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Original Article

The predictors of malignancy in thyroid nodules with atypia of undetermined significance or follicular lesions of undetermined significance

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Abstract

Aim: This study aimed to evaluate clinical, radiological and laboratory (neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, and mean platelet value) features that may better define the rate of malignancy in order to contribute to the management of thyroid nodules with AUS/FLUS.

Material and Methods: The data of patients with histologic findings of AUS/FLUS on FNA, who underwent surgery at General Surgery Department in a tertiary care hospital between January 2012 and December 2019, were reviewed retrospectively. The patients with any other malign and/or inflammatory diseases and continued on corticosteroid therapy and/or chemotherapy were excluded.

Results: The current study included 60 patients (73.3% women), who underwent surgery for 62 thyroid nodules classified as AUS/FLUS. The specimen pathology revealed a thyroid malignancy in 16 patients, including 10 patients with papillary cancer, 5 patients with micro-papillary thyroid cancer, 1 patient with minimally invasive follicular carcinoma. Ten patients had follicular adenoma. The remaining 35 patients (37 nodules) had nodular colloidal hyperplasia and/or chronic lymphocytic thyroiditis. The rates of malignancy (ROM) and neoplasia (RON) were 25.8% and 40.3%, respectively. Nearly half of the cases (41.9%) had chronic lymphocytic thyroiditis. The malignancy rate in cases with chronic lymphocytic thyroiditis was 26.9%, which was similar in cases without (25%). In multivariate analysis, only microcalcifications were found to be positively associated with malignancy (p: 0.1; [OR] 5.185; CI95% 1.4-19.18).

Conclusion: Chronic lymphocytic thyroiditis may lead to overestimation of AUS/FLUS results. It was not associated with malignancy in thyroid nodules with AUS/FLUS. Inflammatory values, such as NLR, PLR and MPV, were not useful markers of malignancy. Among all variables only US findings (microcalcifications according to the current study) may be useful in risk-stratification of malignancy in thyroid nodules with AUS/FLUS.

Keywords: AUS; indeterminate nodule; fine needle aspiration; FLUS; FNA; NLR; PLR; thyroid malignancy; thyroid nodule

INTRODUCTION

Fine needle aspiration (FNA) is an effective diagnostic test for the evaluation and management of thyroid nodules. The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) is accepted universally for the interpretation of FNA (1). Management of thyroid nodules that are classified as atypia of undetermined significance (AUS) or follicular lesions of undetermined significance (FLUS) is a challenge for both pathologists and clinicians due to the limitations of cytopathology results and the shortage of predictors for malignancy. There is no consensus with respect to management, which encompasses observation to surgery. The rate of malignancy (ROM) for these lesions ranges from 5% to 15% in the general population, whereas it is reported to be 6-45.7% in patients undergoing surgery (1-3). The discrepancies in malignancy rates require that research be conducted in order to provide further insights into the stratification and management of this category.

Several studies have evaluated ultrasonography (US) predictors of malignancy in thyroid nodules with AUS/FLUS (4-9). Quite a few investigations have focused on the effect of inflammation on the interpretation of cytopathology results (10, 11). In patients with chronic lymphocytic thyroiditis (CLT) cytopathology findings may be similar to atypical findings in FNA. The reliability of diagnosis in cases with AUS/FLUS accompanied by CLT remains uncertain, something, which poses particular difficulties for pathologists. Conversely, some inflammatory markers may prove convenient for clinicians in relation to decision-making for malignant cases. We know that inflammation plays a critical role in tumor development and spread, affecting the tumor microenvironment and mediating immune response. Furthermore, carcinogenesis

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itself triggers chronic inflammation, which leads to the evaluation of inflammation markers as possible predictors of mortality and morbidity (12). There are few studies investigating the relationship between thyroid malignancy and inflammatory markers, and their results are contradictory (13,14).

