Thyroid Microcalcifications in the Absence of Identifiable Nodules and Their Association With Thyroid Cancer

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Objectives—To determine ultrasound (US) and clinical findings of thyroid microcalcifications in the absence of a nodule and their association with the risk of malignancy.

Methods—The Institutional Review Board approved a 5-year retrospective study. Twenty-one patients with clustered or scattered thyroid microcalcifications in the absence of nodules on US images who underwent fine-needle aspiration biopsies (FNABs) were included. Demographic and clinical data, US findings, and pathologic results were registered. Patients with a suspicion of malignancy or papillary thyroid carcinoma (PTC) on FNAB underwent thyroidectomy. Patients with benign results on FNAB underwent clinical and US surveillance.

Results—The mean age of the 21 patients was 33.2 years (29.5 years in patients with PTC patients and 39.4 years in those with benign findings; $P = .034$). Eleven of 21 patients had clustered microcalcifications (9 had cancer), and 10 of 21 patients had scattered microcalcifications (4 of 10 had cancer; $P = 0.063$). Sixty-two percent of the patients had FNAB findings that were suspicious for cancer or had a diagnosis of cancer. Eleven of 13 patients had surgical thyroidectomy performed in our institution; in all cases, Hashimoto thyroiditis was confirmed. Univariate and multivariate analysis showed that only age was significant (odds ratio, 0.9; $P < .05$).

Conclusions—Our study suggests that the presence of thyroid microcalcifications without a nodule is suspicious for PTC. We found that both patterns were suspicious for PTC, particularly in young patients. Special concern arises for those clustered microcalcifications on a background of Hashimoto thyroiditis.

Key Words—papillary thyroid carcinoma; thyroid microcalcifications; thyroid neoplasm; thyroid nodule; ultrasound; ultrasound-guided fine-needle aspiration biopsy

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Abbreviations

FNAB, fine-needle aspiration biopsy; PTC, papillary thyroid carcinoma; US, ultrasound

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Ultrasound (US) is an excellent tool for diagnosing and monitoring thyroid nodules and selecting suspicious nodules for malignancy.[1] Ultrasound findings in a malignant nodule are described as a hypoechoic or markedly hypoechoic nodule, a taller-than-wide shape, the presence of microcalcifications, the presence of a halo, an irregular or microlobulated contour, a heterogeneous structure, and extrathyroidal extension.[1] Horvath et al[1,2] published and validated the Thyroid Imaging Reporting and Data System, in which these suspicious US features are most frequently grouped into categories 4b and 5.

There is a consensus that the presence of microcalcifications and thick calcifications increases the risk of malignancy of the nodules.[3] It

has also been reported in short publications that the presence of intraparenchymal microcalcifications on US images without an associated nodule can be a special presentation of papillary thyroid carcinoma (PTC).[4] Previous reports had mentioned that the risk of malignancy is increased in patients with Hashimoto thyroiditis, a higher level of thyrotropin within the normal range, and microcalcifications in patients who underwent thyroidectomy for the presence of thyroid nodules.[5] The objectives of this study were to describe US and clinical findings of clustered or scattered microcalcifications in the thyroidal parenchyma in the absence of a US-visible thyroid nodule, to correlate these data with histologic findings, and to establish features associated with the risk of thyroid cancer.

Materials and Methods

Patients and Procedures

This retrospective study was authorized by the Institutional Review Board of our institution. From the database of thyroid aspirations (fine-needle aspiration biopsy [FNAB]) performed between 2008 and 2012, we selected those cases in which FNAB was indicated by the US finding of microcalcifications that were either clustered (group A) or scattered (group B) in the thyroid parenchyma, both without associated nodules. In a retrospective review, 2 experienced radiologists analyzed all of the US images. The presence of fine punctuate bright echoes without acoustic shadowing was characterized as microcalcifications. The radiologists verified that all of the microcalcifications were not related to a nodule and classified them, in consensus, as clustered or scattered. Demographic and clinical data were recorded (age, sex, family history of thyroid cancer, and monitoring period), as well as US findings (echogenicity of the thyroid parenchyma, the diameter of the microcalcified area, the presence of chronic thyroiditis as a coexisting condition, unilateral or bilateral microcalcifications, and the presence of suspicious adenopathies) and the anatomopathologic results of FNAB and the surgical specimens.

