

Concomitant thyroid cancer in patients with primary hyperparathyroidism in an endemic goitre region



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OBJECTIVE: Primary hyperparathyroidism (pHPT) is often accompanied by underlying thyroid pathology and 1 to 36% of these thyroid pathologies are malignant. How the identification of these lesions affects patient management is unclear. We present a single-center experience with the prevalence of concomitant thyroid cancer in patients who underwent parathyroidectomy for pHPT.

MATERIALS AND METHODS: This was a retrospective cohort study. Two hundred-two patients with primary hyperparathyroidism included study. Demographic data, clinical findings, and final histopathological diagnosis were recorded retrospectively.

RESULTS: Preoperative cervical ultrasound examination revealed co-existent thyroid abnormalities in 117 (57.9%) patients. Mean age of these patients was 57.8 ± 12.2 years and 88% were female. Sixty-three (53.9%) of the patients with thyroid abnormalities, underwent preoperative fine needle aspiration biopsy (FNAB). Cytology result was malignant in one (1.6%) patient, benign in 47(85.7%) patients, indeterminate in six (9.5%) patients and Hurthle cell neoplasm in two (3.2%) patients. Ninety-four (80.3%) of the patients underwent simultaneous thyroid surgery. Final pathology of the thyroid specimen was malignant in 26 (12.9%) patients. Sixteen of the malignant patients had preoperative FNAB. Preoperative FNAB result of these patients was malignant in one patient, indeterminate in two patients and benign in 13 patients.

CONCLUSION: By implementing a comprehensive approach to patients with pHPT who present with thyroid disease, concomitant pathology may be elucidated preoperatively. But, this approach will not facilitate the detection of otherwise unsuspected thyroid cancer in an endemic goitre region.

KEY WORDS: Cancer, Parathyroid adenoma, Parathyroidectomy, Thyroid, Thyroidectomy

Introduction

The prevalence of synchronous thyroid pathology varies between 12 to 84 % of patients with primary hyperparathyroidism (pHPT) and 1 to 36% of these thyroid pathologies are malignant¹⁻⁶. There is no guideline for management of these patients. Suspicious thyroid pathol-

ogy, parathyroid malignancy, presence of the intra-thyroid adenoma may be required thyroid resection at the same time of parathyroid surgery⁶.

Minimally invasive parathyroidectomy (MIP) is an alternative to conventional bilateral cervical neck exploration. Preoperative accurate localization of parathyroid adenoma is mandatory for perform MIP⁶.

Imaging is commonly performed using technetium ^{99m}Tc-sestamibi (MIBI) scan and cervical ultrasound (US). A recent evidence-based review recommended MIBI as the first test, with US by an experienced operator as a reasonable alternative⁷. On the other hand preoperative US has been believed to be valuable not only for localizing parathyroid adenomas but also for detecting synchronous thyroid nodules⁷.

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The aim of this study was to determine the prevalence of concomitant thyroid disease in patients with pHPT and the nature of any associated pathology.

Materials and Methods

This was an observational cohort study. We retrospectively reviewed the medical records of 202 patients with pHPT who had undergone surgery between April 2010 and February 2014 at Ankara Numune Education and Research Hospital.

All patients were identified from the hospital records, aided by a computer search. Clinical work-up in advance of surgery included a full medical history and physical examination, routine bloods including full blood count, urea and electrolytes together with preoperative calcium level, parathyroid hormone level, thyroid hormone level and TSH level. All patients underwent radiological assessment which included US and/or MIBI specifically to help localized involved parathyroid tissue. The frequency of simultaneous thyroid surgery carried out during parathyroidectomy and associated pathology was determined on retrospective review of patient charts.

STATISTICAL ANALYSIS

Shapiro-Wilk test was used for assessing normality. If continuous data non-normally distributed presented as median value (interquartile range) otherwise presented as mean±SD. SPSS for Windows 11.5 (Chi. IL., USA) was used for statistical analysis.

Results

Preoperative cervical ultrasound examination revealed co-existent thyroid abnormalities in 117 patients (57.9%). The mean size of these nodules was about 1.4 (2-

80mm)cm. Mean age of these patients was 57.8 ± 12.2 (min: 26, max: 87) years and 88% were female. Preoperatively, the average calcium level was 11.24 ± 1.02 mg/dL, and parathyroid hormone level was 203 (135-270) pg/mL (Table I).

The cause of pHPT was a single adenomatous gland in 98(97.5%) patients, 2 adenomatous glands in 13 (1.7%) patients, and 3 adenomatous glands in 1 (0.8%) patients. Sixty-three (53.9%) of the patients with thyroid abnormalities, underwent preoperative fine needle aspiration biopsy (FNAB). Cytology result was malignant in one (1.6%) patient, benign in 47(85.7%) patients, indeterminate in six (9.5%) patients and Hurthle cell neoplasm in two (3.2%) patients.

