

CLINICAL PRESENTATION AND TREATMENT OF HYPERTHYROIDISM ASSOCIATED WITH THYROID CANCER

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Objective. Hyperthyroidism apparently does not protect the patients from thyroid cancer as believed before. In contrast, hyperthyroidism with concurrent thyroid cancer can be diagnosed after pathological examination of unsuspect nodules. The aim of this study was to evaluate the coexistence of hyperthyroidism and thyroid carcinoma and to discuss the advantages of total thyroidectomy in such cases.

Methods. Between January 2002 and October 2004, 120 hyperthyroid patients underwent surgical treatment in our clinic. All patients with hyperthyroidism in this study underwent fine-needle aspiration biopsy and cytologic examination. Frozen section evaluation was performed in all of these patients during the operation.

Results. Among these patients 10 had concurrent thyroid cancer. Only one of these patients was examined by fine needle aspiration biopsy prior to operation, while the rest of malignancies was diagnosed from unsuspect nodules.

Conclusions. The selection of appropriate operation procedure appears very important to find out and treat concurrent thyroid cancers. We diagnosed 90 % of thyroid cancers incidentally. If there are no technical difficulties, we prefer total thyroidectomy for the patients with toxic multinodular goiter and Graves' disease with nodules.

For details see <www.elis.sk>.

Key words: Thyroid cancer – Hyperthyroidism – Total thyroidectomy

The coexistence of hyperthyroidism and thyroid cancer was believed to be a rare event, hyperthyroidism being considered a protector against developing thyroid cancer and the risk of thyroid malignancy in hyperthyroid patients was reported to be 1-2 % (GITTOES et al. 1998). However, several studies showed higher rates of cancer association with hyperthyroidism such as 21 % and recommended either a near total or total thyroidectomy for these patients (TORRING et al. 1996). Graves' disease is the most common cause of hyperthyroidism and the incidence of thyroid nodules in 20-25 % patients with Graves' disease was reported (PACINI et al 1998; KRAIMPS et al. 2000).

Recently, the incidence of thyroid carcinoma has been reported more frequently. Many reasons may explain this discrepancy, including endemic goiter areas

versus areas without goiter. Although several preoperative examinations such as ultrasonography, scintigraphy, fine-needle aspiration, biochemical investigations and intraoperative frozen section examination have been carried out in a majority of patients, some cases were found after pathologic examinations. This study was undertaken to review our experience and to determine the frequency of coexisting hyperthyroidism and thyroid malignancy in an endemic goitre and iodine-deficiency goiter area. Clinical presentations, diagnostic and therapeutic techniques were also evaluated.

Subjects and Methods

Within a two-year period between January 2002 and October 2004, 120 hyperthyroid patients underwent

Table 1
Thyroidectomy indications

Suspicious cytologic findings after FNAC
Nodules of large diffuse goiter
Side effects of antithyroid drugs
Autonomous goiter
Cold nodules in TDG
Nodular goiter with malignant suspicion in radiological evaluation
Contraindication in RAI
Recurrence after antithyroid drug treatment

surgical treatment in our clinic. Clinical hyperthyroidism was diagnosed by elevated triiodothyronine/thyroxine (T3/T4) ratio and low thyroid stimulating hormone (TSH) levels in combination with clinical symptoms. Among a total of 120 patients, 67 (55.8 %) had multinodular toxic goiter (TMNG), 24 (20 %) had toxic nodular goiter (TNG), 29 (24.2 %) had toxic diffuse goiter (TDG).

Serum levels of thyroid stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) were estimated in all patients. All patients underwent radiiodine (I^{131}) scintigraphy and ultrasonographic (US) imaging preoperatively. Absent "halo" sign, solid or hypoechogenicity, heterogenous echostructure, irregular margin, fine calcifications, extraglandular extension in US (and cold nodules in scintigraphic examination) were accepted as signs of malignancy (TAKASHIMA et al 1995, KAKKOS et al. 2000; NAMOU et al 2003).

All patients with nodular goiter in this study underwent fine-needle aspiration cytologic (FNAC) examination. Surgery was performed after the patients were rendered euthyroid by antithyroid drugs. None of the patient received radioiodine therapy (RAI) preoperatively, and the patients were asked for family history or external radiation. The indications for thyroidectomy are shown in Table 1 (ROMAN et al. 1989).

After preoperative evaluation, operative decision was made in order to prevent recurrence, to investigate and

cure for possible malignancies. For this reason, we prefer bilateral nearly total or total thyroidectomy in TDG patients, unilateral total lobectomy in TNG patients, total thyroidectomy in suspicious TMNG patients, and total thyroidectomy with neck dissection in preoperatively diagnosed metastatic tumours. Intraoperative frozen sections were performed in all patients. Postoperative pathological sections were carried out according to the standart criteria published by ROSAI et al. (1981).

The patients were hospitalised for 2 days postoperatively and controlled on the first week for wound healing, at first month and every 6 months during following 2 years for thyroid function. Hypothyroid patients were medically treated. Patients with carcinoma were followed with physical examination, ^{131}I whole body scanning, radiographic imaging and adjuvant therapy of radioactive iodine ^{131}I and thyroid hormone suppression (ERIC et al. 2003).