Ultrasound equipment with electronic transducers of 12–5 and 17–5 or 18–5 MHz was used. Diagnostic FNABs were performed by 4 radiology experts trained in interventional US procedures, using a 19- or 21-gauge needle attached to a 10-mL syringe with negative pressure maintained until blood appeared on the hub. The drops of blood were placed on glass; the clot was placed in 10% buffered formalin and in paraffin after that; and finally, the specimen was sectioned for a routine histologic study.[1] The biopsy was performed in the area with the major concentration of microcalcifications.

All patients who had suspicious results or a diagnosis of PTC underwent total thyroidectomy. All benign biopsies were followed with clinical and US monitoring.

Statistical Analyses

Univariate and multivariate statistical analyses were performed to assess which US and clinical variables would predict whether the presence of microcalcifications was associated with an increased risk of cancer. Continuous variables were described as mean ± standard deviation, whereas frequencies and proportions were used for categorical variables. A binary logistic regression analysis was used to associate the presence of thyroid cancer with possible prognostic factors. The factors that were associated with a significance level of 25% at most (Hosmer and Lemeshow criteria) were retained for a multivariate model, which was refined by a stepwise forward procedure with a 5% probability of retention. The resulting model was evaluated for the area under the receiver operating characteristic curve, and a sensitive or specific cut point was proposed. The statistical significance level used was 5%. Data were processed with Stata version 14.0 software (StataCorp, College Station, TX).

Results

During a 5-year period, 2698 thyroid FNABs were performed at our institution. Twenty-one patients met the inclusion criteria, presenting microcalcifications in the absence of a thyroid nodule identifiable by US.

Of the total thyroid FNABs, 23% of the patients had a diagnosis of thyroid cancer or were suspected of having thyroid cancer (608 patients); 0.48% of the FNABs were performed for the finding of microcalcifications in the absence of a nodule. Only 2% of the total of PTCs diagnosed in this period had this presentation.

In the 21 patients with the inclusion criteria, the mean age was 33.2 ± 10.6 years (range, 15–53 years). The mean age of the patients with thyroid cancer was 29.5 ± 10.1 years, whereas the mean age of the patients who did not have cancer was 39.4 ± 8.8 years ($P = .0336$).

Of the total number of patients, 18 were female, and 3 were male. All male patients had cancer, whereas 10 of the 18 female patients had cancer. No statistically significant association was found between sex and cancer occurrence ($P = .257$). Only 18 of 21 patients had family information registered on the clinical record. Seven of 11 patients without a family history of cancer had cancer, and 4 out of 7 patients with a family history of cancer had cancer, with no significant association ($P = .583$).

We divided the US results into 2 categories depending on the size of the compromised area. This measurement was retrospective. A 2-cm threshold was chosen because the longitudinal diameter of the thyroid lobe is mostly around 4 cm, and 2 cm is half. Any area bigger than that was considered scattered. These groups were as follows: group A, clustered microcalcifications located in a focal area smaller than 2 cm (Figures 1 and 2); and group B, scattered microcalcifications, with any microcalcifications located in an area bigger than 2 cm or scattered in the lobe or in the parenchyma (Figure 3).

Eleven of the 21 patients had clustered microcalcifications. In this group 9 of 11 patients had thyroid cancer. Ten patients had scattered microcalcifications, and 4 of them had a diagnosis of thyroid cancer. In the patients with scattered microcalcifications, 2 cases were bilateral; in 1 of them, PTC was confirmed, and the other had post-FNAB thyroiditis. Cancer occurrence had no significant difference between the clustered and scattered microcalcification categories ($P = .063$) or between unilateral and bilateral microcalcifications (19 versus 2; $P = .629$).

Almost all of the patients had heterogeneous thyroid parenchyma suggestive of chronic thyroiditis (20 of 21 patients). Another frequent finding was a lobulated contour of the gland, which was observed in 20 of 21 patients (95%; Figure 4).

Figure 1. Ultrasound image showing clustered thyroid microcalcifications.