Ninety-four (80.3%) of the patients underwent simultaneous thyroid surgery. Thyroid resection was performed for optimize operative access or according to FNAB results or cosmetic purposes. Eighty-two (70.1%) patients underwent total thyroidectomy, and 12 (29.9 %) patients underwent lobectomy (Table II).

Final pathology of the thyroid specimen was benign in 62 (30.7%) patients, Well differentiated thyroid tumor

TABLE II - Preoperative cervical ultrasound, FNAB findings and operative procedures.

Preoperative Thyroid Ultrasound Results	Patients (n=202)
Thyroid Nodules	117 (57.9%)
Localized parathyroid abnormality	154 (76.3%)
99m-Technetium Sestamibi Results	Patients (n=154)
Localized parathyroid abnormality	146 (94.6%)
Fine Needle Aspirations Performed	Patients (n=63)
Malignant	1(1.6%)
Indeterminate	6 (9.5%)
Benign	47 (85.7 %)
Hurthle cell neoplasm	2 (3.2%)
Thyroid Operation	Patients (n=94)
Total Thyroidectomy	82 (70.1 %)
Thyroid lobectomy	12 (29.9 %)

TABLE I - Demographics distribution of the primary hyperparathyroidism patients with thyroid nodules.

Demographics	Patients (n= 117)
Age; Mean ± SD (years)	57.8 ± 12.2
Gender (Female - Male)	103 - 14
P	
re-Op Lab Test	
Serum Calcium, mg/dl	11.24 ± 1.02
PTH, pg/ml	203 (135-270)
Free T3 (Triiodothyronine) pg/mL	2.87±0.87
Free T4 (thyroxine) ng/L	1.06±0.26
Thyroid-stimulating hormone (TSH) mIU/L	1.53(0.8-2.72)

TABLE III - Surgical pathology in patients undergoing additional thyroid surgery.

Final pathology	No. of patients	% (n= 202)
Nodular hyperplasia	42	20.8
Micropapillary carcinoma	21	10.4
Papillary thyroid carcinoma	4	2
Well differentiated thyroid tumor of uncertain malignant potential	6	3
Hashimoto thyroiditis	10	5
Lymphocytic thyroiditis	8	4
Hurthle cell adenoma	2	1
Medullary thyroid cancer	1	0.5

of uncertain malignant potential in 6 (3%) and malignant in 26 (12.9%) patients and in malignant group 21 patients were found to have papillary micro carcinoma, four patients were found to have papillary carcinoma and one patient was found to have medullary microcarcinoma (Table III).

The mean size of the thyroid cancers was 9.3 mm with a range of 1-70 mm. Thirteen of the 26 thyroid cancers were multifocal, and six of these were bilateral. Four patients underwent total thyroidectomy with central neck dissection. Positive lymph nodes were found in 2 of four patients with PTC. The patient with medullary thyroid cancer had an abnormal preoperative ultrasound. FNAB of the thyroid lesion was benign; a total thyroidectomy was performed and final histology showed medullary thyroid cancer. This patient was subsequently identified as the index patient of a multiple endocrine neoplasia (MEN) IIA kindred.

Sixteen of the malignant patients had preoperative FNAB. Preoperative FNAB result of these patients was malignant in one patient, indeterminate in two patients and benign in 13 patients.

All cases of pHPT were confirmed to be secondary to parathyroid adenoma. There was no significant difference noted between patients with benign thyroid pathology and those with thyroid cancer in regards to patient age or size of lesion.

Discussion

This study was undertaken to determine the prevalence of concomitant thyroid disease in patients undergoing surgical treatment for pHPT. Synchronous thyroid and parathyroid disease was first described in 1947. Over a quarter century later, Prinz et al⁸ analyzed 351 patients who underwent parathyroidectomy for pHPT and found that 20% patients had nodular disease at the time of operation, of which 14 (4%) were noted to have well-differentiated thyroid cancer.

In another study, 124 of the patients who underwent parathyroidectomy were found to have 54% concomitant thyroid disease intraoperatively; on the other hand 0.4% patients were noted to have parathyroid disease at the time of thyroidectomy². Historically, the prevalence of thyroid cancer in patients with pHPT below 5% in studies from non-endemic areas^{9,10}. In regions where goiter is endemic, thyroid diseases and thyroid carcinoma occur in association with PHPT at a higher rate compared to the non-endemic regions¹¹⁻¹⁵. The range varies between 10.9 and 17.6%. Probable reasons to this situation are environmental factors such as iodine deficiency and use of prophylactic iodine. Relation of iodine deficiency with increased rate of goitre and nodular thyroid diseases is well known. In epidemiological and experimental studies, it is reported that iodine triggers development of thyroiditis and increases incidence of PTC¹⁴.

