Ultrasonographic features of medullary thyroid carcinoma nodules less than 1 cm compare with papillary thyroid microcarcinomas: a retrospective analysis

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Research article

Keywords: medullary thyroid carcinoma, papillary thyroid carcinoma, ultrasound

Posted Date: November 2nd, 2019

DOI: https://doi.org/10.21203/rs.2.16733/v1

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Abstract

Objective: The aim of this study was to retrospectively analyze the ultrasonographic characteristics of medullary thyroid carcinomas (MTCs) with size less than 1 cm (MTMCs) compared with those of papillary thyroid microcarcinomas (PTMCs).

Materials and Methods: This study included 41 patients with 46 MTMCs between January 2008 to April 2017 and 104 consecutive patients with 136 PTMCs between January to June 2015. All thyroid carcinoma nodules were surgically and histologically proved. Age and nodules size were analyzed by independent sample t test. Sex, multiplicity and cervical lymph node metastases were evaluated by χ2 or Fisher’s exact tests. Univariate analysis and multivariate logistic regression analysis were performed on the sonographic features of thyroid carcinoma nodules, including location, composition, echogenicity, shape, margin, boundary, calcifications and vascularization degree.

Results: More MTMCs presented cervical lymph node metastases than PTMCs (36.59% vs 20.19%, p = 0.040). Compared with PTMCs, MTMCs tended to have an ovoid to round shape (P = 0.000, odds ratio [OR], 4.018; 95% CI, 1.295-12.473), more commonly showed solid composition (P = 0.004, OR, 0.13; 95% CI, 0.020-0.842), and macrocalcifications (P = 0.001, OR, 0.085; 95% CI, 0.016-0.454) and hypervascularity (P=0.000, OR, 10.778; 95% CI, 3.939-29.488). There were no significant differences in the location, margin, boundary, echogenicity, peripheral halo ring, the present of calcifications, microcalcifications and between MTMCs and PTMCs.

Conclusion: MTMCs have the ultrasonographic features of general malignant nodules, such as hypoechoic or markedly hypoechoic solid lesions with unique characteristics including ovoid to round shape, macrocalcifications and hypervascularity.

Introduction

Due to the wide use of ultrasound (US), the detection rate of small thyroid nodules has increased, especially the nodules less than 10mm [1, 2]. At present, many controversies still remain regarding the treatment of these small thyroid nodules with malignant features. Papillary thyroid microcarcinomas (PTMCs) is defined as a papillary carcinoma less than 10 mm in diameter with a good prognosis. The American Thyroid Association (ATA) guidelines suggested that an active surveillance could be considered in some PTMC patients. However, medullary thyroid carcinomas (MTCs), which is derived from thyroid follicular C cells and account for 3–4% of all thyroid malignancies, has a high recurrence rate and a poor prognosis [3]. MTCs is not sensitive to radiotherapy and chemotherapy, and 10-year mortality rates can reach 13.5–38% [4–6]. The early diagnosis and treatment of MTCs is critical to improve the disease-free survival and reduce the fatality rate of patients. It also can reduce the number of patients undergoing reoperation due to recurrence or metastasis, which may lead to hypoparathyroidism, recurrent laryngeal nerve injury and other related complications [7]. Therefore, it is very important to differentiate PTMCs from MTCs.
Previous studies on the ultrasonographic features of small thyroid nodules mostly focused on PTMCs, which usually presents as a solid composition, hypoechogenicity, a taller-than-wide shape, an irregular margin, and microcalcifications. However, due to the diversified sonographic features and low incidence of the disease, the sonographic appearances of MTMCs (less than 10 mm in diameter) have been reported in few studies with limited cases. To the best of our knowledge, there were only one reports about sonographic appearances of seven MTMCs that were compared to PTMCs [8]. To expand on these findings, this study was aimed to evaluate the ultrasonographic features of the MTMCs by comparing with PTMCs, which may further define the sonographic features of MTMCs and provided effective differential diagnosis information from PTMCs.