Results

Among 120 patients, 10 (8.3 %) had concurrent thyroid malignancy and hyperthyroidism. Two of these patients were men and the other were women of mean age of 50.1 ± 8.83 years (range 38 to 66). Patient characteristics are listed in Table 2. None of the patients had neck radiation history. Only one patient had a family history of papillary thyroid carcinoma (0.8 %) and 24 patients had family history of benign thyroid disease (20 %). Two of these patients had TDG with thyroid carcinoma. Histopathological examination revealed the presence of papillary carcinoma in 8 cases (6.6 %) with subgroups of 3 occult, 3 follicular variant and 2 classic, and 2 patients had follicular carcinoma (1.6 %). Of these patients, six were affected by TMNG, two by TNG and two by Graves' disease. The characteristics of malignant patients are shown in Table 3.

Only one FNAC and frozen section result was in accordance with pathology results, whereas others did not show any malignancy. The results of FNAC and fro-

Table 2
Patient characteristics and results of statistical analysis

	Hyperthyroidism (n=110)	Hyperthyroidism and carcinoma (n=10)	P
Age	47.00 ± 12.20	50.10 ± 8.83	NS
Sex (F/M)	84/26	8/2	NS
Nodule size	1.407 ± 0.630	1.140 ± 1.234	NS

Table 3
Characteristics of the patients with hyperthyroidism and thyroid carcinoma

Age	Sex	Cause of Hyperthyroidism	Type of Malignancy	Tumor size	Operation type
52	F	TMNG	OPC	0.2 cm	Right Lob. Left Lob.
46	F	TMNG	FC	2.5 cm	TT
48	M	TMNG	OPC	0.2 cm	TT
58	F	TMNG	PC	0.8 cm	TT
57	F	TMNG	FVPC	1.5 cm	TT
53	M	TMNG	FC	4 cm	TT
38	F	TNG	OPC	0.3 cm	Right Lob.
44	F	TNG	PC	1 cm	Right Lob.
66	F	TDG	FVPC	0.4 cm	NTT
39	F	TDG	FVPC	0.5 cm	NTT

- Bil – Bilateral
- FC – Follicular carcinoma
- FVPC – Follicular Variant Papillary Carcinoma
- Lob – Lobectomy
- NTT – Near Total Thyroidectomy
- OPC – Occult Papillary carcinoma
- TT – Total Thyroidectomy

zen section were follicular carcinoma which was in accordance with pathological examination. The sensitivity of FNAC and frozen section was 33 % and 20 %, respectively, while the specificity of FNAC and frozen section is 89 % and 92 %, respectively.

The average tumor size in thyroid carcinoma patients was 1.140±1.234 cm whereas in others it was 1.407±0.630 cm.

The preoperative US examination of patients with thyroid carcinoma showed solid heterogeneous and hypoechogenic nodules in all TMNG and TNG patients. One of TMNG with papillary carcinoma had microcalcification. All but one patients with occult papillary carcinoma had peripheric halo sign. One of TNG patients with papillary carcinoma had microcalcification. All TDG patients had one hypoechogenic solid nodule in preoperative USG examination.

Operation procedure used was total thyroidectomy in TDG patients. Unilateral total thyroidectomy was preferred in TNG cases, since none of these patients had positive FNAC and scintigraphy results related with malignancy. All TMNG patients except one underwent total thyroidectomy. This one underwent unilateral lobectomy and unilateral subtotal lobectomy because of technical difficulties.

TDG patients with malignancy showed diffuse heterogeneity by scintigraphic examination. Four of TMNG patients with malignancies had cold nodules. One of the TNG patient with malignancy had cold nodule.

In postoperative period all patients with malignancy were followed by US, FT3, FT4 and TSH examinations. All patients are still alive with normal FT3, FT4 levels without any recurrence or metastases detected by scintiscan and radiological examinations.

The occurrence of postoperative transient hypocalcaemia was found in 2 patients (1.6 %) and persistent hypocalcemia in 1 patient (0.8 %). Only one patient had an subcutaneous edema which resolved within one week and one patient had an keloid formation.

Discussion

From epidemiological studies it appears that gender factor may influence the risk of benign thyroid diseases and thyroid cancer in women (NEGRI et al. 1999; MEMON et al 2002, 2004). In our series, the incidence of malignancy in female patients was 80 % (8/10), while that in male patients 20 % (2/10). all female patients being postmenopausal.

Toxic thyroid diseases occur most often in areas of endemic goiter (GREGORY et al 1999). The diagnosis is proposed by the history and physical examination and confirmed by findings of suppressed serum TSH level, raised thyroid hormone level and hot nodule in scintiscan. This is associated with thyroid hyperfunction. Differentiated thyroid cancer appears as hypofunctioning by scintigraphy and is associated with normal thyroid function. However, in rare cases it may be associated with a clinical syndrom of hyperthyroidism.