In this current study, 57.9% of patients with pHPT had thyroid concomitant thyroid diseases and final pathology was malignant in 12.9% of the patients. These results are consistent with the literature.

The coincidence of parathyroid and thyroid pathology remains to be fully understood. Some authors have suggested that it may be secondary to close surveillance of the thyroid gland during parathyroidectomy¹⁶. Others have postulated that pHPT may predispose to developing synchronous thyroid disease as a result of long term exposure to elevated calcium levels acting as a goitrogen⁶. In our cohort; thyroid abnormalities and thyroid cancer rates was similar with the Turkish population rates¹¹⁻¹⁸.

The high incidence of synchronous thyroid pathology in patients who underwent parathyroidectomy for treatment of pHPT underscores the importance of considering the potential for co-existent thyroid and parathyroid pathology when performing pre-operative work-up of patients with pHPT.

Weiss and Chen indicate that omitting the preoperative neck ultrasound did not lead to an adverse outcome with respect to the management of clinically relevant thyroid cancer, and avoided fine needle aspirations in a substantial number of patients. As such, they indicate that preoperative cervical ultrasound is optional rather than essential in the work-up of patients with PHPT. However, their overall malignancy rate was 2%¹⁹.

Preoperative US increase recognition of concurrent thyroid pathology. It is not clear if, with this increased recognition, US ultimately improves the care of patients or leads to unnecessary thyroid interventions⁷. Our data suggest that US provides extra information and, with use of FNAB, but benign FNAB findings do not exclude malignant thyroid pathology. Also, delayed diagnosis of a thyroid malignancy coincident with pHPT that should be noted is the requirement of re-operative surgery.

The surgical management of pHPT has evolved over the last decade into MIP with the advent of more refined preoperative localizing studies. But, preoperative meticulous work up is mandatory⁶.

There are some limitations in our study. First, our study was retrospective cohort study. Second, there are a number of factors that may influence the decision to refer a pHPT patient with thyroid nodules to surgical resection. These types of "referral bias" and "selection bias," if present, tend to enrich the prevalence of malignancy within thyroid nodules. Third, as with any evaluation of cytology and US, there is inter- and intra-observer variability in the report of findings.

Conclusion

57.9% of the patients with pHPT had concomitant thyroid pathology. Approximately 13% of these patients were found to have malignant thyroid pathology. Twenty-Two (84.6%) of the carcinomas were < 1 cm in size.

These malignancies might have otherwise been undiscovered, or required a reoperation on the neck in the future. The identity of thyroid pathology was known preoperatively, minimizing difficult intraoperative decision-making without the need for additional biopsies or frozen section. Preoperative benign FNAB does not exclude thyroid malignancy. It should also be kept in mind the rate of malignant lesions in post-operative histopathological examination is relatively high in regions with iodine deficiency and endemic goitre.

Compliance with ethical standards

The study was performed in accordance with the Declaration of Helsinki and permission of the Committee of Ethics, Ankara Numune Education and Research Hospital. This article does not contain any studies with human participants or animals performed by any of the authors.

Riassunto

L'iperparatiroidismo primario (pHPT) si accompagna spesso ad una patologia tiroidea concomitante, che da 1 a 36% è di natura maligna. Non è chiaro in che modo l'identificazione di tali patologia influenzino il trattamento dei relativi pazienti. Qui presentiamo l'esperienza di un singolo centro con rilevamento di un concomitante cancro della tiroide in pazienti sottoposti a paratiroidectomia per pHPT.

Si tratta di uno studio retrospettivo che include 202 pazienti con iperparatiroidismo primario, con verifica dei dati demografici, dei rilievi clinici e diagnosi istopatologica definitiva, ed in 117 di questi pazienti (57,9%) l'ecografia preoperatoria del collo aveva rilevato la coesistenza di anomalie della tiroide, l'età media di questi pazienti è di $57,8 \pm 12,2$ anni con 88% di sesso femminile. In 63 dei pazienti con anomalie tiroidee (53,9%) si era proceduto a FNAB, con citologia indicante natura maligna in un caso (1,6%), natura benigna in 47 casi (85,7%), risultato incerto in 6 pazienti (9%) e 2 casi di carcinoma di Hurthle in 2 pazienti (3,2%).

In 94 pazienti (80,3%) alla paratiroidectomia era stata associata chirurgia della tiroide, con riscontro istopatologico di malignità in 26 casi (12,9%) in 16 di cui era stata effettuata la FNAB preoperatoria, con risultato di malignità in un caso, di incertezza in due casi e referto di benignità nei restanti 13 pazienti.

Esiste dunque la possibilità di chiarire preoperatoriamente la natura della patologia tiroidea concomitante ad pHPT incrementando opportunamente lo studio pre-intervento, ma questo atteggiamento non varrà a facilitare l'individuazione in una regione di gozzo endemico popolazione di cancri tiroidei non sospettabili per altri motivi.

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