The relationship between inflammatory markers and thyroid malignancy, the reliability of FNA in patients with CLT, and the efficacy of preoperative US findings are subjects that warrant clarification. This study aimed to evaluate the clinical, radiological and laboratory features (NLR, PLR and MPV) that may better define the ROM in order to contribute to the management of thyroid nodules with AUS/FLUS.

MATERIAL and METHODS

The data of patients with histologic findings of AUS/FLUS on FNA, who underwent surgery at the General Surgery Department in a tertiary care hospital between January 2012 and December 2019, were reviewed retrospectively. The patients with any other malign and/or inflammatory diseases and who continued to receive corticosteroid therapy and/or chemotherapy were excluded. The surgery was individualized based on physical examination, US findings, and patients' wishes.

The data included demographics, comorbid factors, and laboratory findings, US findings, therapeutic interventions and histopathology results. Based on recorded values, neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios (NLR and PLR) were calculated. US findings included microcalcifications, vascularity, margin (well-defined or irregular), homogeneity (homogenous or heterogeneous), echogenicity (iso-hyperechoic or hypoechoic), composition (solid, semisolid, cystic/predominantly cystic), the largest diameter of the nodule, and the ratio of anteroposterior to transverse (AP/T) diameter of nodule. The rate of malignancy was defined as the ratio of malign cases to all cases. The rate of neoplasia was defined as the ratio of neoplastic cases (malign cases + follicular adenomas) to all cases.

The study was conducted according to the principles set forth by the Helsinki Declaration of 1975. Approval from the Ethics Committee of the Institution was obtained.

Statistical analysis

Data were analyzed using SPSS 17.0 for Windows. Continuous variables were presented as means with SDs, categorical variables were presented as numbers with percentages. A logistic model was set up to describe the relationship between thyroid malignancy and variables associated with malignancy. The Shapiro-Wilk test was used to analyze normality of the groups. Student's t-test was used for continuous variables with normal distribution. The Mann-Whitney U-test was applied for non-normally distributed variables. The Chi-squared test or Fisher's exact test was used for categorical variables. Significant variables were included in multivariate binary logistic regression analysis. A bivariate correlation test was used to determine whether there was a relationship between independent variables to be analyzed before multivariate binary logistic regression analysis. In multivariate binary logistic regression analysis, a backward stepwise method (Likelihood ratio) was used. The level of significance used at the entry of the variables was 0.05, the level of significance used for the removal was 0.1. The level of significance used in testing the model in general was 0.05.

RESULTS

The current study included 60 patients (73.3% women), who underwent surgery for 62 thyroid nodules classified as AUS/FLUS. The mean age was 43.6 ± 13.16 (range: 14-72) years. Forty-three patients presented with bilateral thyroid nodules. The mean maximum diameter of a thyroid nodule based on US measurements was 24.33 ± 12.15 mm (range: 5-75). The rates of malignancy (ROM) and neoplasia (RON) were 25.8% and 40.3%, respectively. Both the ROM and RON of the AUS subcategory were higher than those of the FLUS subcategory, but statistically insignificant (for ROM, 27.65% vs 20%, respectively, p: 0.739; for RON, 44.68% vs 33.3% respectively, p: 0.438). Table 1 shows characteristics of thyroid nodules with AUS/FLUS. The largest diameter of the thyroid nodule was significantly higher in cases with FLUS (p: 0.006).

Fifty-four total thyroidectomies and six lobectomies were performed. Thirty-eight patients (with 40 suspicious nodules) were operated on after the first AUS/FLUS diagnosis. Twenty-two patients had repeated FNAs. The specimen pathology revealed a thyroid malignancy in 16 patients, including 10 patients with papillary cancer (5 had follicular variant, 3 had classic variant, 1 had oncocytic variant, and 1 had Warthin-like variant), 5 patients with micro-papillary thyroid cancer, and 1 patient with minimally invasive follicular carcinoma. In two patients with follicular variant papillary carcinoma, malignant foci were found on the opposite lobe of the gland. Ten patients had follicular adenoma, 1 found incidentally on the opposite thyroid parenchyma. The remaining 35 patients (37 nodules) had nodular colloidal hyperplasia and/or chronic lymphocytic thyroiditis (Table 2). Of all cases, 26 cases (41.9%) had CLT. The malignancy rate in thyroid nodules with CLT was 26.9%, which was similar to cases without CLT.

