Original Article

PREOPERATIVE AND POSTOPERATIVE EVALUATION OF THYROID DISEASE IN PATIENTS UNDERGOING SURGICAL TREATMENT OF PRIMARY HYPERPARATHYROIDISM

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ABSTRACT

Objective: To evaluate the occurrence of thyroid disease in patients undergoing parathyroidectomy for primary hyperparathyroidism.

Methods: In this case series, records of all patients with a diagnosis of primary hyperparathyroidism who underwent parathyroidectomy between January 2005 and December 2008 in our clinic were analyzed retrospectively. Preoperatively, all patients were evaluated with ultrasonography and parathyroid scintigraphy; when needed, thyroid scintigraphy and ultrasound-guided fine-needle aspiration biopsy (FNAB) were used. All patients underwent standard neck exploration. Postoperative histopathologic findings of thyroid tissue were classified as nodular/multinodular hyperplasia, Hashimoto thyroiditis, papillary thyroid carcinoma, or normal.

Results: Fifty-one women and 9 men were included. In the 60 patients, preoperative ultrasonography revealed thyroiditis (without nodules) in 13 (22%), a solitary nodule in 9 (15%) (coexistent with thyroiditis in 7 patients), multinodular goiter in 24 (40%) (coexistent with thyroiditis in 5 patients), and normal findings in 14 (23%). Rates of thyroiditis and nodular goiter were 42% and 55%, respectively. Collectively, prevalence of thyroid disease was 77%. Total thyroidectomy was performed in 27 patients, and hemithyroidectomy was performed in 15 patients. Indications for total thyroidectomy were nondiagnostic or suspicious FNAB results in 5 patients, hyperthyroidism in 4 patients, ultrasonography findings in 11 patients, and intraoperatively recognized suspicious nodularity in 7 patients. Postoperatively, thyroid carcinoma was diagnosed in 9 patients (15%).

Conclusions: Thyroid disease, particularly thyroid carcinoma, is common in patients with primary hyperparathyroidism. This association should be considered when selecting the surgical procedure. Intraoperative evaluation of the thyroid is as important as preoperative evaluation with ultrasonography and FNAB in patients with thyroid disease and primary hyperparathyroidism. **(Endocr Pract. 2010;16:7-13)**

Abbreviations:
FNAB = fine-needle aspiration biopsy; **MIBI** = methoxy-isobutyl-isonitrile; **PTH** = parathyroid hormone

INTRODUCTION

As primary hyperparathyroidism is detected more often by biochemical screening, the frequency of the classic signs and symptoms of this disease is markedly decreasing. The definitive treatment of primary hyperparathyroidism is parathyroidectomy. When performed by experienced endocrine surgeons, this procedure has reported success rates of 90% to 95% with low complication rates. The standard surgical approach is bilateral neck exploration with identification of all 4 parathyroid glands. However, in recent years, with increased success of localizing studies such as sestamibi scanning and ultrasonography and availability of intraoperative parathyroid hormone (PTH) determinations to verify that the disease-producing lesion has been removed during the surgical procedure, a trend towards a less invasive approach like unilateral neck exploration or minimally invasive surgery has occurred (1).

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Increasing evidence has suggested that hyperparathyroidism is associated with thyroid disease, particularly thyroid carcinoma, since synchronous thyroid and parathyroid disease was first described in 1947 (2). Thyroid disease is more prevalent among patients with hyperparathyroidism (3,4). Coexistence of thyroid and parathyroid lesions has raised the concern that thyroid lesions, such as thyroid carcinoma, might be missed by minimally invasive parathyroidectomy. Preoperative thyroid and parathyroid ultrasonography may be important in deciding management and surgical approach in primary hyperparathyroidism. In this study, we aimed to evaluate prevalence of thyroid disease preoperatively and postoperatively in patients undergoing parathyroidectomy for primary hyperparathyroidism.

