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Original Article

Clinicopathological features and ultrasonographic findings of thyroid nodules classified as atypia of undetermined significance/follicular lesion of undetermined significance

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Abstract

Objective: The Bethesda reporting system (BRS) is used as a standard in the evaluation of thyroid fine needle aspiration cytology. Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) is defined as Bethesda category III and the malignancy risk is reported to be 5-15%. Nodules diagnosed with AUS/FLUS remain uncertain in terms of malignancy risk. Our aim is to determine the malignancy risk of aspirations classified as AUS/FLUS in our hospital, where thyroid fine-needle aspiration cytology (FNAC) is performed frequently and to examine whether there is a relationship between ultrasonographic data and the diagnosis of AUS/FLUS.

Methods: The data of 3200 patients who were followed up in our hospital between 2008 and 2018 for thyroid nodules and underwent FNAC were analyzed. There were 150 patients with thyroid nodules diagnosed with AUS/FLUS in this patient group. The clinical information, radiological findings and surgical treatment process of these patients were documented using our hospital database.

Results: A total of 150 out of 3200 cases were diagnosed with AUS/FLUS. Of the patients classified as AUS/FLUS, 13.3% (20/150) underwent immediate surgery and 31.3% (47/150) were followed up with only ultrasonography (US). FNAC was repeated in 62.4% (83/150) of them. Ten percent (16/83) of the group whose FNAC was re-examined were inadequate and 27.3% (41/83) were benign. A second diagnosis of AUS/FLUS was conducted in 26.51% (22/83) of them (14.7% (22/150) of all patients) and 4.82% (4/83) of them (2.7% (4/150) of all patients) were diagnosed with suspected malignancy. The group that was diagnosed with two consecutive AUS/FLUSs and suspected malignancy underwent surgery. In the operated group, 26.08% (12/46) were diagnosed with malignancy. In terms of ultrasonography data, only macrocalcification (41.7% (n: 5/12)) supported the diagnosis of malignancy ($p<0.001$). In terms of AUS/FLUS, our study did not observe ultrasonographic data to support this diagnosis ($p>0.05$).

Conclusion: We believe that the place of FNAC is very important in the approach to thyroid nodules. We recommend that the decision to directly undergo surgery or to send cytology for the second time in cases where AUS/FLUS is detected for the first time in the cytology taken from the patients should be made by the following clinician. In addition, we should emphasize that FNAC and US have an important place in early malignancy detection in the follow-up of thyroid nodules.

Keywords: AUS/FLUS, thyroid cancer, ultrasonography.

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INTRODUCTION

Most patients with thyroid nodules are asymptomatic. The absence of symptoms of the nodule does not exclude malignancy. The main clinical problem in thyroid nodules is distinguishing malignant nodules (1). Approximately 5% of thyroid nodules contain malignancy (2). The annual incidence of thyroid malignancies in the United States increased from 4.9 per 100,000 in 1975 to 14.3 in 2018 (1). For this reason, it is very important to distinguish malignant nodules that require a surgical approach from benign nodules. The use of FNAC allows for a highly effective risk stratification (2,3). FNAC plays a prominent role in managing and work-up of thyroid nodules by approximating the malignancy risk and aiding rational clinical decisions for surgery or observation (4). In fact, more than 50% of surgically resected nodules were ultimately found to be malignant (2,3). In the follow-up of thyroid nodules, high-resolution US, thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3), FNAC and clinical findings are used. Clinical and US risk factors for malignant diseases are always taken into account. All patients with palpable thyroid nodules or clinical risk factors are evaluated with US. It is followed clinically according to the "American Thyroid Association" (ATA), "American Association of Clinical Endocrinologists" (AACE), "American College of Endocrinology" (ACE) and "Associazione Medici Endocrinology Medical" (AME) guidelines (1,5). In the present study, we aimed to present our experience with the malignancy rates of thyroid nodules diagnosed with AUS/FLUS in FNAC at a single center in our city and to examine whether there is a relationship between ultrasonographic data and the diagnosis of AUS/FLUS.

MATERIALS AND METHODS

This is a retrospective study that was conducted in accordance with the Helsinki Declaration. We conducted it after receiving the permission of the Ethical Committee of the Noninvasive Clinical Research Ethics Committee of the University of Amasya (07.08.2021-118).

