-79)
Sex (F/M)	6
Location of parathyroid adenoma (RI/RS)	5/1
Size of the adenomas (cm, median, range)	1.4 (0.5-3.8)
Preoperative work-up of thyroid gland	
US(+/-)*	3/6
Scintigraphy	4/6
FNAB (insignificant/ suspicious for PTC/ PTC)	3/2/1
Thyroid surgery	
(lobectomy / thyroidectomy)	2/4
Frozen section (malignancy/others)	3/2
Histopathological examination (PTC/MPTC)	2/4
Size of thyroid tumours (cm, mean±SD, range)	0.81±0.5 (0.4-1.7)
F: female; M: male; RI: right inferior lobe; RS: right superior lobe; US: ultrasound; FNAB: fine needle aspiration biopsy; PTC: papillary thyroid cancer; MPTC: micro-papillary thyroid carcinoma *US revealed parathyroid adenoma location in four patients and multinodular goitre in three cases.	

Preoperative FNAB of thyroid nodules was applied in all patients while intra-operative frozen section examination was performed in five. FNAB was compatible with PTC and suspicious for PTC in 1 and 2 cases, respectively, while other samples were insignificant. Frozen section examination confirmed papillary malignancy in three cases, oncocyctic changes were reported in other two patients. Four patients underwent total thyroidectomy (one patient with preoperative FNAB result of PTC, other three with frozen examination with PTC) while right lobectomy through unilateral neck exploration was performed in the remaining two (Table 1). None of the patients underwent cervical neck dissection. Histopathological examination revealed papillary microcarcinoma in 4 patients (range: 0.4-0.7 cm in diameter) and PTC in the other two patients (1.2 and 1.7 cm in size) without capsular infiltration. Location of the tumours were mostly on the right side (n=5). In one patient, bilateral micro-papillary thyroid cancer was found. Two patients undergoing right lobectomy, whose pathological examination confirmed micro-papillary thyroid cancer did not require re-operation.

There was no significant correlation between incidental finding of papillary thyroid cancer and age, size of parathyroid adenoma, diameter of thyroid nodule and preopera-

Table 2. Literature review of the studies evaluating the relationship between hyperparathyroidism and thyroid cancer

Study	Year	No. of patients	Type of thyroid cancer (PTC/FTC)	(%) of thyroid cancer	History of RIT (Yes/No)
Calceterra et al. [2]	1979	11	10/1	8	NS
Krause et al. [1]	1991	6	6/0	2.6	Not mentioned
Burmeister* et al. [5]	1997	22	21/1	–	Significant
Seehofer** et al. [17]	2005	9	8/1	2.4	NS
Lehwald et al. [12]	2013	41	35/6	2	22/19

*This analysis included patients with all type of hyperparathyroidism.
**This study analysed the patients with renal hyperparathyroidism.
M: male; F: female; PTC: papillary thyroid cancer; FTC: follicular thyroid cancer, RIT: radioiodine therapy
NS: (Not significant) insignificant relation with predisposing factors

tive calcium values ($r=-0.05$, $p=0.42$; $r=0.01$, $p=0.88$; $r=0.04$, $p=0.56$ and $r=-0.01$, $p=0.86$ respectively.)

In all patients but one, single adenoma removal was performed. One patient underwent subtotal parathyroidectomy (three-and-a-half gland parathyroidectomy), since exploration of other parathyroid glands revealed hyperplasia. The most common location of the parathyroid adenoma was posterior to inferior pole of the right lobe of the thyroid ($n=5$, 83.3%). Only in one case, it was located around superior pole of the right lobe of the thyroid. The median size of adenomas was 1.4 cm (range: 0.5-3.8). All patients were discharged uneventfully on postoperative day 1. Histopathological examinations of the parathyroid glands were consistent with parathyroid adenoma in five patients and hyperplasia in one. In all patients, serum levels of parathyroid hormone and calcium returned to normal levels after surgery.

Discussion

The incidence of thyroid disorders in patients with pHPT is between 2.5% and 40% while the incidence of pHPT in patients with thyroid disorders is found at a lower rate ranging between 0.3% and 8.7% [4-9]. The incidence of thyroid disorders in our series was found to be 37.7%. However, most of the cases were diagnosed with multi-nodular goitre and the incidence of malignancy was only 2.6%. This result complies favourably to the previously reported series in which malignancy rates were between 2.0% and 17% (Table 2) [1, 4-6, 10].

