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The association of papillary thyroid cancer with microcalcification in thyroid nodules with indeterminate cytology based on fine-needle aspiration biopsy

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Background/aim: Microcalcifications are generally accepted as highly specific for thyroid malignancy, especially for papillary thyroid carcinoma (PTC). The aim of this study was to determine the significance of microcalcification within nodules that were classified as being of "indeterminate cytology" (IC) according to fine-needle aspiration biopsy.

Materials and methods: Patients who underwent thyroidectomy between January 2010 and 2013 were included in the study. Nodules identified as "atypia/follicular lesion of undetermined significance", "follicular neoplasm/suspicious for follicular neoplasm", or "suspicious for malignancy" were categorized as IC. Patients were subcategorized depending on the presence of microcalcification (Group 1) or its absence (Group 2). The relationship between microcalcification and PTC was evaluated in the IC group retrospectively.

Results: Indeterminate cytology was detected in 135 (28.5%) of 473 patients. Microcalcification was detected in 27 (20%) of 135 nodules and classified as Group 1, while the remaining 108 (80%) patients were classified as Group 2. According to the final pathology results, PTC was diagnosed in 13 of 27 (48.1%) patients in Group 1 and 29 of 108 (26.8%) patients in Group 2. A statistically significant relation between microcalcification and malignancy was determined in the IC group ($P < 0.05$).

Conclusion: Surgery might be considered primarily for patients harboring nodule(s) with IC accompanied by microcalcification due to increased risk of PTC.

Key words: Thyroid malignancy, microcalcification, indeterminate cytology

1. Introduction

Palpable thyroid nodules are present in 5% to 10% of the population (1), and the probability of nodule detection increases with ultrasound examination, which is the most sensitive diagnostic test to detect thyroid nodules. Microcalcification (MC) is encountered more with papillary thyroid carcinoma (PTC) than other thyroid diseases (2). The presence of MC is a significant ultrasound finding that increases the malignant risk of nodules (3). Fine-needle aspiration biopsy (FNAB) has 70% sensitivity and 96% specificity for diagnosis of thyroid nodules (4). The Bethesda System (BS) has been a widely accepted scoring system regarding prediction of the cancer risk of thyroid nodules since 2007 (5). The BS has led to the standardization of FNAB reports based on six diagnostic categories. Categories located in the "indeterminate cytology" (IC) group have a wide spectrum for the probability of PTC that varies from 15% to 75%. In this study we aimed to determine the predictive value of the presence of MC in thyroid nodules with an indeterminate FNAB report.

2. Materials and methods

This retrospective study was approved by the Scientific Ethics Committee of the İstanbul Medeniyet University School of Medicine. The study included 473 consecutive patients (391 women and 82 men) who underwent thyroidectomy at our institution between January 2010 and January 2013. Indications for thyroidectomy were risk of malignancy, compressive symptoms, thyrotoxicosis, and cosmetic reasons. Patient charts were reviewed for clinical and ultrasound findings and FNAB reports. Ultrasonography was used to examine the nodules within 1 month before thyroidectomy. FNAB was

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performed by radiologists that specialized in thyroid ultrasonography. Cytological diagnosis was made based on the BS by pathologists who had experience in thyroid cytopathology. Patients whose final pathology report revealed nonpapillary thyroid cancers and who had a cystic nodule defined as more than 90% of the nodule being cystic were excluded from the study. According to the Bethesda classification, nodules defined as "atypia or follicular lesion of undetermined significance" (AUS/FLUS), "follicular neoplasm/suspicious for a follicular neoplasm" (FN/SFN), or "suspicious for malignancy (SM)" were included in the IC group. Presence of MC was revealed in ultrasound examination. MC was defined as echogenic foci of calcification of less than 1 mm at the longest diameter. Patients were subcategorized into two groups: those with nodules with MC were categorized as Group 1 and those without MC as Group 2. Findings were compared statistically between these groups.

Statistical analysis was performed using the Pearson chi-square test and the Fisher test with SPSS 20.0. $P < 0.05$ was considered statistically significant. The sensitivities and specificities of MC existence were determined to diagnose PTC.