Associations with demographic characteristics, US findings and inflammatory markers (NLR, PLR, and MPV) with malignancy are shown in Table 3. In univariate analysis, microcalcifications and solid composition were significantly associated with malignancy. In multivariate analysis, only microcalcifications were found to be positively associated with malignancy (p: 0.1; [OR] 5.185; CI95% 1.4-19.18). In subgroup analysis, among US findings, only solid composition was associated with malignancy in the AUS group (p: 0.026), but not in the FLUS group (p: 0.5). Microcalcifications were associated with neither of them (p: 0.075 vs. p: 0.08).

Table 1. Characteristics of thyroid nodules with AUS/FLUS

Characteristics	AUS (n: 47) mean ± SD or n (%)	FLUS (n: 15) mean ± SD or n (%)	Total (n: 62) mean ± SD or n(%)	(p)
Rate of malignancy	13 (27.7)	3 (20)	16 (25.8)	0.739
Age (years)	42.31 ± 13.6	46 ± 11.4	43.2 ± 13.1	0.53
Gender				
Male	12 (25.5)	4 (26.7)	16 (25.8)	0.93
Female	35 (74.5)	11 (73.3)	46 (74.2)	
Number of FNA				
Single	28 (59.6)	11 (73.3)	39 (62.9)	0.33
Repeat	19 (40.4)	4 (26.7)	23 (37.1)	
Microcalcification				
No	37 (78.7)	12 (80)	49 (79)	0.91
Yes	10 (21.3)	3 (20)	13 (21)	
Vascularity				
No	20 (42.6)	8 (53.3)	28 (45.2)	0.465
Yes	27 (57.4)	7 (46.7)	34 (54.8)	
Margin				
Irregular	3 (6.4)	1 (6.7)	4 (6.5)	0.96
Well-defined	44 (93.6)	14 (93.3)	58 (93.5)	
Homogeneity				
Homogeneous	13 (27.7)	5 (33.3)	18 (29)	0.748
Heterogeneous	34 (72.3)	10 (66.7)	44 (71)	
Echogenicity				
Iso-hyperechoic	24 (51)	4 (26.7)	28 (45.2)	0.098
Hypoechoic	23 (48.9)	11 (73.3)	34 (54.8)	
Composition				
Solid	15 (31.9)	7 (46.7)	22 (35.5)	
Semisolid	21 (44.7)	4 (26.7)	25 (40.3)	0.436
Cystic/predominantly cystic	11 (23.4)	4 (26.7)	15 (24.2)	
Largest diameter of the nodule (mm)	22.78 ± 12.6	29.2 ± 9.3	24.3±12.1	**0.006**
AP/T diameter of the nodule*	1.37 ± 0.3	1.49 ± 0.2	1.4 ± 0.3	0.105
Chronic lymphocytic thyroiditis				
No	26 (55.3)	10 (66.7)	36 (58.1)	0.438
Yes	21 (44.7)	5 (33.3)	26 (41.9)	
Neutrophil-to-lymphocyte ratio	2.1 ± 1.6	2.1 ± 0.75	2.1 ± 1.46	0.43
Platelet-to-lymphocyte ratio	121.1 ± 37.5	127.9 ± 43.3	122.7 ± 38.7	0.88
Mean platelet volume	10.2 ± 0.8	9.7 ± 1.1	10.1 ± 0.9	0.24

*** AP/T: Anteroposterior to transverse diameter of the nodule**

Table 2. The cytopathology results of thyroid nodules with AUS/FLUS

Cytopathology	AUS cases n: 47	FLUS cases n:15	Total cases n: 62
Papillary thyroid ca	8	2	10
Follicular variant	4 (one bilateral)	1 (bilateral)	5
Classic variant	2	1	3
Oncocytic variant	1	-	1
Warthin-like variant	1	-	1
Micro-papillary thyroid ca	5	-	5
Minimally invasive follicular ca	-	1	1
Follicular adenoma	7	2	9
Colloidal hyperplasia and/or CLT	27	10	37