Materials And Methods

Patients

This retrospective study was approved by the Institutional Review Board, with waiver of informed consent. A systematic review consisted of the MTMCs diagnosed from January 2008 to April 2017. The lesions were excluded due to only ultrasonographic examination was available, or no surgery, or MTCs with diameter above 10 mm. A total of 41 patients with 46 MTMCs were eventually included in this study. All patients were evaluated by sonography, and were surgically and pathologically diagnosed as MTCs at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. Of the 41 patients, 35 patients (85.37%) had a sporadic type of MTCs, 5 patients (12.20%) presented with multiple endocrine neoplasia (MEN) types II A, and one patients (2.43%) presented with MEN II B. As a control group, 104 consecutive patients with 136 PTMCs from January to June 2015 were comprised in the retrospective study.

Sonography Imaging analysis

US examinations were performed with Philips IU22 (New York), GE LOGIQ E9 (New York), or My Lab 90 (Italy) instrument equipped with a 5–12 MHz probe linear array transducer. All the examinations were performed by two radiologists with more than 10 years of experience in thyroid imaging.

The US examination included the transverse, longitudinal plane of the thyroid and the cervical lymph nodes, and routinely gray scale and color Doppler ultrasonography were performed. All US images of the thyroid nodules were retrospective analyzed by the same radiologist who was blinded to pathological findings. The sonographic features of thyroid nodules were carefully evaluated, including: the location, composition, echogenicity, shape, margin, boundary, calcification, peripheral halo ring and vascularization degree.

The location was determined as upper and lower pole. According to the proportion of solid components, the composition was classified as solid, > 50% solid. Compared with the adjacent normal thyroid tissue the echogenicity was categorized into markedly hypoechoic, hypoechoic, hyperechoic and isoechoic. Margin was divided into smooth, spiculated and poorly defined. Shape was assessed as ovoid to round,
taller than wide and irregular. Calcifications were recorded as none or present. When calcification was observed, it was categorized into microcalcifications (with diameter < 2 mm) and macrocalcifications (with diameter ≥ 2 mm or coexisted with microcalcifications). Peripheral halo ring was defined as none or present. Vascularization degree was classified as avascularity, normal vascularity and hypervascularity [9]. We defined the avascularity as low or none vascularization. And the rest were classified as hypervascularity nodules.

**Data and Statistical Analyses**

Statistical analysis was performed by SPSS 20.0 software package (SPSS, Chicago, IL). Statistical significance was determined as P < 0.05.

The independent-sample t test was used to analyze age and size. Categories variables, including sex, lymph node metastasis, location, composition, shape, margin, boundary, echogenicity, calcification, and vascularization were analyzed by χ² test or Fisher’s exact test. The variables with statistical significance, then were included in the multivariate regression model. B, Wals χ², ratio (OR) and 95% CI were recorded.

**Results**

**Clinical characteristics of MTMCs and PTMCs**

The clinical features of all patients were summarized in Tab 1. Age (41.78 years vs 44.07 years, P = 0.323), sex (female: male ratio, 23:18 vs 70:34; P = 0.205) and tumor size (6.30±2.27 mm vs 6.06±2.16 mm, P = 0.605) were not significantly different between the MTMCs patients and PTMCs patients. The prevalence of single nodule (87.80% vs 70.19%, P = 0.027) and cervical lymph node metastases (36.59% vs 20.19%, P = 0.040) were higher in the MTMCs compared with PTMCs.

**Univariate analysis of US features**

The US characteristics analysis findings were summarized in Tab 2, 3 and Fig 1. The US findings of MTMCs and PTMCs were analyzed by univariate location, margin, echogenicity, peripheral halo ring, the present of calcifications between the MTMCs and PTMCs groups (P > 0.05). The nodules of both MTMCs and PTMCs were mostly hypoechoic, without halo and calcification.