PATIENTS AND METHODS

In this case series, records of all patients diagnosed with primary hyperparathyroidism at the Ankara Ataturk Education and Research Hospital, Department of Endocrinology and Metabolism, between January 2005 and December 2008 were analyzed retrospectively. Parathyroidectomy was performed in general surgery clinics of the same hospital. The local ethics committee approved the study protocol. Exclusion criteria included secondary or tertiary hyperparathyroidism, history of thyroid or parathyroid operation, and/or family history of multiple endocrine neoplasia. None of the patients had a history of previous head and neck radiation exposure. Hyperparathyroidism was diagnosed by documenting high concentrations of serum PTH and calcium and a low concentration of serum phosphorus. Twenty-four–hour urinary calcium excretion and bone mineral density were assessed before the surgical procedure. Preoperatively, all patients were evaluated with ultrasonography and parathyroid scintigraphy; when needed, thyroid scintigraphy and ultrasound-guided fine-needle aspiration biopsy (FNAB) were used. In all patients, neck exploration was performed to expose parathyroid tissue with or without thyroidectomy.

Preoperative thyroid ultrasonography was performed in all cases (MPX and 10 MHz probe, Esaote Technos, Geneva, Italy). Results were classified into the following categories: normal, thyroiditis, solitary nodule, multinodular goiter, or coexistence of thyroiditis and nodular goiter. Thyroid hormones and thyroid antibodies were measured to diagnose and define the cause of hypothyroidism or hyperthyroidism, if present.

FNAB was performed with ultrasound guidance (Logic Pro 200 and 7.5 MHz probe, GE, Kyunggi-do, South Korea), and written informed consent was obtained from all patients after explanation of the procedure. FNAB cytologic results of concomitant thyroid nodules and postoperative histopathologic diagnosis were recorded and compared. Cytologically, findings from the FNAB were reported as benign, nondiagnostic, suspicious, or malignant. Thyroid scintigraphy and iodine uptake were executed with technetium Tc 99m and iodine 131, respectively. Technetium Tc 99m methoxy-isobutyl-isonitrile (MIBI) was used for parathyroid scintigraphy.

Postoperative histopathologic findings of thyroid tissue were classified as nodular/multinodular hyperplasia, Hashimoto thyroiditis, papillary thyroid carcinoma, or normal. Pathologic parathyroid findings were classified as parathyroid adenoma, parathyroid hyperplasia, or parathyroid carcinoma. Clinical cure was defined as a parathyroid lesion confirmed in histopathologic examination and normal serum calcium and PTH concentrations after the surgical procedure.

The preoperative values of the following were obtained from medical records: serum thyroperoxidase antibodies (reference range, 0-35 IU/mL), serum thyroglobulin antibodies (reference range, 0-40 IU/mL), calcium (reference range, 8.5-10.5 mg/dL), phosphorus (reference range, 2.5-4.9 mg/dL), PTH (reference range, 11-67 pg/mL), 25-hydroxyvitamin D (reference range, 20-120 ng/mL), and 24-hour urinary calcium excretion. Thyroid antibody levels above the upper limit of the reference range were considered to be positive.

Data are presented as mean ± standard deviation for continuous variables and as number of cases (%) for nominal variables.

RESULTS

Fifty-one women and 9 men were included in the study. Mean age was 52.45 ± 9.14 years (range, 35-76 years). The following mean laboratory values were observed: serum calcium, 11.7 ± 1.6 mg/dL (range, 10.2-19.5 mg/dL); serum phosphorus, 2.7 ± 1.1 mg/dL (range, 1.2-3.9 mg/dL); PTH, 408.9 ± 509.2 pg/mL (range, 84-2500 pg/mL); and 25-hydroxyvitamin D, 15.7 ± 8.7 ng/mL (range, 5.5-40.1 ng/mL). Mean 24-hour urinary calcium excretion was 440.7 ± 209.9 mg/24 h (range, 140-878 mg/24 h). Among the 60 patients, 21 (35%) had nephrolithiasis and 29 (48%) had osteoporosis.