Concurrence of the parathyroid and thyroid disorders makes treatment process more complicated. In their recent study, Onkendi et al. [11] suggested (99 m) technetium sestamibi-scintigraphy for pHPT patients with concurrent thyroid disorders to detect any thyroid malignancy. Nevertheless, overlooked thyroid pathology can cause misdiagnosis of PTC and reoperation for completion thyroidectomy or neck dis-

section. Papillary microcarcinoma was the confirmed pathology in four cases and the features of the tumour in other two such as tumour size and capsular invasion provide no need for further surgery. In their series investigating the concomitant nonmedullary thyroid cancer in patients with pHPT, Lehwald et al. [12] also reported papillary microcarcinoma as the most common pathology (68.8%) and 86% of the cases had benign features with no extrathyroidal extension or lymph node involvement.

In recent years, it is well known that frequency of thyroid procedures and incidental findings of thyroid cancer has been arising with an average rate of 10% [13, 14]. Particularly, incidental finding of papillary microcarcinoma has been reported in a large number of patients undergoing thyroidectomy for benign thyroid disease, reaching up to 24% [15]. Likewise, papillary microcarcinoma was the most commonly seen pathology in the present study.

These cases underlined the need for a high index of suspicion for synchronous hyperparathyroidism and differentiated thyroid cancer. In their large series, Lehwald et al. [12] noted the predominance of middle-aged female patients and right side location of tumours. In our study, favourable results on these parameters were observed. Most of the coincidental thyroid cancers were reported as PTC and in small size, particularly micro-papillary carcinoma [5, 12, 16, 17]. Likewise, in our series, no need for further intervention was required due to majority of papillary microcarcinoma and small sized PTC without capsular infiltration.

The mechanisms underlying the relationship between pHPT and PTC have not been established, so far. The clinical role of pHPT compared to secondary and tertiary HPT is controversial [5, 6]. However, an increased risk of non-parathyroid cancers in patients with pHPT has been reported in several studies [18]. Miccoli et al. [13] reported thyroid malignancy as the most prevalent cancer among those patients in whom pHPT was

the primary disorder and leading factor for newly diagnosed cancer. While some authors suggested this concurrence as a coincidental pathology [4, 5, 17, 19-21], others investigated several predisposing factors such as exposure to neck radiation, goitrogenic effect and increased mitotic activity induced by hypercalcemia [22, 23]. In addition, tumour-promoting effect of parathyroid hormone and subsequent genetic predisposition to new malignancies were also noted [16, 24]. Increased overall risk of cancers with persistent features throughout years, even after parathyroidectomy was also emphasized and, surgery was not found as risk-reducing but delaying factor for cancer occurrence [22]. This phenomenon set us on a course of thinking that exposure to increased parathyroid hormone levels cause to initiate a step in the cancer process in altering the DNA, as it is also known that parathyroid hormone is confirmed with its catabolic effects. Further research is still needed to develop a reliable explanation for relationship between pHPT and non-medullary thyroid cancer.

This study reinforces previous data about patients with pHPT. The frequency of concomitant thyroid disease is found in one of three cases, while the incidence of thyroid cancer at a rate of 6.9% is quite lower, that seems to be a coincidental occurrence. A limitation of this study is the small size of the pHPT patients, which did not permit establishing a reliable association between these two entities. We are in the process of initiation of a prospective comparative cohort study of incidental finding of thyroid cancer in patients who underwent thyroid surgery for benign thyroid disorders and patients with pHPT undergoing concomitant thyroid surgery.

Ethics Committee Approval: Ethics committee approval was obtained.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.Y. M.U.; Design - P.Y.; Supervision - M.U., M.M.; Funding - P.Y.; Materials - E.B., N.A.; Data Collection and/or Processing - N.A., E.B.; Analysis and/or Interpretation - P.Y.; Literature Review - P.Y., E.B.; Writer - P.Y.; Critical Review - M.U., M.M.

Acknowledgements: Authors would like to thank Emre Bozkurt, MD for his help and assistance with data collection.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