Table 3. The univariate analysis for malignancy in the thyroid nodule with AUS/FLUS

Characteristics	Benign (n:46) mean ± SD or n (%)	Malignant (n:16) mean ± SD or n (%)	(p)
Age (years)	43.52 ± 13.29	42.37 ± 13.11	0.766
Gender			
Male	11 (68.6)	5 (31.3)	0.741
Female	35 (76.1)	11 (23.9)	
Cytopathology type			
AUS	34 (72.3)	13 (27.7)	0.739
FLUS	12 (80)	3 (20)	
Number of FNA			
Single	29 (74.4)	10 (25.6)	0.969
Repeat	17 (73.9)	6 (26.1)	
Microcalcifications			
No	40 (81.6)	9 (18.4)	**0.028**
Yes	6 (46.2	7 (53.8)	
Vascularity			
No	21 (75)	7 (25)	0.895
Yes	25 (73.5)	9 (26.5)	
Margin			
Irregular	2 (50)	2 (50)	0.272
Well-defined	44 (75.9)	14 (24.1)	
Homogeneity			
Homogeneous	11 (61.1)	7 (38.9)	0.2
Heterogeneous	35 (79.5)	9 (25.8)	
Echogenicity			
Iso-hyperechoic	20 (71.4)	8 (28.6)	0.652
Hypoechoic	26 (76.5)	8 (23.5)	
Composition			
Solid	12 (54.5)	10 (45.5)	
Semisolid	22 (88)	3 (12)	**0.027**
Cystic/predominantly cystic	12 (80)	3 (20)	
Largest diameter of the nodule (mm)	23.45 ± 10.27	26.87 ± 16.58	0.865
AP/T diameter of the nodule*	1.43 ± 0.329	1.32 ± 0.208	0.295
Chronic lymphocytic thyroiditis			
No	27 (75)	9 (25)	0.864
Yes	19 (73.1)	7 (26.9)	
Neutrophil-to-lymphocyte ratio	2.20 ± 1.64	2.03 ± 0.75	0.955
Platelet-to-lymphocyte ratio	123.31 ± 39.8	121.27 ± 36.5	0.879
Mean platelet volume	10.12 ± 0.932	10.16 ± 1.07	0.711

*AP/T: Anteroposterior to transverse diameter of the nodule

DISCUSSION

In this study, the ROM of thyroid nodules with AUS/FLUS (25.8%) was found to be higher than the acceptable threshold of 5% to 15% in the general population (1). However, it was in concordance with the reported values of those in patients undergoing surgery (2, 3). Repeat FNAs had no effect on the ROM (25.6% vs. 26.1%), which was compatible with findings from previous studies (15, 16). However, this result was in contrast with findings from other studies, which concluded that repeat FNAs for the initial AUS/FLUS category were associated with an increased malignancy rate compared with those without repeat FNAs (17, 18). A possible explanation lies in the retrospective study design, which included a relatively small number of surgically resected cases. Contrary to expectations, the ratio of surgery was high (62.9%) after single FNA. Its retrospective design may have obscured the ratio of FNAs, which were performed previously at other centers. Moreover, in the current study, surgery was not solely based on histopathologic results. It was individualized based on physical examination, US findings, and patients' wishes. All patients were adequately informed about the histologic findings of AUS/FLUS on FNA. Forty-three patients, who presented with bilateral

thyroid nodules underwent total thyroidectomy. Eleven patients, who presented with unilateral thyroid nodules, also preferred total thyroidectomy because they did not wish to be re-operated in cases of malignancy.