Our study examined all FNAC records made in our hospital between 2008 and 2018 and included cases with thyroid nodules in these records and diagnosed with AUS/FLUS by our hospital pathologists according to the Bethesda reporting system (BRS). Accordingly, nondiagnostic; category 1, benign; category 2, AUS/FLUS; category 3, suspected follicular neoplasia and follicular neoplasia (FNS/FN); category 4, suspected malignancy (SFM); category 5, finally malignant; were grouped histopathologically as category 6 (6,7). Cases are followed by our clinic based on ATA, AACE, ACE or AME guidelines. Our study examined all reports of cases diagnosed with AUS/FLUS. FNAC was applied to the cases for the second time. Second FNAC results were also classified as unsatisfactory, benign, AUS/FLUS, suspected malignancy and malignant categories. Clinical variables were determined as age, sex, and nodule size. US findings were divided into anechoic, hypoechoic, very hypoechoic, isoechoic-hyperechoic, heterogeneous, homogeneous, hypovascularization, hypervascularization, microcalcification, peripheral calcification, macrocalcification and no calcification (8,9) cystic, spongiform architecture, mixed cystic and solid and solid (1). Nodules containing these features simultaneously were indicated and grouped one by one. Some of the patients were followed only by US. The FNAC was not performed for the second time. The pathology reports of the thyroidectomy materials of the operated cases were examined and categorized as hyperplasia, papillary thyroid cancer, follicular thyroid cancer and others (thyroiditis, etc.). An attempt was made to establish a relationship between US results and pathology reports in patients diagnosed with AUS/FLUS.

FNAC was sampled by the radiologist and/or endocrinologist in one to three passes using a 21-gauge needle under ultrasound guidance. Air-dried slides were stained with Giemsa stain and alcohol-fixed slides were stained with Papanicolaou.

Operation criteria were determined in accordance with the guidelines. Patients with sonographic features, rapidly growing nodules, cases with clinical suspicion, patients with large multinodular goiter due to patient/physician preference, and patients diagnosed with AUS/FLUS twice in a row were operated. Some patients whose first FNAC result was AUS/FLUS were followed up with US, and surgery was recommended when the above mentioned conditions occurred.

Statistical analysis

The obtained data were analyzed using SPSS (Statistical Package for the Social Sciences) version 16.0. At this point, the data did not show a normal distribution, as the significance values of the Shapiro–Wilk test were less than 0.05. Therefore, the data were analyzed with the "Mann–Whitney U" test, one of the nonparametric tests. During the statistical analyses, p values less than 0.05 were considered statistically significant.

RESULTS

Between 2008 and 2018, AUS/FLUS was detected in 150 of 3200 patients who were followed up for thyroid nodules and underwent FNAC. Of these patients, 83.3% (125/150) were female, 16.7% (25/150) were male and the mean ages for men and women were 47 and 52, respectively. The median nodule diameter was 22 mm. A total of 13.3% (20/150) of the patients with AUS/FLUS underwent direct surgery. The patients in this group had hyperthyroidism that is resistant to drug therapy. Direct thyroidectomy was performed for treatment. While 31.3% (47/150) of patients who did not approve FNAC for the second time were followed up with US, 62.4% were followed up for second cytology (Table 1). Of the patients who underwent FNAC for the second time, 18.1% (15/83) were inadequate, 49.4% (41/83) benign, 26.51% (22/83) a second time AUS/FLUS and 4.82% (4/83) were diagnosed with suspected malignancy (Table 2).

Table 1. General data of the patients

	n: 150	Mean age (year)	Maximum value	Minimum value
Male	25	47	80	22
Female	125	52	79	18
		Mean value	**Maximum value**	**Minimum value**
Nodule diameter median (mm)		21	68	6
	n: 150	**%**		
Direct surgery	20	13.3		
Only US follow-up	47	31.3		
Second FNAC	83	62.4		
Surgery after FNAC	26/83	31.3		

Abbreviations: FNAC: Fine-needle aspiration cytology, US: Ultrasonography. SPSS descriptive analysis is used in this table.

Table 2. Cytology findings of the second FNAB

	n: 83	%
Inadequate	16	10
Benign	41	27.3
AUS/FLUS	22	14.7
Suspicion of malignancy	4	2.7
Malignant	0	0

Abbreviations: AUS/FLUS: Atypia of undetermined significance/follicular lesion of undetermined significance, SPSS descriptive analysis is used in this table.