Preoperative Ultrasonography Evaluation

In the 60 patients, preoperative ultrasonography revealed thyroiditis (without nodule) in 13 (22%), a solitary nodule in 9 (15%) (coexistent with thyroiditis in 7 patients), multinodular goiter in 24 (40%) (coexistent with thyroiditis in 5 patients), and normal findings in 14 (23%). Regarding ultrasonography findings and the presence of thyroid antibodies, thyroiditis existed in 25 patients (42%). In addition, nodular goiter (solitary and multiple) was present in 33 patients (55%). Collectively, thyroid disease in patients with primary hyperparathyroidism was observed in 46 patients (77%). Parathyroid disease was detectable with ultrasonography in 58 patients (97%); MIBI scintigraphy showed parathyroid disease in 42 patients (70%).

Consequently, in all patients, parathyroid disease was localized preoperatively by ultrasonography, MIBI scintigraphy, or both. Mean parathyroid size visualized on ultrasonography was 1.7 ± 1.1 cm (range, 0.5-5 cm).

Three patients with Graves disease and 1 patient with toxic multinodular goiter were receiving antithyroid medication (7%). Eleven patients (18%) in whom the diagnosis was hypothyroidism secondary to Hashimoto thyroiditis were taking levothyroxine. Thus, functional thyroid abnormality was concomitant with primary hyperparathyroidism in 15 patients (25%). Among 56 patients with available values of thyroid antibodies, 19 (34%) had positive thyroperoxidase antibodies and 17 (30%) had positive thyroglobulin antibodies (either or both thyroid antibodies were detected in 21 of 56 patients [38%]). Forty-five nodules in 30 patients were aspirated by FNAB. Results were categorized as suspicious in 3 patients, nondiagnostic in 2 patients, and benign in the others.

Surgical Procedure

Neck exploration was the surgical approach for parathyroidectomy in all patients, and the extent of surgery was determined considering the intraoperative aspect of thyroid and parathyroid glands. In 42 of 60 patients (70%), thyroidectomy was performed with parathyroidectomy. Of these 42 patients, 27 underwent total thyroidectomy, while 15 underwent hemithyroidectomy. Total thyroidectomy indications were FNAB results (nondiagnostic or suspicious) in 5 patients, hyperthyroidism in 4 patients, ultrasonography findings (like nodule number or size) in 9 patients, suspicious ultrasonography features in 2 patients, and intraoperatively recognized suspicious nodularity in 7 patients. Hemithyroidectomy was performed in 13 patients because of the presence of ipsilateral thyroid nodules with parathyroid adenoma or because of technical reasons after thyroid mobilization. Additionally, in 2 patients, hemithyroidectomy was inevitable because of the intrathyroidal location of the parathyroid adenoma. Eighteen patients underwent no surgical thyroid intervention either because the thyroid gland was normal or because only thyroiditis was present. Surgical interventions in patients with preoperatively identified thyroid disease are summarized in Table 1.

Postoperative Histopathologic Results

Histopathologically, in the 60 patients, parathyroid adenoma was reported in 54 (90%), parathyroid hyperplasia in 3 (5%), and parathyroid carcinoma in 3 (5%). Mean diameter of diseased parathyroid glands was 1.9 ± 1.1 cm (range, 0.6-6 cm). Thyroid carcinoma was detected histopathologically in 9 of the 60 patients (15%). Among 5 patients who underwent thyroidectomy because of FNAB results, 4 had thyroid carcinoma. Of the 37 patients for whom indication for thyroid surgery was ultrasonography or intraoperative findings, 5 had thyroid malignancy. All thyroid tumors were papillary thyroid carcinoma, and 8 of the 9 were micropapillary (tumor diameter ≤1 cm). Mean tumor diameter was 6.1 ± 4.1 mm. Clinical features, preoperative ultrasonography findings, FNAB results, and histopathologic characteristics of tumors in patients with thyroid carcinoma are shown in Table 2.

