RESEARCH ARTICLE

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Evaluation of Ultrasonographic Characteristics and Cytopathological Results of Autonomous (Toxic) Thyroid Nodules

ABSTRACT

Objective: Thyroid nodules are clinical conditions frequently encountered in the community and known to be associated with malignancy. In this study, it was aimed to determine the frequency of malignancy in patients diagnosed with autonomous (toxic) thyroid nodules (TTN). In addition, the effectiveness of ultrasonography (US) findings and fine needle aspiration (FNA) results in helping the diagnosis of malignancy were investigated.

Methods: Autonomous (Toxic) thyroid nodule was diagnosed by presence of nodule on US in the presence of subclinical or clinical hyperthyroidism, and detection of suppression in other parts of the gland with increased activity in scintigraphy performed with Tc-99m pertechnetate. Fine-needle aspiration was performed on patients who were considered suspicious by ultrasonographic findings. The histopathology results of the patients who were found to need surgical resection were recorded.

Results: 125 patients with autonomous (toxic) thyroid nodules were included in the study. Of the patients, 82 (65.60%) were female and 43 (34.40%) were male, with a mean age of 63.55±11.13 years. Ultrasonography revealed that nodules were less frequently located in the isthmus and left upper pole. The presence of microcalcification was detected in 8 (6.4%) patients. Histopathologically, the nodules of 2 (1.6%) patients were found to be malignant. Both patients who were found to be malignant were male and their nodules were seen as hypoechoic on US.

Conclusions: Since it has been seen that autonomic (toxic) thyroid nodules may be related to malignancy, careful evaluation of male patients with a hypoechoic image on US was considered appropriate.

Keywords: Toxic Thyroid Nodule, Malignancy, Ultrasonography.

Otonom (Toksik) Tiroid Nodüllerinin Ultrasonografik Özelliklerinin ve Sitopatolojik Sonuçlarının Degerlendirilmesi

ÖZET

Amaç: Tiroid nodülleri toplumda sık karşılaşılan ve maligniteyle ilişkili olduğu bilinen klinik durumlardır. Bu çalışmada otonom (toksik) tiroid nodülleri (TTN) tanısı konulan hastalardaki malignite sıklığını belirlemek amaçlandı. Ayrıca ultrasonografi (US) bulguları ve ince iğne aspirasyonu (İİA) sonuçlarının malignite tanısına yardımcı olmadaki etkinliği araştırıldı.

Gereç ve Yöntem: Otonom (Toksik) tiroid nodülü tanısı, subklinik veya klinik hipertiroidi varlığında US'de nodül ve Tc-99m perteknetat ile yapılan sintigrafide nodül veya nodüllere uyan alanlarda aktivite tutulumda artış ile birlikte bezin diğer kısımlarında supresyon saptanması ile kondu. Ultrasonografi bulguları ile şüpheli olarak değerlendirilen hastalara ince iğne aspirasyonu yapıldı. Cerrahi rezeksiyon gerekliliği saptanan hastaların histopatoloji sonuçları kaydedildi.

Bulgular: Çalışmaya otonom (toksik) tiroid nodülü saptanan 125 hasta dahil edilmiştir. Hastaların 82'si (%65,60) kadın, 43'ü (%34,40) erkek olup yaş ortalamaları 63,55±11,13 idi. Ultrasonografide nodüllerin isthmus ve sol üst polde daha az sıklıkla yerleştiği saptanmıştır. İzoekoik nodül görüntüsünün hipoekoik ve karışık eko görüntüden daha az olduğu görülmüştür (p<0,001). Mikrokalsifikasyon varlığı ise 8 (%6,4) hastada tespit edilmiştir. Histopatolojik olarak 2 (%1,6) hastanın nodülü malign olarak tespit edilmiştir. Malign olarak saptanan iki hasta da erkekti ve nodülleri US'de hipoekoik olarak görülmüştür.

Sonuç: Otonom (toksik) tiroid nodullerinin malignite ile ilgili olabileceği görüldüğünden, US'de hipoekoik görüntüsü olan erkek hastalarda dikkatli değerlendirme yapılmasının uygun olduğu düşünülmüştür.

Anahtar Kelimeler: Toksik Tiroid Nodulü, Malignite, Ultrasonografi.

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INTRODUCTION

Thyroid nodules are frequently encountered in the community. It is important in terms of affecting thyroid functions, mass effect and being associated with thyroid cancer at a rate of 7-15% (1). Autonomous (toxic) thyroid nodules (TTN) are formed by focal and/or diffuse hyperplasia of thyroid follicle cells and increased functional capacity, independent of the effect of thyroid stimulating hormone (TSH). With subclinical or clinical thyrotoxicosis, the presence of nodules is seen on physical examination or ultrasonography (US). Absence of thyroid antibodies and increased radioactivity uptake in the nodule or areas matching nodules on thyroid scintigraphy are used to detect TTN in order to differentiate it from other causes of thyrotoxicosis (2). Radioactive iodine (RAI) and thyroidectomy are applied as the definitive treatment method for TTN. The treatment method is preferred according to the patient's demographic and clinical characteristics, preference and the facilities of the health center (2).