Twenty-six patients with a second diagnosis of AUS/FLUS or suspected malignancy were operated. Overall, 30.6% (46/150) of the cases were operated. Regarding the pathology results of the specimens, 69.5% (32/46) of them were found to be hyperplastic, 26% (12/46) were papillary thyroid carcinoma (PTC) and 4.3% (2/46) were other diagnoses (thyroiditis, etc.) (Table 3). As a result, malignancy was detected in 26.08% (12/46) of those who underwent surgery after cytology. None of the patients who were followed up with US were operated based on US results.

Table 3. Postoperative pathological features

	n: 46	%
Hyperplasia	32	69.5
Papillary carcinoma	12	26
Follicular carcinoma	0	0
Others	2	4.3

Considering the US data of the nodules in the general group, in terms of echogenic focus, 86% (129/150) of the patients were grouped as no calcification, 2.7% (4/150) as microcalcification, 11.3% (17/150) as macrocalcification and 0% (0/150) as peripheral calcification. In terms of content, 77.3% (116/150) of the patients were grouped as having a homogeneous internal structure and 22.7% (34/150) were grouped as having a heterogeneous internal structure. In terms of vascularization, 6% (9/150) of the patients were grouped as hypovascularization and 94% (141/150) were grouped as hypervascularization. In terms of echogenicity, 42% (63/150) were grouped as anechoic, 16.6% (25/150) as isoechoic-hyperechoic, 6.7% (10/150) as hypoechoic and 34.7% (52/150) as very hypoechoic. In terms of composition, 18% (27/150) of the patients were grouped as cystic, 8.7% (13/150) as spongiform architecture, 56% (84/150) as mixed cystic and solid and 17.3% (26/150) as solid (Table 4).

Considering the US data of the nodules in the second AUS/FLUS, in terms of echogenic focus, 13.6% (3/22) of the patients were grouped as no calcification, 0% (0/22) as microcalcification, 13.6% (3/22) as macrocalcification, and 72.8% (16/22) as peripheral calcification. In terms of content, 13.6% (3/22) of the patients were grouped as having a homogeneous internal structure, and 86.4% (19/22) were grouped as having a heterogeneous internal structure. In terms of vascularization, 0% of the patients were grouped as hypovascularization, while 100% (22/22) were grouped as hypervascularization. In terms of echogenicity, 27.3% (6/22) of the patients were grouped as anechoic, 27.3% (6/22) as isoechoic-hyperechoic, 18.1% (4/22) as hypoechoic and 27.3% (6/22) as very hypoechoic. In terms of composition, 18.1% (4/22) of the patients were grouped as cystic, 4.6% (1/22) as spongiform architecture, 50% (11/22) as mixed cystic and solid, and 27.3% (6/22) as solid (Table 4).

When the observed ultrasonographic data were compared with the group diagnosed as malignant, they could not distinguish the diagnosis of AUS/FLUS ($p>0.05$) (Table 4).

Considering the US data of the nodules in the malignant group in terms of echogenic focus, 41.7% (5/12) of the patients were grouped as no calcification, 0% (0/12) as microcalcification, 0% (0/22) as macrocalcification and 58.3% (7/12) as peripheral calcification. In terms of content, 16.7% (2/12) of the patients were grouped as having a homogeneous internal structure, while 83.3% (10/12) were grouped as having a heterogeneous internal structure. In terms of vascularization, 8.3% (1/12) of the patients were grouped as hypovascularization and 91.7% (11/12) were grouped as hypervascularization. In terms of echogenicity, 41.7% (5/12) of the patients were grouped as anechoic, 8.3% (1/12) as isoechoic-hyperechoic, 0% (0/12) as hypoechoic and 50% (6/12) as very hypoechoic. In terms of composition, 0% (0/12) of the patients were grouped as cystic, 8.3% (1/12) as spongiform architecture, 41.7% (5/12) as mixed cystic and solid, and 50% (6/12) as solid. (Table 4).

Some US data show that malignant nodules are more common than benign nodules. Regarding the US data of the nodules in the PTC group, 41.7% (5/12) had macrocalcifications. When these US data were compared with the general group, they were found to be supporting the diagnosis of carcinoma ($p=0.001$). These data, detailed

in Table 4 in terms of composition, echogenicity, vascularization content and echogenic foci, were found to be insignificant for the diagnosis of carcinoma (p>0.05).