Figure 2. Ultrasound image showing the needle for FNAB of clustered thyroid microcalcifications.

Figure 3. Longitudinal US image showing scattered microcalcifications in the thyroid parenchyma.

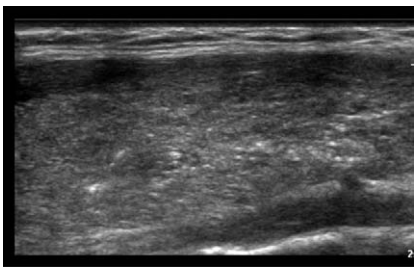
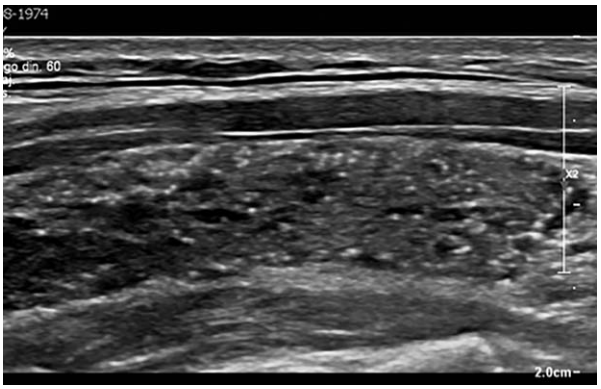


Figure 4. Ultrasound image showing irregular hypoechoic thyroid parenchyma with a lobulated contour, suggestive of chronic thyroiditis with scattered microcalcifications.



Only 1 patient whose US analysis showed homogeneous thyroid parenchyma had positive FNAB results for PTC. Homogeneous versus heterogeneous echogenicity of the thyroid parenchyma was not associated with the occurrence of thyroid cancer ($P = .619$).

Five of our patients had suspicious jugular or central adenopathies by the presence of spots inside the lymph nodes. All of them had PTC on the surgical biopsy (Figure 5).

When a diagnostic model of thyroid cancer was estimated by variables such as age, family history, and clustered microcalcifications, only age was significant, with an odds ratio of 0.9 ($P < .05$; 95% confidence interval, 0.8–1.0) and a discrimination ability (area under the receiver operating characteristic curve) of 79.3%. This finding means that the probability of developing thyroid cancer decreases with age (Figures 6 and 7).

Eleven of 13 patients with positive FNAB results for thyroid cancer underwent total thyroidectomy at our center and the other 2 in different centers. Of those 11 patients with thyroid cancer who underwent thyroidectomy in our institution, on macroscopy, 9 had irregularity and pseudonodules, and only 2 had an identifiable nodule. The pathologic specimens showed that 6 were multifocal; 2 had extrathyroidal extension; and 7 had lymph node involvement (jugular or central). All patients had histologic evidence of Hashimoto thyroiditis. Only 1 patient had the tall-cell variant; the rest had conventional PTC (Figure 8).

Figure 5. Ultrasound image showing suspicious adenopathies with echogenic spots.

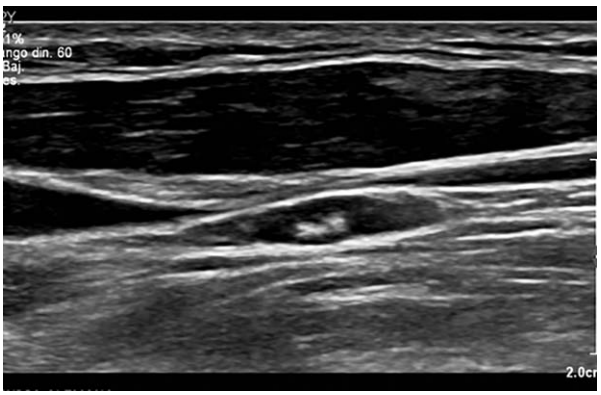


Figure 6. Receiver operating characteristic curve for age.