The incidence of malignancy in TTN can range from 3% to 18.3% (3-6). The high rates detected show the importance of examining TTN in detail. Fine needle aspiration (FNA) is the gold standard method for differentiating benign and malignant thyroid nodules (2). In ultrasonography, hypoechoic appearance, solid structure, presence of microcalcification, contour irregularity, increased vascularity and increased strain index in elastsonography are suspicious findings in terms of malignancy (7,8).

In this study, it was aimed to determine the frequency of malignancy in patients diagnosed with TTN by physical examination, US and scintigraphy evaluations. In addition, the effectiveness of US findings and FNA results in helping the diagnosis of malignancy were investigated.

MATERIAL AND METHODS

Patients who applied to the Düzce Atatürk State Hospital Endocrinology and Metabolic Diseases outpatient clinic between June 2021 and December 2022 and were diagnosed with an autonomous (toxic) thyroid nodule were included in the study. Age, gender, TSH, fT3, fT4 values, ultrasound findings, cytology and histopathology results of the patients were saved.

Autonomous (toxic) thyroid nodule was diagnosed by presence of nodule on US in the presence of subclinical or clinical hyperthyroidism, detection of increased activity uptake in the nodules and suppression in other parts of the gland in scintigraphy performed with Tc-99m pertechnetate.After providing euthyroidism with beta-blocker and/or antithyroid treatment, FNA was performed on the indicated nodules.

Preoperative US and FNA procedures were performed using Siemens Medical Solution brand and MCMD01AA model USG device (Italy). Nodule volume, increased anterior-posterior diameter, contour irregularity, echogenicity, presence of microcalcification, thyroid pole where the nodule is located, and nodule dimensions were determined by US. The volumetric assessment of the thyroid nodule was calculated based on the use of the ellipsoid model. In this model, the height, width and depth of each nodule were measured and multiplied, and the result was then multiplied by the mathematical constant or correction factor (0.524) to calculate the volume of the nodules (9,10).

Fine-needle aspiration was performed on patients who were considered suspicious by US findings. For FNA, 10 ml injectors with 27 gauge needles were used. FNABs were performed with the patient in the supine position without the use of anesthesia. In the supine position, the neck was extended and the area to be biopsied was cleaned with 10% povidone-iodide. FNAB was performed under US guidance. Liquid-based cytology technique was used. The cytology results of the FNA samples evaluated in the pathology laboratory of our hospital were grouped as benign, malignant and atypia of uncertain significance according to the Bethesda classification. The histopathology results of the patients who were found to need surgical resection were recorded.

The study was approved by the local Clinical Research Ethics Committee with the decision dated 28.07.2023 and numbered 242.

Statistical Analysis: IBM SPSS 23.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, USA) statistical package program was used for the statistical evaluation of the research data. Categorical data were summarized as frequency and percentage. Chi-square Test, Fisher's Exact and Fisher-Freeman-Halton Tests were used to evaluate the statistical difference of categorical data. p value of <0.05 was considered statistically significant.

RESULTS

125 patients with autonomous (toxic) thyroid nodules were included in the study. Of the patients, 82 (65.60%) were female and 43 (34.40%) were male, with a mean age of 63.55±11.13 years. Histopathologically, the nodules of 2 (1.6%) patients were found to be malignant. Ultrasonography revealed that nodules were less frequently located in the isthmus and left upper pole. It was observed that the isoechoic nodule image was less than the hypoechoic and mixed echo image ($p<0.001$). The presence of microcalcification was detected in 8 (6.4%) patients. A total of 78 (62.4%) patients underwent FNA. One of the two patients who were evaluated

as malignant as a result of FNA was also found to be malignant histopathologically. The laboratory, US, FNA and histopathology results of the patients are shown in Table 1.

Table 1. The laboratory, US, FNA and histopathology results of the patients

Laboratory results	Mean±SD		
TSH (n=121)	0.075±0.082		
fT3 (n=88	3.456±0.935		
fT4 (n=113)	2.129±10.431		
Nodule volume.	10.423±16.512		
US results			p
Nodule site	n	%	
Right upper pole	13	10.4	<0.001
Right middle pole	25	20.0	
Right lower pole	30	24.0	
Left upper pole	**7**	**5.6**	
Left middle pole	22	17.6	
Left lower pole	24	19.2	
Isthmus	**4**	**3.2**	
Nodule	n	%	
Mixed echo	62	49.6	**0.049**
Hypoechoic	50	40.0	
Isoechoic	**13**	**10.4**	
Microcalcification	n	%	
Yes	8	6.4	
No	117	93.6	
Contour	n	%	
Yes	-	-	
No	125	100	
Increased anteroposterior diameter	n	%	
Yes	5	4	
No	120	96	
FNA (n=78)	n	%	
Benign	75	60	
Malign	2	1.6	
AUS	1	0.8	
Histopathology	n	%	
Benign	9	81.8	
Malign	2	18.2	

SD: Standard deviation, AUS: Atypia of uncertain significance, FNA: Fine needle aspiration, US: Ultrasonography