In the current study, the majority of malign cases were papillary thyroid cancers. The ROM did not differ significantly between AUS and FLUS cases (27.2 % and 20%, respectively). Although not malignant, follicular adenomas require surgical excision to rule out follicular carcinoma. The neoplastic rate, which also includes follicular adenoma, is rarely reported in the literature, with a range of 18.98% to 74% for surgically proven cases (19-21). The RON was 40.3% in this study. Ten follicular adenomas, of which one was found incidentally on the opposite lobe, were surgically confirmed.

Quite a few investigations have focused on the effect of inflammation on the interpretation of cytopathology results (10, 11). In patients with CLT, cytopathology findings may be similar to atypical findings in FNA. Cytology atypia due to CLT may give rise to an increase in AUS/FLUS results in thyroid nodules, which may lead to an overestimation of malignancy rates (11). Reliability of diagnosis in cases with AUS/FLUS accompanied by CLT remains uncertain. The current study did not include all FNAs, but only those with AUS/FLUS. Thus, no conclusive findings for the effects of CLT on the overestimation of malignancy could be provided. However, based on the fact that nearly half of the cases (41.9%) had CLT, we concluded that CLT may lead to an overestimation of the AUS/FLUS results. We also concluded that CLT was not associated with malignancy in thyroid nodules with AUS/FLUS, because the ROM in thyroid nodules with CLT was 26.9%, which was similar to cases without CLT (25%).

Inflammation plays a critical role in tumor development and spread, affecting the tumor microenvironment and mediating the immune response. Neutrophils, lymphocytes and platelets are all part of the immune system and have been used as noninvasive and cost-effective markers (22-24). The NLR, PLR and mean platelet volume (MPV) have been used as prognostic markers for the stratification of mortality and morbidity in some inflammatory, infectious and malignant diseases (22-24). Few studies have investigated the relationship of thyroid malignancy with inflammation, and their results are contradictory (13, 14). Seretis et al. were the first to report NLR as a potential biomarker in the context of the detection of underlying malignancy in benign thyroid disease (13). To our knowledge, those markers (NLR, PLR, and MPV) have never been evaluated with respect to a prediction of malignancy in thyroid nodules with AUS/FLUS. According to our results NLR, PLR and MPV values do not have any utility as markers of malignancy in thyroid nodules with AUS/FLUS.

There are several studies evaluating US predictors of malignancy in thyroid nodules with AUS/FLUS (4-9). Each of them applied different US features. In a study, microcalcifications and irregular margins were found to be associated with malignancy (25). In another study, a taller-than-wide shape, hypoechogenicity, marked hypoechogenicity, microcalcifications and macrocalcifications showed a significant difference in favor of malignancy (26). In the current study, according to the univariate analysis, a solid component of the thyroid nodule and microcalcifications was significantly associated with malignancy. In multivariate analysis, however, only microcalcifications were found to be positively associated with malignancy. Some studies reported that US findings predicting malignancy were common in the AUS group, but not in the FLUS group (9, 25, 27). The current study resulted in similar findings. However, the small number of FLUS cases may be a possible limitation in advancing a definitive conclusion. The largest diameter of the nodules was significantly higher in favor of FLUS cases (29.2 ± 9.3, 22.78 ± 12.6; respectively), which was a possible factor in the preference for surgery in the FLUS group.

This study had a number of limitations. First was its retrospective design and small number of cases. Second was the potential for inter-observer variability in interpretations of US features between radiologists. Third, NLR, PLR and MPV values might have been affected by several factors. The study's strength was the inclusion of nodules, which were all confirmed by surgery.

CONCLUSION

In conclusion, CLT may lead to an overestimation of AUS/FLUS results. CLT was not associated with malignancy in thyroid nodules with AUS/FLUS. Inflammatory values, such as NLR, PLR and MPV, were not useful markers of malignancy. Among all variables only US findings (microcalcifications according to the current study) may be useful in a risk-stratification of malignancy in thyroid nodules with AUS/FLUS. However, thyroid nodules with AUS/FLUS are still a challenge, both for pathologists and clinicians. To prevent under-diagnosis of malignancy and to reduce unnecessary surgery, further research is required.

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