DAVIT KALMAKHELIDZE [1], ZURAB ZAALISHVILI [1], ASHWIN ACHUTHAPRASAD [1], TEKLE DARTSIMELIA [1], LEVAN KALMAKHELIDZE [2]

PAPILLARY THYROID CARCINOMA CONCOMITANT WITH THYROTOXICOSIS

[1]USMD program, Tbilisi State Medical University, Tbilisi, Georgia
[2]Mardaleishvili Medical Centre, Tbilisi, Georgia

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Abstract

Contrary to the preconceived belief, the occurrence of hyperthyroidism in patients with thyroid cancer is gaining in incidence. The research team retrospectively analysed studies such as serum TSH and T4 levels, thyroid ultrasound results, and the histopathology reports of 9 patients (age range 20-67) from Mardaleishvili Medical Center. All patients were diagnosed with PTC. 7 patients had microcarcinoma (mean 6.1mm) and 2 – large tumors (mean 14mm). Graves' disease was found in 5 patients, toxic nodular goiter in 3 and one patient's record was lacking comorbid disease information. One patient had confirmed lymph node involvement. All patients underwent total thyroidectomy. Overall, all 9 patients with hyperthyroidism were subsequently diagnosed with thyroid cancer. Management of such patients has questioned the validity of the guidelines published by the ATA and emphasizes the fact that malignancy should not be excluded in patients with thyrotoxicosis.

Introduction

The incidence of well-differentiated thyroid cancer saw a great increase in the first decade of the 21st century [1]. Recent cancer research studies have projected that thyroid cancer will overtake colorectal cancer as the fourth leading cancer diagnosis by 2030 [4]. Patients with thyroid cancer rarely present with a palpable thyroid nodule [2] and hence depend on ultrasound and cytologic findings. The guidelines released by American Thyroid Association in 2015 recommended against the cytologic evaluation of hyperfunctioning nodules as they are deemed to be rarely malignant [3]. This case series presents patients who presented with symptoms of thyrotoxicosis and were eventually diagnosed with papillary thyroid cancer thus underlining the importance of keeping thyroid malignancy in the differential diagnosis even with hyperfunctioning nodules. Thyrotoxicosis usually presents with symptoms of heat intolerance and palpitations which can prove to be detrimental if not treated. The treatment usually involves surgery. The underlying etiology is often due to Graves' disease or lymphocytic thyroiditis with concurrent papillary thyroid cancer. The ramifications of these findings will influence the management guidelines of patients presenting with hyperthyroid symptoms.

Methods

This case series study was established on the comprehensive data about nine patients collected from Mardaleishvili Medical Center. Obtained information included patient history, complete blood count, serum TSH and T4 levels (the method used immunochemiluminometric assay [ICMA], thyroid ultrasound results (Device - Philips Affinity 50), histopathology report, and the surgery protocol. Other non-relevant tests were filtered out. The research team retrospectively analysed obtained patient data. Each member of the research team was responsible for analysing the particular aspects of each patient's portfolio (eg, tumor size, histopathology report, surgery protocol, etc.). Tables were created based on the comparison of the different patient variables.

Results

From 9 patients we found with papillary thyroid carcinoma and thyrotoxicosis, 5 patients (55.5%) were from 20 to 29 years old, 3 patients (33.3%) were more than40, and just 1 (11.1%) was in the 30 to 39-year range. All of them were females. The mean age of patients with PTC and toxicosis was 34.7 (range 20-67). 5 patients (62.5%) had Graves' disease and 3 patients (37.5%) had a toxic nodular goiter. There was no data about 1 patient regarding their comorbidity. Tumor size ranged from 3mm to 15mm with a mean of 7.8mm. 77.8% of patients (7 patients) had microcarcinoma (≤10 mm) with a mean size of 6.1mm and 22.2% (2 patients) had large size tumors (>10 mm) with a mean size of 14mm.

Table 1 shows the mean tumor size in different age groups. In the 20-29 age group we had 5 patients and the mean tumor size was 9.8 mm. Only 1 patient was in the 30-39 age group with a tumor

size of 3 mm. 3 patients were in the 40+ group with a mean tumor size of 6.17 mm. We compared tumor size and comorbidities (**Table 2**) and found that the mean size of the tumor in patients with toxic nodular goiter was 6.3 mm and in Graves' disease - 8.7 mm.

Table 1. Mean tumor size in age groups

Age Group	Number of Patients	Mean size (mm)
20-29	5	9.8
30-39	1	3
40+	3	6.17

Table 2. Correlation of patient comorbidity and tumor size

Patient N	Comorbidity	Size (mm)	Mean size (mm)
1	Unknown	8	8
2	Chronic autoimmune thyroiditis	7	6.3
5	Toxic nodular goiter	8	
6	Toxic nodular goiter	4	
3	Graves' disease	7.5	8.7
4	Graves' disease	13	
7	Graves' disease	15	
8	Graves' disease	3	
9	Graves' disease	5	

As for staging, only 1 patient (11.1%) had confirmed regional lymph node metastasis, 4 (44.4%) had confirmed localized tumor and lymph nodes could not be assessed in 4 (44.4%) patients. Comparing age and stage (**Table 3**), we found that the mean age in the pT1aN0Mx group was 28.3 years and in pT1aNxMx - 42.5 years (mean age in combined in T1a group was 36.4 years). We had 1 (one) 29- year-old patient in the pT1bN1aMx group and 1 (one) 28-year-old patient in pT1bN0Mxwith a mean age of 28.5 (combined T1b group).

