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ORIGINAL ARTICLE

Thyroid Cancer in Patients with Hyperthyroidism

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ABSTRACT

Background and objective: Malignant tumors of the thyroid gland are the most common of the endocrine malignancies. Although, patients with thyroid cancer have high 5 years survival rate, thyroid cancer is the most seen cause of mortality among cancers of the endocrine organs. The incidence of thyroid cancer in hyperthyroid patients varies from 0.1 to 21% in the literature. We aimed in this study to analyze the frequency of coexisting thyroid cancer and hyperthyroidism in our experience.

Results: Total 230 patients, who were operated for hyperthyroidism without the suspicion of thyroid malignancy between January 2005 and September 2010 were included in our study. Toxic multinodular goiter, toxic adenoma and Graves' disease were diagnosed preoperatively in 187, 16 and 27 patients respectively. Histopathological thyroid malignancy was detected in 13 patients (5.7%).

Conclusion: Thyroid cancer with variable incidence up to 21% should be remembered in differential diagnosis of hyperthyroid patients.

Keywords: Graves' disease, Hyperthyroidism, Thyroid cancer.

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INTRODUCTION AND OBJECTIVE

Thyroid cancer is the most common of the endocrine tumors, and it represents approximately 1% of all malignancies.[1] Although thyroid cancer incidence is increasing rapidly in men, the women have 3-fold higher rates.[2] The thyroid cancer has low mortality rate, but the rate of disease recurrence or persistence is high.[3]

The relation between thyroid function, and thyroid cancer was investigated and hypothyroidism was considered as a protective against thyroid cancer.[4,5] Today, this belief has been changed with new reports about togetherness of hyperthyroidism and thyroid cancer. The rate of combination of hyperthyroidism with thyroid cancer was reported up to 21% in the literature.[6] The variable rates may be due to environmental factors (e.g. the amount of iodine uptake), differences in management of hyperthyroidism (e.g. patient selection, type of surgery), and accuracy and reliability of histopathological analysis.[6,7]

Adequate iodine intake protects society from goiter and this environmental factor is responsible in epidemiology of thyroid cancer.[8] It has been reported that thyroid function abnormalities reduce the possibility of malignancy; if so the incidence of cancer in hyperthyroid patients would be lower in the endemic regions.[7]

In this study, we aimed to review the rate of thyroid cancer and treatment methods in patients who underwent thyroidectomy due to hyperthyroidism, which was generally considered endemic in our country.

MATERIALS AND METHODS

In this study, we retrospectively analyzed total 230 patients who were operated in Ankara Training and Research Hospital in 2nd and 3rd Department of General Surgery between January 2005 and September 2010 with the diagnosis of hyperthyroidism with benign thyroid fine needle aspiration biopsy (FNAB).

From the records, we examined thyroid functions free triiodothyronine 3, (FT3), free triiodothyronine 4 (FT4), thyroid-stimulating hormone (TSH) of the patients and noted familial history of thyroid cancer and multiple endocrine neoplasia (MEN) syndromes, the presence of any radiation history in the head and neck region and the preoperative radioactive iodine treatment (RAI).

On clinical examination, attention was paid to the presence of a palpable nodule, nodule characteristics (texture, size, mobility) and the presence of cervical lymphadenopathy. Thyroid ultrasonography and thyroid scintigraphy was performed to all patients during the preoperative period. They were consulted to endocrinology department, and the FNA was performed to dominant and mostly palpable nodules of the toxic multinodular goiter (MNG) and from the solitary nodule in patients with a solitary nodule.

Our surgical indications for hyperthyroidism included suspicion of cancer, unresponsiveness to medical therapy or developing side effects of the drugs, development of nodules on toxic diffuse goiter, patients' request

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and the presence of large goiter with pressure symptoms. In the preoperative period, propylthiouracil (PTU) was used to ensure euthyroidism.

Near total, subtotal or total thyroidectomy was performed in the patients with Graves' and multinodular toxic goiter, while near total or total lobectomy with isthmectomy was carried out in the patients with toxic solitary nodule without suspicious of cancer. Age, metastasis, extend of disease, size (AMES) scoring criteria were used to identify the risk of thyroid cancer. Cancer classification was made according to World Health Organization (WHO) criteria including 1 cm diameter and tumors smaller than 1 cm were accepted as microcarcinomas.

The treatment of histopathologically diagnosed with thyroid cancer were organized with the consultation of Department of Nuclear Medicine, Ankara Training and Research Hospital.