3. Results

The mean age of 473 patients was 49.9 ± 12.4 years (range: 17–83 years), and the male-to-female ratio was 1:4.8 (82:391). All nodules were classified according to the BS (Table 1). One hundred and thirty-five (28.5%) of them were categorized in the IC group according to FNAB reports with a 31.2% malignancy rate. The AUS/FLUS, FN/SFN, SM, and benign categories were assigned to 14.2%, 6.3%, 8%, and 68.4% of the FNABs respectively with 13.4%, 33.3%, 47.9%, and 7.7% malignancy rates, respectively. Papillary thyroid cancer was diagnosed in 73 (15.4%) of 473 patients.

Ultrasound findings of patients were reviewed regarding the existence of MC, which was detected in 95 (20.1%) of nodules, and 24 (25.3%) of these were malignant, while only 12.9% (49/378) of nodules were malignant in Group 2 (Table 2). Malignancy was detected as being significantly higher in cases of existence of MC within nodules than in nodules without MC ($P = 0.003$). The presence of MC within a nodule had 32.9% sensitivity, 82.3% specificity, 25.3% positive predictive value, and 86.1% negative predictive value for the prediction of PTC.

Table 1. Comparison of FNAB results and final histologic evaluation of surgical specimens.

Final pathology / Bethesda classification	Benign (n = 400)	Malignant (n = 73)	Total (n = 473)
DC-I (nondiagnostic)	11 (91.7%)	1 (8.3%)	12 (2.5%)
DC-II (benign)	299 (92.3%)	25 (7.7%)	324 (68.4%)
IC	93 (68.8%)	42 (31.2%)	135 (28.5%)
- DC- III (AUS/FLUS)	58 (86.6%)	9 (13.4%)	67 (14.2%)
- DC-IV (FN/SFN)	20 (66.6%)	10 (33.3%)	30 (6.3%)
- DC-V (SM)	15 (39.5%)	23 (47.9%)	38 (8%)
DC-VI (malignant)	-	2 (100%)	2 (0.4%)

DC: Diagnostic category, IC: indeterminate cytology, AUS/FLUS: atypia/follicular lesion of undetermined significance, FN/SFN: follicular neoplasm/suspicious for a follicular neoplasm, SM: suspicious for malignancy.

Table 2. Comparison of malignancy rate due to the presence of microcalcification.

	Benign (n = 400)	Malign (n = 73)	P-value
Group 1 (%)	71 (74.7%)	24 (25.3%)	0.003*
Group 2 (%)	329 (86.1%)	49 (12.9%)	

Pearson chi-square test, *$P < 0.05$.

Diagnostic categories were compared regarding existence of calcification associated with PTC (Table 3). All categories were separated into two subgroups in terms of the presence of MC. Twenty-seven of the patients that were categorized as IC were in Group 1, while 108 were in Group 2. The malignancy rate of IC nodules for these groups was 48.1% (13/27) and 26.8% (29/108), respectively. The odds ratio was detected as 1.79 for the risk of papillary cancer. Presence of MC in nodules with IC revealed a significantly higher rate of papillary cancer than nodules without MC (P = 0.033). Papillary cancer was detected in 16.6% (9/65) of the patients with benign cytology and in Group 1, and in 7.9% (19/259) of the patients in Group 2. Presence of MC increased the risk of papillary cancer in all thyroid nodules. However, benign, malignant, or nondiagnostic nodules did not reveal a statistically significant difference in terms of the association of PTC with the presence of nodular MC.

4. Discussion

A thyroid nodule is defined as a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding parenchyma (6). Controversial issues about the terminology and morphologic criteria of thyroid nodules caused the formation of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC). This system led to standardization of FNAB reports based on six diagnostic categories regarding the clarity of interdisciplinary communication: I = nondiagnostic, II = benign, III = atypia of undetermined significance, or follicular lesion of undetermined significance, IV = follicular neoplasm/suspicious for a follicular neoplasm, V = suspicious for malignancy, and VI = malignant (5). The BSRTC has proven to be an effective classification to guide the treatment options of thyroid nodules (7). Diagnostic categories III, IV, and V according to the BSRTC are grouped as IC. FNABs yield IC diagnosis in 15% to 30% of all biopsies (8).