It was believed that hyperthyroidism is a protector against the carcinoma of thyroid (VAIANA et al. 1999). On the other hand, several investigators have found high frequency of carcinoma associated with hyperthyroidism, e.g. such as 21 % (LIVADAS et al. 1976). In contrast, some authors have reported the frequency of less than 1 % (VAIANA et al. 1999). Among various explanations of this discrepancy; the most reasonable might be the epidemiological one as related to the difference between endemic goiter areas and areas with low goiter prevalence. Our findings were similar and our incidence of thyroid cancer in the patients with hyperthyroidism was 8.3 %. The histopathological types of malignancies were similar to these reported in the literature. All our patients were from endemic areas of Turkey (AHUJA et al 1991; GABRIELE et al 2003). There were 27 (22,5 %) patients with family history of goiter. The high prevalence of family history in thyroid carcinoma is an expected result in endemic areas.

Thyroid carcinomas associated with Graves' disease (GD) were reported more aggressive than these associated with non-autoimmune hyperthyroidism or in euthyroid patients (BELFIORE et al 1990; PELLEGRITI et al 1998). Some authors reported that patients with Graves' disease and thyroid nodule have a very high risk of thyroid cancer (KRAIMPS et al 2000). In several studies 18-31 % incidence of Graves' disease with nodular goitre was reported (PACINI et al 1998; BELFIORE et al 1990). Incidence of thyroid cancer in GD patients was 2-4 % (BELFIORE et al 1990; OZAKI et al 1990), while that of thyroid cancer in GD associated with nodular lesions was 14-22 % (YOKOZAWA et al. 1995; PACINI et al 1998). Ultrasonography and FNAC should be carried out in the patients with thyroid nodule, since thyroid cancer risk is relatively high in Graves' disease patients. In one study thyroid cancer was detected in 15 % patients with nodule. Several authors recommended the surgery in Graves' disease patients in which also nodules were found (KRAIMOS et al. 2000). The incidence of thyroid carcinoma is increasing in patients with Graves' disease

associated with nodule. Explanations for the increasing incidence could include better nodule detection differences in the extend of thyroid resection and the number of histological sections examined per specimen. FNAC is not reliable for the patients with Graves' disease. FNAC results of follicular neoplasm is common in Graves' disease. Because of uncontrolled stimulation of TSH by the autoantibodies, follicular cells proliferation increases.

In all patients with thyroid malignancies "halo sign" an solid hypoechogenic nodule were found by US. Also scintigraphic examination included 5 cold nodules in 10 patients with coexisting hyperthyroidism and thyroid malignancy. Sonography has been reported to have a satisfactory sensitivity of 75 %, specificity of 61-83 % in the diagnosis of thyroid cancer (WATTERS et al 1992; KHURANA et al 1998; KAKKOS et al 2000). We conclude that the incidence of coexisting hyperthyroidism and thyroid malignancy is associated with the patients who have malignant patterns of US and scintigraphic examination (TAKASHIMA et al 1995; KAKKOS et al 2000, NAMOU et al. 2003]. In general, tissue calcifications can be detected by imaging techniques and in many cases they are associated with malignancy (WATTERS et al 1992; COX et al. 1991; KAKKOS et al 2000). In our series, calcifications were sonographically detected in 30 % (3/10) of patients with thyroid cancer and in 37,5 % (3/8) of those with papillary carcinomas.

In a multicenter study, Graves' disease with thyroid carcinoma rate was 15 per cent and the diameter of tumour ranged from 2 to 25 mm (KRAIMPS et al. 2000). Some of the cases could not be diagnosed preoperatively because the diameter of these nodules was either very small or unsuspected, but they were diagnosed incidentally with pathological examination. In our study, the average size of nodules in patients with thyroid carcinoma was 1.31 cm whereas in others it was 1.45 cm. The incidence of thyroid was not associated with the nodule size both in malignant and nonmalignant diseases ($P > 0,05$).

To achieve euthyroidism is the main purpose for these patients and justifies the risk of operation (TORRE et al. 1998]. Some authors recommended total or neartotal thyroidectomy instead of subtotal thyroidectomy because of the relatively high risk of cancer association with hyperthyroidism. The relationship and management of these patients remains uncertain.

The advantage gained with initial total thyroidectomy for Graves' disease includes no recurrence, no progression of ophthalmopathy and the small benefit of elim-

inating occult cancers (RAZACK et al 1997; LIU et al 1998). Postoperative hypothyroidism can be treated easily by replacement of thyroxine. In experienced clinics and surgeons the complications rate is as same as subtotal thyroidectomy. In our study there is no recurrent laryngeal nerve pulsy and only one permanent hypocalcemia. These complications are acceptable for these kind of operations. If your choice of operation is subtotal thyroidectomy, some of these patients need completion thy-

roidectomy. You must hospitalise and operate these patients again. The completion thyroidectomies are technically more difficult than the first operations. So we recommend total thyroidectomy for such patients.

In conclusion it appeared that concurrent hyperthyroidism and thyroid cancer is not as rare as thought in the past. The aim of surgery should not be only to maintain euthyroidism but also be to protect the hyperthyroid patients from the cancer risk.

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