- Krause U, Olbricht T, Metz K, Rudy T, Benker G. Coincidence of non-medullary thyroid cancer and hyperparathyroidism. *Chirurg* 1991; 62: 536-9.
- Calcaterra TC, Paglia D. The coexistence of parathyroid adenoma and thyroid carcinoma. *Laryngoscope* 1979; 89: 1166-9. [\[CrossRef\]](#)
- Palazzo FF, Delbridge LW. Minimal-access/minimally invasive parathyroidectomy for primary hyperparathyroidism. *Surg Clin North Am* 2004; 84: 717-34. [\[CrossRef\]](#)
- Bentrem DJ, Angelos P, Talamonti MS, Nayar R. Is preoperative investigation of the thyroid justified in patients undergoing parathyroidectomy for hyperparathyroidism? *Thyroid* 2002; 12: 1109-12. [\[CrossRef\]](#)
- Burmeister LA, Sandberg M, Carty SE, Watson CG. Thyroid carcinoma found at parathyroidectomy: association with primary, secondary, and tertiary hyperparathyroidism. *Cancer* 1997; 79: 1611-6. [\[CrossRef\]](#)
- dell'Erba L, Baldari S, Borsato N, et al. Retrospective analysis of the association of nodular goiter with primary and secondary hyperparathyroidism. *Eur J Endocrinol* 2001; 145: 429-34. [\[CrossRef\]](#)
- Morita SY, Somervell H, Umbricht CB, Dackiw AP, Zeiger MA. Evaluation for concomitant thyroid nodules and primary hyperparathyroidism in patients undergoing parathyroidectomy or thyroidectomy. *Surgery* 2008; 144: 862-6. [\[CrossRef\]](#)
- Ogawa T, Kammori M, Tsuji E, et al. Preoperative evaluation of thyroid pathology in patients with primary hyperparathyroidism. *Thyroid* 2007; 17: 59-62. [\[CrossRef\]](#)
- Sidhu S, Campbell P. Thyroid pathology associated with primary hyperparathyroidism. *Aust N Z J Surg* 2000; 70: 285-7. [\[CrossRef\]](#)
- Lee JK, Obrzut SL, Yi ES, Deftos LJ, Bouvet M. Incidental finding of metastatic papillary thyroid carcinoma in a patient with primary hyperparathyroidism. *Endocr Pract* 2007; 13: 380-3. [\[CrossRef\]](#)
- Onkendi EO, Richards ML, Thompson GB, Farley DR, Peller PJ, Grant CS. Thyroid cancer detection with dual-isotope parathyroid scintigraphy in primary hyperparathyroidism. *Ann Surg Oncol* 2012; 19: 1446-52. [\[CrossRef\]](#)
- Lehwald N, Cupisti K, Krausch M, Ahrazoglu M, Raff el A, Knoefel WT. Coincidence of primary hyperparathyroidism and non-medullary thyroid carcinoma. *Horm Metab Res* 2013; 45: 660-3. [\[CrossRef\]](#)
- Miccoli P, Minuto MN, Galleri D, et al. Incidental thyroid carcinoma in a large series of consecutive patients operated on for benign thyroid disease. *G Chir* 2013; 34: 21-6.
- Bradly DP, Reddy V, Prinz RA, Gattuso P. Incidental papillary carcinoma in patients treated surgically for benign thyroid diseases. *Surgery* 2009; 146: 1099-104. [\[CrossRef\]](#)
- Sakorafas GH, Stafyla V, Kolettis T, Tolumis G, Kassaras G, Peros G. Microscopic papillary thyroid cancer as an incidental finding in patients treated surgically for presumably benign thyroid disease. *J Postgrad Med* 2007; 53: 23-6. [\[CrossRef\]](#)
- Goswami S, Ghosh S. Hyperparathyroidism: cancer and mortality. *Indian J Endocrinol Metab* 2012; 16 (Suppl 2): S217-20.
- Seehofer D, Rayes N, Klupp J, et al. Prevalence of thyroid nodules and carcinomas in patients operated on for renal hyperparathyroidism: experience with 339 consecutive patients and review of the literature. *World J Surg* 2005; 29: 1180-4. [\[CrossRef\]](#)

18. Palmer M, Adami HO, Krusemo UB, Ljunghall S. Increased risk of malignant diseases after surgery for primary hyperparathyroidism. A nationwide cohort study. *Am J Epidemiol* 1988; 127: 1031-40.
19. Kambouris AA, Ansari MR, Talpos GB. Primary hyperparathyroidism and associated neoplasms. *Henry Ford Hosp Med J* 1987; 35: 207-10.
20. Cinamon U, Turcotte RE. Primary hyperparathyroidism and malignancy: "studies by nature". *Bone* 2006; 39: 420-3. [\[CrossRef\]](#)
21. Asik M, Anaforoglu I, Kose M, Karyagar S, Mollamehmetoglu B, Algun E. Papillary thyroid carcinoma with primary hyperparathyroidism: a report of two cases and a brief literature review. *Turk JEM* 2013; 17: 12-14.
22. Nilsson IL, Zedenius J, Yin L, Anders E. The association between primary hyperparathyroidism and malignancy: nationwide cohort analysis on cancer incidence after parathyroidectomy. *Endocr Relat Cancer* 2007; 14: 135-40. [\[CrossRef\]](#)
23. LiVolsi VA, LoGerfo P, Feind CR. Coexistent parathyroid adenomas and thyroid carcinoma. Can radiation be blamed? *Arch Surg* 1978; 113: 285-6. [\[CrossRef\]](#)
24. Posen S, Clifton-Bligh P, Reeve TS, Wagstaffe C, Wilkinson M. Is parathyroidectomy of benefit in primary hyperparathyroidism? *Q J Med* 1985; 54: 241-51.