In patients with thyroid carcinoma, preoperative ultrasonography and thyroid antibodies revealed diffuse Hashimoto thyroiditis in 1, a solitary nodule in 2 (coexistent with Hashimoto thyroiditis in 1 patient), and multinodular goiter in 6 (coexistent with Hashimoto thyroiditis in 2 patients). In postoperative examination, 3 patients had parathyroid adenoma, papillary thyroid carcinoma, and Hashimoto thyroiditis. A more striking finding was a patient with parathyroid carcinoma, papillary thyroid carcinoma, and Hashimoto thyroiditis. Additionally, in another patient with parathyroid carcinoma and Hashimoto thyroiditis, gastric carcinoma was detected during the preoperative evaluation.

DISCUSSION

Coexistent thyroid disease in patients with primary hyperparathyroidism has been elucidated in different studies with a prevalence ranging from 17.8% to 84.3% (3-6). The variation in frequency is thought to depend on

Table 1
Surgical Intervention in Patients With Primary Hyperparathyroidism and Preoperatively Identified Thyroid Disease

Preoperative findings	Surgical intervention, No. of patients		
	Total thyroidectomy	Hemithyroidectomy	No intervention
Multinodular goiter (n = 24)	20	4	0
Solitary nodule (n = 9)	4	5	0
Thyroiditis only (n = 13)	3	4	6
Normal (n = 14)	0	2	12

Table 2
Clinical Features, Preoperative Ultrasonography Findings, Fine-Needle Aspiration Biopsy Results, and Histopathologic Characteristics of Tumors in Patients With Primary Hyperparathyroidism and Thyroid Carcinoma

Patient No.	Age (sex)	Ultrasonography finding	FNAB cytology	Histopathology	PTC diameter, mm	Capsular invasion	Vascular invasion
1	57 (F)	Multinodular goiter	Suspicious	Parathyroid adenoma, PTC	9	Absent	Absent
2	51 (F)	Multinodular goiter	Benign	Parathyroid adenoma, PTC	4	Absent	Absent
3	50 (F)	Multinodular goiter	Non-diagnostic	Parathyroid adenoma, PTC	7	Present	Present
4	53 (F)	Solitary nodule, thyroiditis	Not performed	Parathyroid carcinoma, PTC, Hashimoto thyroiditis	2	Absent	Absent
5	44 (F)	Multinodular goiter, thyroiditis	Benign	Parathyroid adenoma, PTC, Hashimoto thyroiditis	6	Absent	Absent
6	52 (F)	Multinodular goiter	Benign	Parathyroid adenoma, PTC	4	Present	Absent
7	56 (F)	Solitary nodule	Suspicious	Parathyroid adenoma, PTC	6	Absent	Absent
8	43 (F)	Thyroiditis	Not performed	Parathyroid adenoma, PTC, Hashimoto thyroiditis	2	Absent	Absent
9	40 (F)	Multinodular goiter, thyroiditis	Suspicious	Parathyroid adenoma, PTC, Hashimoto thyroiditis	15	Absent	Absent

Abbreviations: FNAB, fine-needle aspiration biopsy; PTC, papillary thyroid carcinoma.

the method of examination, patient selection, and surgical indications and procedure. In our study of patients with primary hyperparathyroidism, preoperative ultrasonography showed thyroid nodules in 55% and thyroiditis in 42%. Additionally, the prevalence of any type of thyroid disease was 77%. Preoperatively, Ogawa et al examined 85 patients with sporadic primary hyperparathyroidism who underwent surgical treatment and detected thyroid nodules in 25%. In their study, thyroid nodules were classified as benign or malignant, and the presence of thyroiditis was not assessed (7). In a recent study, nodular thyroid disease was detected preoperatively in 51% of patients with primary hyperparathyroidism (8). Until now, the highest reported rate of concomitant thyroid disease in patients with primary hyperparathyroidism was 84.3% (6). An important finding of our study is the higher prevalence of thyroiditis (42%) than previously reported (range in the literature, 3.8% to 10.9%) (4,5,9).