Data were evaluated using statistical package for the social sciences (SPSS) for Windows ver. 11.5 (SPSS Inc., Chicago, IL, USA). Chi-square test used for evaluation of categorical data, and one-way analysis of variance (one-way ANOVA) technique for comparing means of samples. $p < 0.05$ values were considered as statistically significant. Values and categorical data were expressed in numbers and percentages. Standard deviation was used for the mean values of calculated data.

RESULTS

Our study included 230 patients with hyperthyroidism, 174 of them (75.7%) were female. The mean age of the patients was 43.6 years (min. 15, max. 75). According to physical examination and thyroid ultrasonography, toxic MNG for 187 patients, toxic adenoma for 16 patients and Graves' disease for 27 were diagnosed (Table 1). None of the patients had palpable cervical lymphadenopathy (LAP), history of thyroid cancer, radioiodine treatment and MEN syndrome.

Cancers were detected histopathologically in 13 patients (5.7%) (Table 1). Five (38.5%) of these cancer cases were papillary thyroid carcinoma, and 8 (61.5%) of them were papillary microcarcinoma (PMC) (Table 2). There were no history of radiation exposure to the head and neck region among these patients diagnosed with thyroid cancer. Preoperative diagnoses of the patients with thyroid cancer were toxic MNG for 11 patients (84.6%), and Graves' and toxic adenoma each for 1 patient (7.7%). Cancer rates in toxic MNG, Graves', and toxic adenoma patients were 5.9, 3.7 and 6.3% respectively (Table 1). The highest cancer rate was identified in patients with toxic adenoma, and the lowest rate was found in Graves' disease patients, but there were no significant differences between these diseases ($p > 0.05$).

Table 1: Presence of thyroid cancer and distribution of the patients according to diagnosis and gender

	Presence of thyroid cancer		
Diagnosis	*Present*	*None*	*Total*
Toxic MNG	11 (5.9%)	176 (94.1%)	187 (100%)
Toxic Adenoma	1 (6.3%)	15 (93.7%)	16 (100%)
Graves' disease	1 (3.7%)	26 (96.3%)	27 (100%)
Gender			
Male	50 (89.3%)	6 (10.7%)	56 (100%)
Female	167 (96.0%)	7 (4.0%)	174 (100%)

MNG: multinodular goiter

Table 2: Some feature of patients with thyroid cancer

	Years	*Sex*	*Diagnosis*	*Pathology*	*Surgical treatment*
1	66	M	TMNG	Papillary carcinoma	NTT
2	63	F	TMNG	Papillary carcinoma	BTT
3	54	M	TMNG	Papillary carcinoma	BTT
4	44	F	TMNG	Papillary microcarcinoma	BTT
5	44	M	TDG	Papillary microcarcinoma	BTT
6	42	F	TMNG	Papillary microcarcinoma	BTT
7	40	F	TMNG	Papillary microcarcinoma	STT
8	40	F	TMNG	Papillary carcinoma	BTT
9	37	M	TMNG	Papillary carcinoma	STT
10	37	F	TMNG	Papillary microcarcinoma	NTT
11	37	F	TMNG	Papillary microcarcinoma	BTT
12	29	M	TA	Papillary microcarcinoma	STT
13	25	M	TMNG	Papillary microcarcinoma	BTT

TDG: Toxic diffuse goiter (Graves); TMNG: Toxic multinodular goiter; TA: Toxic adenoma

Also there were no significant relation with cancer, and age or gender ($p > 0.05$). Type of surgical managements of the cancer patients were shown in Table 2. Completion thyroidectomy was required for only one patient, because of positive surgical margin, and none of the patients underwent cervical lymph node dissection.

Postoperative transient hypocalcemia occurred in only one patient detected clinically. The median follow-up period was 12 months (min. 6, max. 44) and there were no recurrence occurred.

DISCUSSION

When thyroid function is associated with thyroid cancer, abnormal thyroid function and, particularly, the presence of hyperthyroidism were believed to reduce the possibility of the malignancy and it was accepted as a guarantee against thyroid cancer in the past.[4,7] However, many studies have been conducted for incidence of cancer in people with hyperthyroidism, and reported ratios in the literatures ranging from 0.2 to 21%.[4-7,9] In our study, we found the rate of cancer as 5.7% in patients with hyperthyroidism, and this is compatible with the literature.