Table 3. Correlation of staging and age

Patient N	Age	Staging	Mean age	Mean age in the same "T" group
1	20			
2	42			
5	23	pT1aN0Mx	28.33	
3	41			
6	67			
8	35			
9	27	pT1aNxMx	42.5	36.43
4	29	pT1bN1aMx	29	
7	28	pT1bN0Mx	28	28.5

T stands for tumor size, N for lymph nodes (LNs), M for metastasis.

TX: primary tumor cannot be assessed, T0: no evidence of primary tumor, T1: tumor 20 mm or smaller (T1a: 10 mm or smaller, T1b >10 mm but not more than 20 mm), T2: >20 mm but not bigger than 40 mm, T3: larger than 40 mm or has begun to grow outside the thyroid, T4a: any size that has grown extensively beyond the thyroid, T4b: any size that has grown towards spine or into nearby large blood vessels.

NX: regional LNs cannot be assessed, N0: has not spread, N1: has spread to regional LNs (N1a: spread to pretracheal, paratracheal or prelaryngeal LNs, N1b: cervical, retropharyngeal or superior mediastinal. MX: distant metastasis cannot be assessed, M0: no metastasis, M1: has spread to distant LNs, internal organs, bones, etc.

All (100%) of patients had a total thyroidectomy. In addition, 4 (44.4%) patients had extended sparing excision of cervical lymph nodes. Pre-euthyroid TSH andFT4 levels were not available for all patients, and we decided to exclude this data. **Table 4** depicts all the data we gathered in a single table.

Table 4. Depicting all patients' data

Patient N	Age/Sex	Presenting Symptoms	Comorbidities	Size (mm)	Stage
1	20/F	Insomnia	--	8	pT1aN0Mx
2	42/F	Tachycardia, tremor	Chronic autoimmune thyroiditis	7	pT1aN0Mx
3	23/F	Tachycardia	Toxic diffuse goiter	7.5	pT1aNxMx
4	41/F	Tachycardia, muscle pain	Toxic diffuse goiter	13	pT1bN1aMx
5	67/F	Tachycardia	Toxic nodular goiter	8	pT1aN0Mx
6	35	Tachycardia	Toxic nodular goiter	4	pT1aNxMx
7	27	Tachycardia, tremor	Toxic diffuse goiter	15	pT1bN0Mx
8	29	Tachycardia, dry mouth	Toxic diffuse goiter	3	pT1aNxMx
9	28	Tachycardia, sweating	Toxic diffuse goiter	5	pT1aNxMx

Discussion

The foundation for the thought that cold nodules are more likely to be malignant was laid by studies conducted in the 1960s when the prime method of investigating thyroid nodules was by radio-iodine scintigraphy [1]. The increased use of imaging by ultrasound has led to the discovery of many more microcarcinomas which now constitute 32.1% of all papillary thyroid cancer cases [2]. The case series showcases patients with Graves' disease, autonomous functioning thyroid nodules (AFTN), and chronic autoimmune thyroiditis presenting with histologically proven papillary thyroid cancer. The presentation of thyrotoxicosis in such patients can either be due to concurrent non-functional thyroid cancer with thyrotoxicosis due to Graves' disease or other autonomous hot nodules, or it could be due to hyperfunctioning thyroid cancer nodules. This can be differentiated with the help of radio-iodine intake which was not done on our patients.

Just as in studies done previously, papillary thyroid cancer is the predominant type of cancer seen in graves and AFTN patients .100% of our patients were diagnosed with PTC compared to 88% in a study conducted by Joy U L Staniforth et al [3]. This study also reaffirms the notion that most cases of Graves diseases presenting with thyroid cancer are seen in young females [4]. All the cases seen in this study are female with most of them between the ages of 20-29. 7 out of the 9 cases were below 1 cm and hence are classified as microcarcinomas which is consistent with the findings conducted by Pzaitou-Pannayiotou et al [5]. When comparing the sizes of the nodules, the mean size of PTC nodules in Graves'disease was larger than in AFTN. This is in contrast to a study by Sunil Dutt Sharma et al. that showed cancer in AFTN patients had larger tumor sizes and were more aggressive [6]. The potential for malignant spread cannot be determined because all our patients presented before the tumor could metastasize.

The management of patients with hyperthyroidism due to Graves usually entails medical treatment which does not prevent the progression of cancer if present. This highlights the importance of cytologic studies with FNA to further analyse the thyroid nodules which may help the physician to uncover cancerous nodules and proceed with total thyroidectomy as was seen with the patients in our studies. The prognosis for patients with papillary microcarcinoma in conjugation with Graves or AFTN is excellent when treated with total thyroidectomy.

It has also been suggested that occurrence of thyroid cancer in patients with hyperthyroidism is because of the fact that increasing number of total thyroidectomies are performed in patients with refractory hyperthyroidism and subsequent investigation of the whole gland is associated with discovering microcarcinomas incidentally [1].

In our study all 9 patients underwent total thyroidectomies, however only one patient had

thyroidectomy because of refractory hyperthyroidism. In this case no nodule was discovered on ultrasound and microcarcinoma was detected on histological investigation incidentally. 7 patients had suspicious nodules discovered on routine ultrasound and only one had palpable thyroid nodule on physical examination.

Conclusion

Even though there is no clear association between thyrotoxicosis and thyroid cancer, patients with a history of hyperthyroidism have an increasing incidence of detecting malignancy. In this study 9 Patients with history of hyperthyroidism due Graves disease, toxic multinodular goiter and chronic autoimmune thyroiditis were diagnosed with papillary thyroid cancer during their disease course. In all cases malignancy was detected before metastasis and patients were managed with total thyroidectomy. Increasing incidence could be explained by the fact that patients with hyperthyroidism undergo more extensive investigations and routine screenings with ultrasound that increases the probability of detecting microcarcinomas. However, previous belief stating that thyroid cancer should be suspected in euthyroid patients with non-functional nodules is largely questioned.

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