More importantly, thyroid cancer was found in 1.9% to 10.6% patients being treated for primary hyperparathyroidism (3,7). Even higher rates were reported in 2 studies from Turkey and Japan, 17.6% and 17.4%, respectively (6,9). Masatsugu et al attributed this high frequency to the study setting—a clinic where patients with potential thyroid disease were seen (9). The largest study in the last 10 years regarding thyroid malignancy in patients with primary hyperparathyroidism by Milas et al found coexisting thyroid disease in 40% of patients and thyroid malignancy in 4.6%. They concluded that this high prevalence mandates vigilant diagnosis and preparation for possible simultaneous parathyroid-thyroid surgery (10). In postoperative histopathologic examination in our study, prevalence of

thyroid carcinoma was 15% (all were papillary thyroid carcinoma). This is one of the highest rates reported in the literature.

Instances of thyroid dysfunction (hypothyroidism or hyperthyroidism) in patients with primary hyperparathyroidism have been published as case reports in the literature, and most instances are suggested to be coincidental (11,12). In our series, 4 (7%) patients were hyperthyroid and 11 (18%) were hypothyroid clinically. These rates, particularly the occurrence of hypothyroidism, cannot be explained as coincidence. Further molecular and clinical studies are needed to confirm this finding and reveal the underlying mechanisms.

The high prevalence of thyroiditis, nodular goiter, thyroid dysfunction, and thyroid malignancy in the patients in the current study may have multiple explanations. Severe or moderate iodine deficiency exists in most regions of Turkey where the study was conducted. Iodine deficiency is related to increased prevalence of goiter and nodular thyroid disease. Goiter prevalence detected by ultrasonography in Turkish school-aged children ranges between 5% and 56%. Salt iodization in Turkey became compulsory in 1999 (13). Epidemiologic and experimental trials demonstrate that iodine has a triggering effect on the development of thyroiditis (14). Also, iodine deficiency is a known risk factor for follicular and anaplastic thyroid cancers; iodine prophylaxis is reported to increase the incidence of papillary thyroid carcinoma (15). Iodine-related environmental factors may have an important role in the coexistence of thyroid disease with primary hyperparathyroidism in Turkey.

Another explanation for the high prevalence of thyroid disease and dysfunction in our series may be that we routinely measure calcium levels in patients seen in our clinic for treatment of thyroid disease. Thus, this may have resulted in early diagnosis of asymptomatic primary hyperparathyroidism. Several studies have been conducted regarding the presence of primary hyperparathyroidism in patients who primarily present with thyroid disease. One large study found the incidence of primary hyperparathyroidism in patients with thyroid disease to be 3 times the frequency found in patients without thyroid disease (16).

In addition, we performed thyroid ultrasonography in all patients with the diagnosis of primary hyperparathyroidism. Besides nodular formations, we also detected thyroiditis in approximately 42% of patients according to ultrasonographic findings and presence of thyroid autoantibodies. Some studies examining thyroid disease in patients with primary hyperparathyroidism have identified only nodular diseases, omitting thyroiditis as a pathologic finding. This may have contributed to high rates in our series. Also, in 4 patients with thyroid carcinoma, Hashimoto thyroiditis was proven by the presence of thyroid autoantibodies and by ultrasonographic and histopathologic findings. Various studies show the rate of thyroid carcinoma to be increased in patients with Hashimoto thyroiditis, and a meta-analysis of the published material by Singh et al confirms this, with a significantly higher thyroid cancer rate in these patients (odds ratio, 1.89) (17).

The cause of the association between thyroid disease and primary hyperparathyroidism remains unclear. Some authors suggest coincidence; however, most suggest that increased endogenous calcium, growth factors, epithelial growth factors, and goitrogenic factors have a role (18,19). Also, the coexistence of thyroid and parathyroid disease is hypothesized to be a part of multiple endocrine neoplasia syndromes, with a possible common gene responsible (20). The high prevalence of thyroid disease in patients with primary hyperparathyroidism in our series may be a coincidental finding in accordance with the high prevalence of goiter due to iodine deficiency in Turkey. Nevertheless, high PTH or calcium concentrations may directly or indirectly affect thyroid tissue by unknown mechanisms.