Table 4. Relationship and correlation of groups and US data.

	General group		Second AUS/FLUS			Malign group		
	n: 150	%	n: 22	%	p	n: 12	%	p
As echogenic foci								
Microcalcification	4	2.7	3	13.6	0.727	0	0	0.375
Macrocalcification	17	11.3	3	13.6	0.003	5	41.7	0.017
Peripheral calcification	0	0	0	0	-	0	0	-
No calcification	129	86	16	72.8	<0.001	7	58.3	<0.001
As content								
Heterogeneous	34	22.7	3	13.6	<0.001	2	16.7	<0.001
Homogeneous	116	77.3	19	86.4	<0.001	10	83.3	<0.001
As vascularization								
Hypervascularization	9	6	0	0	<0.001	1	8.3	0.021
Hypovascularization	141	94	22	100	<0.001	11	91.7	<0.001
As echogenicity								
Anechoic	63	42	6	27.3	<0.001	5	41.7	<0.001
Isoechoic-hyperechoic	25	16.6	6	27.3	0.001	1	8.3	<0.001
Hypoechoic	10	6.7	4	18.1	0.180	0	0	<0.001
Very hypoechoic	52	34.7	6	27.3	<0.001	6	50	<0.001
As a composition								
Cystic	27	18	4	18.1	<0.001	0	0	<0.001
Spongiform architecture	13	8.7	1	4.6	0.002	1	8.3	0.002
Mixed cystic and solid	84	56	11	50	<0.001	5	41.7	<0.001
Solid	26	17.3	6	27.3	0.001	6	50	0.001

Abbreviations: AUS/FLUS: Atypia of undetermined significance/follicular lesion of undetermined significance, US: Ultrasonography. This table is used with the chi-square test. p<0.05 is accepted significant.

DISCUSSION

Thyroid nodules are common in the community. Approximately 85-90% of these nodules are benign (10,11). Thyroid nodules are observed in 5.3-6.4% of women and 0.8-1.6% of men. The prevalence may reach 50% when considering ultrasound and even 65% when considering autopsy series (12). In our study, approximately 5 times more nodules were detected in the thyroid gland of women (83.3% female and 16.7% male).

Advanced age, iodine deficiency, female sex, obesity, radiation (especially in the cervical region) and familial association with thyroid diseases are important risk factors for thyroid nodules. Cancer is observed in 5 to 10% of these nodules (12). The detected nodules are reported as malignant at rates of 1.7% and 7% in men and women, respectively (13). There has been an increase in the frequency of thyroid cancers in the population in recent years (10,11). In 2020, thyroid cancers accounted for 3% of the world's cancer incidence, with an estimated 580,000 new

patients. In the last 30 years, the incidence and death rate of thyroid cancer have shown significant variability between countries (14). Malignancy was detected in 8% of all cases included in our study, with75% of them being women. This rate was found to be 90% for North Korea and 87% for China (15).

Despite the benefits of FNAC, the interpretation of cytopathology reports in past years has been challenging. Definitions such as "atypical", "indeterminate" or "cannot be excluded" have caused confusion in clinical follow-up (6). These terms have caused different perceptions by pathologists, endocrinologists and surgeons, especially among institutions (16). The use of BRSs has resulted in understandable and standard pathology reports. Unnecessary thyroidectomy operations were prevented (17). In BRS, Category III AUS/FLUS is used as the last choice in cases in between. It is expected that 7% or less of FNAC performed will receive this diagnosis (6,18). In our study, AUS/FLUS was detected in 4.68% (150/3200) of the first FNAC of all patients examined. In general, there are publications stating that the rate of diagnosis of AUS/FLUS should be around 3-6%, even if it differs between laboratories (11). However, the inconsistent use of the diagnosis of AUS/FLUS among different clinics has caused controversy (6,18).

In our study, 26.5% (22/83) of the patients who received FNAC were diagnosed with AUS/FLUS twice in a row. Malignancy was found in 8% (12/150) of all nodules detected in AUS/FLUS. In patients with a second AUS/FLUS, this rate was slightly higher than that in the literature and malignancy was detected in 36.3% (8/22) of them. According to the estimations of the Bethesda consensus publication, nodules diagnosed with AUS/FLUS, which do not contain other suspicious features, can have a low malignancy potential (5-15%). Consequently, it is recommended to conduct further follow-up FNAC (6,17).