One of the two patients with histopathologically malignant lesion had a nodule with regular contours, hypoechoic and microcalcification in the lower pole of the left thyroid lobe (size 37*49*52 mm), with regular contours, as US finding, and the result of FNA was also found to be malignant. Post-operative malignant lesion was also detected in the left lobe, consistent with US. The second patient had a histopathologically malignant lesion in the right lobe, and a hypoechoic nodule (16*17*20 mm) was observed only in the lower pole of the left lobe as US finding, and FNA was not performed. In the US evaluation of the nodule of a patient with malignant cytology by FNA, it was observed that the nodule was in the middle lobe of the thyroid, with mixed echogenicity, without microcalcification, with regular contours, and no increase in anteroposterior diameter, and the post-operative histopathological result was found to be benign. The US and FNA characteristics of the thyroid nodules of patients who were found to be histopathologically malignant are summarized in Table 2.

Table 2. Characteristics of the thyroid nodules of patients who were found to be histopathologically malignant

	Patient 1	Patient 2
Age	64	63
Gender	Male	Male
US results		
Thyroid site	Left lower pole	Left lower pole
Echogenicity	Hypoechoic	Hypoechoic
Microcalcification	Yes	No
Increased anteroposterior diameter	No	No
Contour irregularity	No	No
FNA result	Malign	None

FNA: Fine needle aspiration, US: Ultrasonography

DISCUSSION

Thyroid cancer is one of the most common endocrine tumors and its incidence is increasing all over the world. Thyroid nodules, which are mostly detected by physical examination or imaging methods, are detected as the first finding of thyroid cancers (2).The incidence of malignancy in patients with TTN has been reported at different rates in studies. Mohammed et al., Smith et al. and Tam et al. reported that thyroid malignancy rate of TTN patients as 21.43%, 18% and 19.2%., respectively (11-13). Choong et al. (14) in total, seven (4.7%) of the 148 patients were found to have thyroid cancer; 1 (3.2%) of the 31 patients from 1990 to 1999, 3 (4.2%) of the 72 patients from 2000 to 2009, and 3 (6.7%) of the 45 patients from 2010 to 2014. Preece et al. (15) reported this rate as 6.4%. In our study, the malignancy rate in TTN patients was found to be 1.6%, and this rate was found to be lower than other studies. It was thought that this difference in studies could be related to patient selection and method differences, geographical and ethnic differences, iodine status of the population in which the study was conducted, the scope of the surgery (total or hemithyroidectomy) or histopathological examination.

It is known that male gender is a risk factor for thyroid cancer (16). Mohamed et al. (11) found the male sex ratio to be 15.58% in TTN patients who were found to be benign, and 38.1% in those with malignant ones. Smith et al. (12) reported

these rates as 11% and 27%, respectively. In our study, it was observed that both patients (100%) who were found to be malignant were male. These results suggested that male gender may also be a risk factor for TTN related thyroid malignancies.

Being under the age of 20 and being old are known risk factors for thyroid cancer (16). However, Preece et al. (15) reported that the mean age of their patients with thyroid nodules was 54 in both malignant and benign patients. Ozdemir et al. (2) found these averages to be 55.5 and 56, respectively, in their study. The mean age of all patients with TTN in our study was 63.55, and the mean age of the two patients who were found to be malignant was 63.5 years. Age wasn't seen a determining factor in the evaluation of nodules as benign or malignant.

Thyroid US is easy, practical, inexpensive and the most sensitive method for imaging the thyroid gland. With thyroid USG, the size of the thyroid gland, the size of the nodule, its structure (cystic, solid or mixed) and echogenicity (hypoechoic or hyperechoic), calcifications, the status of the lymph nodes can be visualized, and biopsy can be performed on the thyroid nodules under US guidance. In addition, since some findings on US may suggest malignancy, they are effective in the decision of biopsy and surgery (14). Contour irregularity, anteroposterior diameter increase, presence of microcalcification are among these US findings. Ozdemir et al. (2) found these findings at a similar rate in benign and malignant nodules in their study. In our study, there was no increased anterior-posterior diameter and contour irregularity in both patients who were found to be malignant, and only one patient had microcalcification. Ozdemir et al. (2) also found a hypoechoic image on US in 15.38% of the nodules they detected as malignant and in 6.20% of the nodules they detected as benign. Önver et al. (17) reported the presence of hypoechoic nodules on US in 21 (84%) of 25 patients with thyroid nodules that they found to be malignant, and in 22 (40%) of 56 patients they found benign. In addition, the second patient did not have a suspicious appearance, except that he had a hypoechoic nodule. This showed that nodule echogenicity is important in the suspicion of malignancy.

It should be kept in mind that thyroid cancer can be encountered in the contralateral lobe in TTN patients. Tam et al. (13) incidence of cancer detection in the contralateral lobe was 10%, Satta et al. (18) reported this rate as 5%. In our study, malignancy was found in two of 125 patients. In one of these patients, the presence of cancer was reported not in the lobe with active nodule detected by US, but in the contralateral lobe without biopsy indication.

The limited number of patients with toxic thyroid nodules is the limitation of the study.

In conclusion, hypoechoic image in US findings and male gender were considered as risk factors for malignancy in TTN patients.

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