Increased success of preoperative imaging studies and availability of quick intraoperative PTH measurement have given rise to surgeons' preference of minimally invasive parathyroidectomy. However, a downside of this method is that the intraoperative thyroid evaluation that could be performed by gross inspection and palpation during neck exploration is not possible (21,22). As our study and previous studies emphasize, thyroid disease—importantly, malignant thyroid tumors—is common in patients with primary hyperparathyroidism. The ability of the minimally invasive approach to evaluate and treat coexisting thyroid disease is limited, and this may lead to thyroid cancer going undetected until the disease process manifests itself separately. As a precaution, it seems reasonable to preoperatively survey for concomitant thyroid nodules with ultrasonography to detect any indeterminate lesion that requires additional evaluation with FNAB. This can result in challenging clinical decision making regarding care of these patients and selection of the surgical procedure. If thyroid disease remains undetected at the initial operation, a second operation to treat a thyroid lesion that manifests clinically in the future will be more difficult and may have higher rates of surgical complications.

Thyroid ultrasonography and FNAB are the most important tools in evaluating thyroid nodules. A 2005 study was the first to advocate ultrasound-guided FNAB of thyroid nodules in the setting of primary hyperparathyroidism (9). However, it is still possible to miss thyroid disease with these interventions. Regal et al reported concomitant thyroid disease in 52% of 54 patients with primary hyperparathyroidism, detecting 71% preoperatively and 29% intraoperatively (23). In a recent study, preoperative cytologic specimens to detect carcinoma were available in only 3 of 12 patients with malignant disease (8). Also, Kösem et al detected malignancy preoperatively by FNAB only in 4 of 9 patients with thyroid carcinoma concomitant with primary hyperparathyroidism (6). In our study, thyroid

carcinoma was found in 4 of 5 patients operated on based on cytologic findings and in 5 of 37 patients operated on because of preoperative ultrasonography or intraoperative findings. This shows that we were able to suspect malignancy preoperatively in 4 patients; the other instances were diagnosed incidentally, although 8 patients with thyroid malignancy had thyroid nodules detected by ultrasonography. These results suggest that although evaluation with preoperative ultrasonography and FNAB are important to detect thyroid disease, especially malignancy in patients with primary hyperparathyroidism, they still may not be sufficient. Intraoperative evaluation of the thyroid by the surgeon is also valuable. Although it is not realistic to suggest neck exploration and thyroidectomy for all patients undergoing parathyroidectomy, intraoperative evaluation seems to be as important as preoperative evaluation of the thyroid gland in these patients.

In recent surgical series, the prevalence of thyroid microcarcinoma range from 1.5% to 10% (24), whereas in autopsy series, the prevalence ranges from 6.2% to 35.6% (25,26). Iodine status of the geographic region, dietary habits, ethnicity, and screening methods of studies may affect these results. However, there are considerable debates in the literature about clinical significance and necessity for vigorous treatment of these occult tumors. Also, it is difficult to interpret therapeutic effectiveness of surgical or medical treatment because the mortality rate in patients with these carcinomas is extremely low. In our series, 8 of 9 thyroid carcinomas were micropapillary and capsular and/or vascular invasion was detected in 2 patients, which demonstrates that a small lesion may still potentially be aggressive biologically. We can infer from this observation that if preoperative ultrasonography was not conducted, cancer would have gone undetected in most of these patients. However, we are not able to comment on the importance of thyroid microcarcinomas detected incidentally in patients with primary hyperparathyroidism until large prospective studies examining the outcomes of these tumors are executed.

CONCLUSION

Thyroid disease, particularly thyroid carcinoma, is common in patients with primary hyperparathyroidism. Preoperative imaging methods to visualize the parathyroid glands and the thyroid gland help determine the optimal surgical procedure. In patients with primary hyperparathyroidism, both preoperative and intraoperative evaluation of the thyroid is important for detecting thyroid disease and for selecting the surgical procedure, especially in geographic regions where iodine deficiency is a concern.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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