The rate of benign reporting of FNAC results varies from 10 to 28% in the literature, while this rate was 27.3% in our study (19). Four cases of suspected malignancy were diagnosed as malignant following the operation (100%). This high rate was associated with the low number of cases. However, in the literature, Bethesda category IV nodules have a risk of 15-30% in terms of malignancy. Surgical follow-up is recommended in terms of malignancy risk. Contrary to the Bethesda consensus recommendations, the guidelines published by the AACE/AME defined both nodules defined as Bethesda categories III and IV as uncertain (6,7).

Thyroid nodules are usually detected incidentally on US of the neck. The important thing here is to determine which nodule has a malignant character and/or the possibility of its transformation into malignancy. For this reason, nodules are followed by US and US-guided FNAC (10). Our study examined 3200 cases were followed up regularly with US and FNAC. As US findings, composition, echogenicity, vascularization, content and echogenic foci (7). Ultrasonography, which is the most preferred first diagnostic method in thyroid diseases, is a reliable and rapid method in the evaluation of thyroid nodules (10). There are many advantages to using US for imaging the thyroid gland. These are the ability to characterize the nodule (solid or cystic), to reveal the presence of other nodules, to be useful in the follow-up of detected nodules, to give an idea about the presence of thyroiditis, to recognize accompanying pathological cervical lymph nodes and to guide biopsy. However, no single US scan has high sensitivity and specificity (20). Research evaluating the role of US in thyroid nodules reported a 3-fold increase in cancer risk in the presence of microcalcifications and a 2-fold increase in the presence of macrocalcifications (9,17). In our study, malignancy was found in 5 of 12 cases with macrocalcification. When these data were compared with the noncancer group, macrocalcification increased approximately 4-fold in cancer. ($p<0.002$). The sensitivity of sonographic microcalcification for nodular malignancy was 76%, the specificity was 44% and the positive predictive value was 77.9% (9, 21). In a study conducted by Kwak et al., malignancy was found in 92 (86%) out of 107 patients with irregular borders in the nodule and 111 (68.5%) out of 162 patients with microcalcifications on US examination (22). In our study, cancer was not found in any of the four cases with microcalcifications in the nodule. Hypervascularization was observed in one out of 12 malignant nodules, an isoechoic-hyperechoic appearance in one out of 12 and a very hypoechoic appearance in six out of 12. However, it was not statistically significant ($p>0.05$).

Ultrasonographic data are used to accurately distinguish malignant cases. The American College of Radiology Thyroid Imaging Reporting and Data System (TIRADS) is a 5-level classification system used to determine cancer risk in thyroid nodules, taking into account US data and nodule size. Surgical removal of malignant nodules is

ensured by supporting US data with FNAC diagnoses. Thus, unnecessary surgical procedures are avoided in patients with benign nodules (10).

Our study comprehensively examined the US data of the group diagnosed with AUS/FLUS Bethesda category III for the second time in a row. I-II-III, considered a benign group according to Bethesda classification, can detect malignancies in the early period when evaluated together with the TIRADS system.

When I-II-III, considered a benign group according to Bethesda, especially Bethesda III, are evaluated together with the TIRADS system, malignancies can be detected in the early period. Thus, the number of unnecessary surgeries can be reduced by the use of US (10). However, when the ultrasonographic data observed in our study were compared between the group diagnosed with malignancy and the group without malignancy, there was no distinctive characters for the diagnosis of AUS/FLUS ($p>0.05$). We believe that it would be beneficial to conduct new studies with a larger number of cases.

Limitations:

This study has some limitations. Its sample sizes are small. We examined all cases with a diagnosis of Bethesda III in our hospital. However, we know that it is difficult to evaluate the relationship between US and AUS/FLUS based on the current number of cases. More cases need to be reviewed for more information.

CONCLUSION

There was no significant relationship between AUS/FLUS and US data. However, it may be useful to conduct further studies with larger patient groups. As seen in our study, a skeptical approach to thyroid nodules should be adopted first. Each case should be followed up with US first. Necessary nodular TIAs should be taken. In addition, we recommend that suspicious nodules should be followed up according to the Bethesda classification and more caution should be exercised in category III nodules.

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