In a series of 1848 cases, Rieger et al[7] did not detect cancer in patients with Graves' disease, but they found

the highest rate of cancer in patients with toxic MNG (1.6%). However, Mazefferi et al found that the frequency of cancer in patients with Graves' disease was 2.5-fold higher than toxic adenoma, and they also reported that the cancers in patient with Graves' were more aggressive.[10] Differ to these we found highest cancer rate in the patients with toxic adenoma, but this was not significant. However, in some studies investigating the relationship between hyperthyroidism and cancer, it was found that the risk of cancer in patients with toxic adenomas was higher than Graves' disease, consistently with our results.[6,7,11] In a study by Olen, and Klinck with 2114 cases, they found 53 cancer cases included 42 patients with Graves' disease.[4] Dobyns et al found the cancer rate as 0.2% in all patients with hyperthyroidism, and also found similar rates (0.4–0.3%) in patients with Graves' disease and toxic adenoma.[5] Additionally, Terzioglu et al found that the rate of cancer was 5.8% in patients with hyperthyroidism, while there were no significant difference between patients with Graves' disease, and toxic adenoma in their subgroup analysis.[9]

In genetic studies on the development of cancer in patients with hyperthyroidism, TSH is thought to be an important factor.[4,6,9,12-15] In the cases of thyroid gland failure, continuous and intense TSH stimulation causing increased cyclic adenosine monophosphate (cAMP) levels in follicular cells to increase and grow-up follicular cells was reported. The same stimulation has been shown in adenomatous and carcinomatous tissues.[16] Iodine deficiency, inability of producing thyroid hormone and goitrogens taken as diet or medication lead to increase in the TSH level and so causes the risk of thyroid cancer increased.[17] The presence of TSH receptor in differentiated thyroid carcinomas supports this view.[6,9] Although, TSH is suppressed in patients with thyrotoxicosis, the cancer development suggests that oncogenic effect induce tumor growth with high TSH stimulation in early period before the toxic condition appears and TSH suppression.[6] But the relation between thyroid cancer and elevated TSH secretion remains unclear. Hancock et al argued that prolonged TSH stimulation by goitrogens on the thyroid gland leads to hyperplasia and then neoplasia.[12] The interaction of high thyroid stimulating immunoglobulin (TSI) with TSH receptor in thyroid tissue instead of TSH is believed having carcinogenic effects in patients with Graves' disease.[13,15,17] Moreover, it is thought that cancer in patients with Graves' disease are more aggressive due to the continuous stimulation of the TSI.[10]

Rieger et al detected the cancer ratio as 0.8% among 1848 hyperthyroid patients for endemic goiter and stated the decreased incidence of cancer for endemic goiter in hyperthyroid patients.[7] We determined this rate as 5.7% for our country, which is in an endemic goiter region. In their study similarly to our results, Terzioglu et al identified this ratio as 5.8%, but this was not statistically significant in cancers with euthyroidism patients.[9] Increased rate of follicular hyperplasia was found followed by nodule, and adenoma development with low-iodine animal model.[17] However, it was reported low rate of papillary cancer in endemic goiter region and the rate of papillary carcinoma was increased with the addition of iodine to the diet.[6] In our study, all of the patients which were from an endemic area had papillary thyroid cancer and no follicular thyroid cancer was detected.

We found the ratio of PMC as 61.5% in cancer cases and this ratio was 3.5% in all operated hyperthyroid patients. The cancer developed on Graves' disease was papillary microcarcinoma (PMC). Iada et al have also emphasized the association between PMC and Graves' disease.[18] The increase in differentiated thyroid carcinoma has been shown to be resulted from radiotherapy received in childhood for diseases, such as Hodgkin's disease.[19] In a study by Behar et al including the patients with Graves' disease, who received radiation to the head and neck region was found to be the most important risk factor.[20] Similarly, Farbota et al found that the ratio of cancer in patients who did not undergo radiation treatment was 3.5%, but this rate was found as 50% in those underwent radiotherapy and the authors agreed about the external radiation as a significant risk factor for hyperthyroid patients as well as euthyroidism.[13] In our study, external radiation treatment to the head and neck region in childhood was not detected in our patients. Both thyrotoxicosis and thyroid carcinomas, are more common in women.[12] In our study, similar to the literature female/male ratio was found as 3.1 in patients with thyrotoxicosis and 1.1 in the cancer patients.

In literature, the incidence of hypocalcemia varied from 1.6% to more than 50%.[21] Postoperative hypocalcemia was identified in only one of our patients and this was low. Clinical evaluation for postoperative hypocalcemia and the limited number of patients may be the reason of this result.

CONCLUSION

Presence of hyperthyroidism should not exclude the thyroid cancer, and togetherness of thyroid cancer and hyperthyroidism must be remembered in the management of the patients.

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