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Clinical, sonographical and cytological comparison of toxic and non-toxic thyroid nodules

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ABSTRACT

Aim: To compare patients with toxic and non-toxic nodular/multinodular goiter in terms of clinical, sonographical and cytological features.

Material and Method: The medical data of 326 patients were reviewed retrospectively. Clinical and sonographic features were examined. Four hundred and eighty-one nodules were compared sonographically and cytologically. One hundred twenty-four patients had toxic nodular goiter and 202 of them had non-toxic nodular goiter.

Results: The toxic nodular goiter group was older, they had more male sex, more multi-nodularity, larger thyroid glands and nodules with more sonographically suspicious features ($p<0.05$). One hundred sixty-five of 481 nodules belonged to the toxic group. Nodule size was > 40 mm in 13.9% of the nodules in the toxic group and 5.4% of those in the non-toxic group ($p= 0.003$). Central vascularization ($p <0.0001$) and hypoechogenicity ($p =0.005$) were higher in nodules of the toxic group. The two groups were similar in terms of fine needle aspiration biopsy (FNAB) results.

Conclusion: Toxic nodules can have sonographically suspicious features like non-toxic nodules, and their evaluation with FNAB should not be avoided or postponed, thus ensuring more adequate treatment and follow-up of toxic nodular thyroid disease.

Keywords: Thyroid nodule, toxic, sonography, biopsy, malignancy risk

INTRODUCTION

Hyperthyroidism is characterized by increased thyroid hormone synthesis and release in the thyroid gland. Toxic adenoma (TA) and toxic multinodular goiter (TMNG) are the most common causes of hyperthyroidism after Graves' disease and their incidence increases with age (1).

The treatment of TA and TMNG is radioactive iodine or surgery (2). However, there is an opinion that, because thyroid stimulating hormone (TSH) is suppressed in hyperthyroidism, oncogenesis is also inhibited and thus hyperthyroidism has a protective effect against thyroid cancer (3). While thyroid cancer affects 7-15% of the population, early publications showing that the incidence of cancer is lower in hyperthyroidism (4). Therefore, cytological evaluation for toxic (or hot) nodules has not been considered. Previously, the estimated cancer risk of non-functioning nodules is around 10-20%, while this rate is very low for hot nodules (5,6). However, there are more recent studies showing that the cancer risk is higher in hyperthyroidism (7).

In a recent study investigating the risk of malignancy in hot nodules, a similar risk of malignancy was found between hot nodules and cold nodules. The risk in hot nodules was determined as 4.3% (8).

According to American Thyroid Association (ATA) 2015 guideline, fine needle aspiration biopsy (FNAB) is not recommended for toxic nodules as they are rarely considered malignant (9). However, as mentioned above, hot nodules may not be as benign as it seems. In this study, we compared hot nodules with non-toxic nodules in clinical, sonographic and cytological terms. And so, we tried to determine the malignancy risk of toxic nodules.

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MATERIAL AND METHOD

Ethical approval was obtained from Amasya University Hospital Non-Invasive Ethics Committee (Date: 07.01.2021, Decision No: 18). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This is a multicenter study. It included 326 patients who were diagnosed as TA, TMNG and non-toxic nodular goiter between 2018-2020.

Patients with toxic nodular goiter (TNG) were diagnosed according to the following diagnostic criteria: suppressed serum TSH levels with elevated serum free thyroid hormones and increased uptake on thyroid scan. Patients with non-toxic nodular goiter (non-TNG), had 1 or more nodules and their thyroid functions were euthyroid or hypothyroid.

Patients who were<18 years of age or pregnant or had active infections, chronic organ failure and/or malignancy were excluded.

Age, gender, TSH, thyroid ultrasonography (USG) and FNABs were examined. Thyroid USG (first center's USG is Aloka, Mollsfeld, Meerbusch, Germany, second is Toshiba TA700, Japan) and FNABs were performed by two endocrinologists educated from the same center. Thyroid gland and thyroid nodules were reported in three dimensions as antero-posterior, transverse and longitudinal. Thyroid volume was calculated with this formula: Anterior-posterior diameter x transverse diameter x longitudinal diameter x0.52. USGs were reported according to ATA guideline (9). 99mTc pertechnetate scintigraphy was performed to separate hot-cold nodules. Size (>1 cm), content (solid-mix), echogenicity (hypoechoic), vascularization (central), calcification (microcalcification), margin structure (irregular edge), anteroposterior/transverse diameter ratio (>1) of the nodules were evaluated with USG. FNAB was applied by aspirating method to 481 nodules with at least 1 suspicious feature. Thyroid functions of the patients in the toxic group were in the subclinical hyperthyroid and euthyroid stages while FNABs were performed. FNABs were reported as benign, malignant, suspicious for malignancy, follicular neoplasia, atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (AUFL) according to the Bethesda classification (10). Performing sonography and biopsy procedures by endocrinologists following the patients is an important difference of this study.