The clinical and radiological findings supported by pathological parameters have great significance to predict PTC (9–11). Ultrasound examination of the thyroid gland is widely used to detect the existence of calcification in nodules preoperatively (4,12). Several studies showed that various ultrasound characteristics such as predominantly solid texture, hypoechogenicity, vascularity pattern of the nodule, presence of MC, and absence of a halo are considered as indications that the nodule is more likely to be malignant (13–15). The presence of MC is one of the most significant ultrasound findings to evaluate the malignancy risk of thyroid nodules. The clinical significance of calcification and the molecular mechanism that is responsible for calcification in PTC is still uncertain (2). The rapid proliferation of cancer cells may lead to necrosis, resulting in calcium deposits (16). Histopathologically, calcifications can be seen as psammoma bodies and dystrophic calcifications, or psammoma bodies and stromal calcifications (2). Psammoma bodies are basophilic, laminated, spherical accretions that are specific for PTC, although they are occasionally detected in benign thyroid nodules (17,18). Although calcification can be present in both benign and malignant thyroid lesions, a remarkable association between PTC and MC has been consistently noted in several reports (4,12,17,19). Other types of calcifications such as macrocalcifications, coarse, eggshell, and rim calcifications were thought to be more common in benign thyroid nodules than PTC (4). Contrarily, other calcification patterns can also be observed in nodules with PTC. Wang et al. (20) reported MC in 53.5% of patients with PTC. Sieberling et al. (4) found that macrocalcifications were equally distributed between benign and malignant

Table 3. Comparison of malignancy rates of groups according to diagnostic categories of fine-needle aspiration biopsy.

Final pathology / FNAB	Malignancy rates % (malign n/total n)			P-value
	Group-1 (n = 95)	Group-2 (n = 378)	Total (n = 473)	
Indeterminate cytology	48.1% (13/27)	26.8% (29/108)	31.2% (42/135)	0.033*
AUS/FLUS	42.9% (3/10)	10.5% (6/57)	13.4% (9/67)	0.125[a]
FN/SFN	33.3% (3/9)	33.3% (7/21)	33.3% (10/30)	0.669[a]
SM	87.5% (7/8)	53.3% (16/30)	60.5% (23/38)	0.114[a]
Benign	16.6% (9/65)	7.9% (19/259)	9.5% (28/324)	0.095
Malignant	100% (1/1)	100% (1/1)	100% (2/2)	0.350
Nondiagnostic c.	50% (1/2)	0% (0/10)	(1/12)	0.025

AUS/FLUS: Atypia/follicular lesion of undetermined significance, FN/SFN: follicular neoplasm/suspicious for a follicular neoplasm, SM: suspicious for malignancy. *: Pearson chi-square test, [a]: Fisher exact test.

lesions. The same study revealed that 62% of patients with MC had malignant nodules. A further study reported that the existence of MC in a solid nodule increases the patient's cancer risk by about threefold (3). Our study revealed that PTC risk increases approximately 1.8-fold for patients in the IC category accompanied with MC. Presence of MC in a thyroid nodule has been shown to have a high predictive value (42%–94%) but a low sensitivity rate (26%–59%) in the diagnosis of PTC (10,21,22). In our study, the presence of MC within the nodules has been shown to reveal 32.9% sensitivity, 82.3% specificity, 25.3% positive predictive value, and 86.1% negative predictive value in the diagnosis of PTC. Presence of MC within a nodule increased the rate of PTC from 12.9% to 26.1%. On the other hand, the PTC rate significantly increased from 12% to 46% in cases with MC accompanied by IC.

To date, few reports have assessed the clinical significance of MC in PTC, particularly in the IC category. This study focused primarily on the importance of the presence of MC in patients with an IC report. In conclusion, during the diagnostic assessment of thyroid nodules, other risk factors for PTC including the presence of a history of exposure to external radiation, male sex, young age, presence of enlarged cervical lymph nodes, and ultrasound findings of the nodule such as solid texture, hypoechogenicity, vascularity, and absence of a halo should be evaluated as well as the presence of MC before making the decision for surgery. However, the presence of MC is an important finding to predict PTC, especially for nodules with IC. Therefore, surgery might be considered primarily for nodules detected to represent the combination of IC and the presence of MC.

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