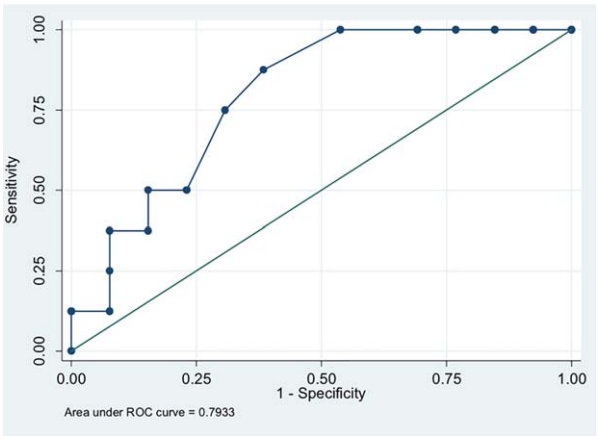


Figure 7. Presence of PTC by age.

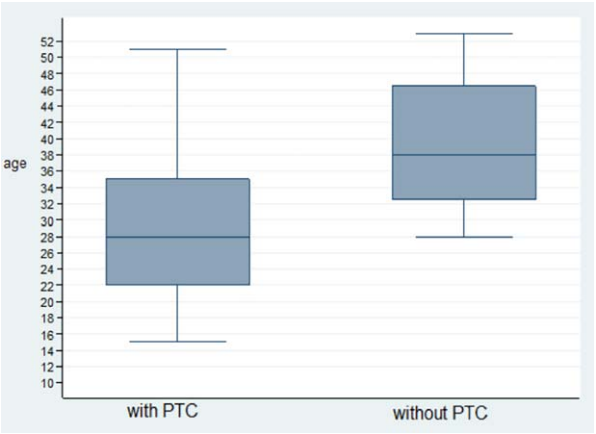
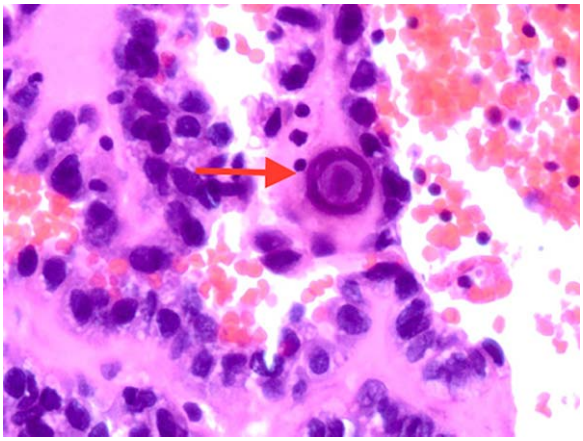


Figure 8. Microscopic view showing characteristic psammoma calcification with concentric layers (arrow; hematoxylin-eosin, original magnification ×40).



Discussion

The presence of microcalcifications is a risk factor when they are found together with a thyroid nodule.[1,3] However, there are very few studies that have described the presence of diffuse microcalcifications as a risk factor for PTC in the absence of a thyroid nodule.[4] Ye et al[5] reported that the risk of malignancy was increased in patients with Hashimoto thyroiditis, a higher level of thyrotropin within the normal range, and microcalcifications in patients who underwent thyroidectomy for the presence of thyroid nodules.[5]

In this study, 2% of PTC were present as microcalcifications without a nodule, associated with chronic thyroiditis. Sixty-two percent of thyroid microcalcifications in the absence of a nodule on US imaging were diagnosed as cancer. Both clustered and disperse microcalcifications had an increased risk of cancer. Microcalcifications in PTC occur because of the presence of psammoma bodies. However, they can also be found in chronic thyroiditis because of the presence of dystrophic calcifications.[6,7]

In our study, we found that age was the only factor that best discriminated the presence of thyroid cancer. The risk of finding malignant microcalcifications was higher in younger patients. No statistically significant differences were shown regarding cancer risk between clustered and scattered microcalcifications. In those patients who underwent total thyroidectomy, most had conventional PTC; we did not find the diffuse sclerosing variety, as described in other studies.[8]

The most important limitation of our study was the small sample size, but this condition is an infrequent thyroid US presentation. Only further multicenter studies can reduce this problem.

In conclusion, our study suggests that the presence of thyroid microcalcifications without a nodule is suspicious for PTC, particularly in young patients. Special concern arises for those clustered microcalcifications on a background of Hashimoto thyroiditis. We recommend performing thyroid FNAB in any case of a US microcalcification pattern.

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