Statistical Analysis

Statistical analysis were made by IBM SPSS for Windows Version 25.0. Numerical variables were summarized with mean±standard deviation or median (min-max). Categorical variables were indicated by number and percentage. The Pearson chi-square test, Continuity Correction or Fisher's exact test were used to determine whether there was any difference between the groups in terms of categorical variables. The Kolmogorov Smirnov test, mean/standard deviation ratio, Skewness/Kurtosis, histogram and detrended normal graphics were used to determine whether the normal variables showed normal distribution, and the homogeneity of the variance was examined by the Levene test. Differences between two independent groups in terms of numerical variables; t-test and Mann Whitney U were used. Post-hoc analysis was used to determine which subgroup made the difference. The significance level was taken as $p < 0.05$.

RESULTS

The patients with TNG consisted of 124 individuals and 202 of the patients had non-TNG. General characteristics of the participants are given in **Table 1**. Age 65 and over was defined as geriatric age. The TNG group was older, they had more male sex, more multi-nodularity, larger thyroid glands, nodules with more suspicious features and, as expected, lower TSHs. (**Table 1**).

Binary logistic regression analysis was performed for the effect of these parameters on toxicity; Only TSH and age were significantly different between two groups (**Table 2**), no meaningful results were reached for other parameters (these were not shown in the table).

Table 1. Comparisons of two groups according to individual characteristics

Parameter	Toxic goiter (n=124)	Non-toxic goiter (n=202)	P
Age, year	58.49±10.906	50.79±11.282	<0.0001*
Geriatric age, n (%)	40 (32.3)	21 (10.4)	<0.0001*
Male gender, n (%)	36 (29)	34 (16.8)	0.009*
Subgroup (according to nodule number), n (%)			
NG	19 (15.3)	54 (26.7)	
MNG	105 (84.7)	148 (73.3)	0.016*
Right thyroid volume, mm^3	23332.49±16128.059	17873.14±13342.562	0.001*
Left thyroid volume, mm^3	21244.21±14253.341	15811.78±12649.67	<0.0001*
Number of nodules with suspicious features	1.78±1.079	1.42±0.703	0.003*
TSH	0.10 (0.001-7.66)	1.30 (0.01-9.44)	<0.0001*

NG: nodular goiter, MNG: multinodular goiter, TSH: thyroid stimulating hormone *: statistically significant p value

Table 2. Binary logistic regression analysis for parameters that differ significantly in Table 1

Parameter	β	P	Exp(B)	95% CI for Exp(B)	
				Lower	Upper
Geriatric age	-1.230	0.018*	0.292	0.105	0.810
TSH	1.740	<0.0001*	5.697	3.468	9.358

*: statistically significant p value

A total of 481 FNABs were received. TNG group had 165 nodules. The comparison of the two groups in terms of the nodules undergoing FNAB was given in **Table 3**. Chi square analysis was performed for categorical variables; Which subvariables caused the difference was determined by post-hoc analysis and these were marked with letters. Accordingly, it was found that the nodules in the TNG group were larger, had more smooth edges, more calcification, worse blood flow patterns (central, central + peripheral), and more hypoechoic pattern. There was no difference in biopsy results and nodule content (**Table 3**).

Table 3. Comparison of two groups according to the biopsied nodules

Parameter	Toxic group (n=165)	Non-toxic group (n=316)	P
Biggest diameter	27.86±11.310	21.131±10.227	<0.0001*
Size, n (%)			0.003*
< 10 mm	4 (2.4)	15 (4.7)	
10.01-39.99 mm	138 (83.6)	284 (89.9)	
> 40 mm	23 (13.9)[a]	17 (5.4)[b]	
Content, n (%)			0.282
Solid	57 (34.5)	125 (39.6)	
Mixed	108 (65.5)	191 (60.4)	
Edge, n (%)			0.014*
Smooth	141 (85.5)[a]	236 (74.7)[b]	
Irregular	14 (8.5)[a]	57 (18)[b]	
Unclear	10 (6.1)	23 (7.3)	
Calcification, n (%)			0.038*
Absent	122 (73.9)[a]	268 (84.8)[b]	
Micro	11 (6.7)	11 (3.5)	
Macro	19 (11.5)	21 (6.6)	
Micro+macro	7 (4.2)	5 (1.6)	
Eggshell	6 (3.6)	11 (3.5)	
Vascularization, n (%)			<0.0001*
Absent	94 (57)	206 (65.2)	
Peripheral	43 (26.1)	91 (28.8)	
Central	7 (4.2)[a]	1 (0.3)[b]	
Peripheral+central	21 (12.7)[a]	18 (5.7)[b]	
Echogenicity, n (%)			0.005*
Isoechoic	31 (18.8)	70 (22.2)	
Hypoechoic	38 (23)[a]	47 (14.9)[b]	
Hyperechoic	0[a]	16 (5.1)[b]	
spongiform	96 (58.2)	183 (57.9)	
FNAB result, n (%)			0.152
Benign	122 (73.9)	197 (62.3)	
Malign	1 (0.6)	1 (0.3)	
Susp for malign	3 (1.8)	9 (2.8)	
FN/ Suspicious FN	0	2 (0.6)	
AUS / AUFL	18 (10.9)	51 (16.1)	
ND	21 (12.7)	56 (17.7)	

FN: follicular neoplasia, AUS / AUFL: unspecified atypia / indeterminate follicular lesion, *: statistically significant p value, a: There was a significant difference with compared non-toxic group in post-hoc comparison., b: There was a significant difference with compared toxic group in post-hoc comparison.

DISCUSSION

The results of the study: Patients with TNG were older, they had more male gender than patients with non-TNG, had larger thyroid glands and more nodules with suspicious features. The toxic nodules had larger size, more central blood supply, and hypoechogenicity rather than the other group. However FNAB results show similar cytological risk with the non-TNG. Since only 12% of the patients were thyroidectomy, the FNAB results could not be confirmed by pathological data. Undoubtedly, the Covid-19 pandemic had an unfavourable effect on this. In our country, as in many countries, elective hospital admissions and elective surgeries have decreased significantly due to the pandemic. The patients had to be followed conservatively with antithyroid drugs instead of primary treatment.

The frequency of TNG in areas of iodine deficiency increases up to 50% and is more common in the elderly (11). There is no distinct gender dominance in toxic nodular goiter (12). In our study, patients with toxic goiter were older and they had more geriatric age patients (>65 years) than non-TNG group. Female gender was higher in both groups, but individuals with male gender had a larger ratio in TNG. (29% vs 16.8, p=0.009, **Table 1**). Since women in our country apply to hospitals more than men, there may be such a difference with the literature in terms of gender. Besides, in logistic regression analysis, the high number of getriatric patients was significant, while no significant effect of gender was observed (**Table 2**).

Thyroid nodules are usually seen as multiple nodules but may also be single (13). In this study, MNG was higher in both groups, but the rate of multinodularity was higher in the toxic group (84.7% vs 73.3%, p=0.016). The reason for this is that the number of nodules increases with age and the TNG patients were older.

In the study, the TNG group's thyroid volumes were higher and they had more nodules with

suspicious features (**Table 1**). The development of toxic nodular/multinodular goiter depends on many factors. Chronic stimulation of thyroid gland causes diffuse enlargement of the gland, which progresses to goiter and nodule formation. In addition to the autonomic activity of nodules, toxic nodular/multinodular goiter develops with the effect of other factors such as genetic factors, iodine deficiency, stress, gender, and drugs (14). Therefore, the detection of larger thyroid gland and higher number of nodules in the toxic group seems compatible with the literature.

FNAB is the most appropriate method for preoperative evaluation of the malignancy risk for thyroid nodules. Performing it with USG increases its effectiveness. FNAB is recommended for nodules with suspicious features such as largest diameter > 1 cm, hypoechogenicity, poorly

defined margin, absence of halo, presence of micro-calcification, antero-posterior diameter/transverse diameter ratio > 1, and intranodular vascularization (9). In toxic nodular thyroid diseases, radionuclide scintigraphy is performed, in this procedure, non- or hypo-functioning nodules have high risk of malignancy. It is recommended to perform FNAB of these nodules, but if the nodule is hyperfunctioning, FNAB is not recommended (15). In practice, FNAB of hyperfuntioning nodules is not performed (16). In addition, if biopsy is performed on a hot nodule, it may show a follicular pattern, which is not associated with malignancy.

However, an increasing number of follicular cancers and follicular variant papillary thyroid cancers are detected in hot nodules. For this reason, the diagnosis of follicular neoplasia in the biopsy of hot nodules is not as reassuring as previously thought (17).

Therefore, if hot nodule has suspicious sonographic feature(s), it should be considered for FNAB. In our study, FNABs were performed for 481 suspicious nodules and the two groups were compared. The TNG group had suspicious sonographic features such as larger size, central blood supply, hypoechogenicity, and they had lower risk in terms of calcification and margin structure and are at similar risk with the other group for nodule content. Hence, it can be said that toxic nodules carry suspicious features like non-toxic nodules or more than them. All in all, FNAB results were similar in both groups. Interestingly, there is no result with follicular neoplasm in the toxic group. The meaningful result of our work is that, toxic nodules are not less risky than non-toxic.

Limitation

Essentially, the patients should be operated and histopathological diagnosis should be seen to tell the actual malignancy risk, but unfortunately, we could not confirm the FNAB results. Because of the pandemic, only 26 were operated, appropriate follow-up of most of the patients could not be performed.

CONCLUSION

In summary, toxic nodules have significant suspicious patterns like non-toxics, and their evaluation with FNAB should not be avoided, thus ensuring more adequate treatment and follow-up of toxic nodular thyroid disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from Amasya University Hospital Non-invasive Ethics Committee (Date: 07.01.2021, Decision No: 18).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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