**Multivariate Logistic regression analysis of US features**

The proportion of MTMCs with ovoid to round shape was higher than that of PTMCs (54.35% vs 9.56%, P = 0.007) (Fig.1 A, B), but PTMCs with taller than wide shape was much more than MTMCs (59.56% vs 19.57%, P = 0.000) (Fig.1 C, D). Most MTMCs and PTMCs were solid, and more MTMCs have solid internal composition >50% compared with PTMCs (13.04% vs 1.47%, P = 0.014). Calcifications were not
commonly found, when occurred, macrocalcification were more often seen in MTMCs than in PTMCs (21.74% vs 6.62%, \( P = 0.004 \)) (Fig. 1 A), while the contrary was true for microcalcification although without statistical significance (10.87% vs 29.41%, \( P = 0.214 \)) (Fig. 1 D). Most PTMCs showed avascularity, but hypervascularity nodules of MTMCs accounted for the majority (80.15% vs 58.70%, \( P = 0.000 \)). 56.52% of MTMCs were clear boundary and 86.03% of PTMCs were not clear (\( P = 0.188 \)).

**Discussions**

Thyroid microcarcinoma was the thyroid tumors \( \leq 1 \) cm in maximum diameter; in view of the fact that the vast majority of thyroid cancers were papillary thyroid carcinomas (PTCs), thyroid microcarcinomas were often referred to as PTMCs \([10]\). In this study, there was no significant difference between MTMCs and PTMCs in age, sex and size. Previous researches had showed MTCs patients were more common in females and most were single nodule \([11, 12]\). In accord with the earlier reports, there was a slightly higher number of women than men in MTMCs patients in this study. Only 5 cases had two MTMCs nodules and the rest were single. The youngest patient with MTMCs (MEN II B) was a 14-year-old boy with one lesion on each side. Because of the family history of MTCs, regular examinations were performed. The maximum diameter of the nodule in the left thyroid lobe was only 2 mm. Our results showed that there was significantly different in lymph node metastasis between MTMCs and PTMCs. In PTMCs group, 21 (20.19%) patients had lymph node metastasis; the prevalence of which was similar to that in previous reports \([13–15]\). MTMCs were more likely to have lymph node metastases, which indicated the strong invasive characteristics of MTCs. This also suggests that although the incidence of MTCs is very low, early diagnosis of MTCs is of great significance.

Zhou et al \([8]\) found that MTMCs had no significant difference from PTMCs in internal composition, calcifications, echogenicity, margin, and shape (\( P > 0.05 \)). In our study, there were no significant differences in the location, margin, boundary, echogenicity, peripheral halo ring, the presence of calcifications between the two groups (\( P > 0.05 \)). But there were statistic differences in the characteristics as follows: internal composition, shape, the type of calcifications and vascularity, which were not exactly consistent with the results in Zhou's. The possible reasons may be the different sample size, imaging instrument and evaluation standard of the ultrasonic characteristic.

Cystic change was not common in PTMCs and MTMCs \([8, 12]\). Our results also showed that the majority of cases in both PTMCs (98.53%) and MTMCs (86.96%) exhibited solid composition, >50% solid composition was significantly more frequent in MTMCs than in PTMCs. In 46 MTMCs, >50% solid composition was observed in 6 (13.04%) lesions. Although the mechanism of cystic change is unclear, solid-cystic nodules might result from degeneration of solid nodules, with the accumulation of fluid probably due to intranodular necrosis. MTCs tended to display less differentiated and grow faster than PTCs, and cystic change in MTCs was most likely induced by necrosis as a result of cell proliferation that exceeds the available blood supply. Lee et al \([12]\) also reported that cystic change was significantly more common in MTCs compared with in PTCs, and the tumor size had no significant relationship with cystic changes.
The PTCs nodules usually had a large intensive fibrosis, and its compressibility was reduced compared to benign tumors, resulting in its standing-like morphology [16]. A taller-than-wide shape had been regarded as an ultrasonographic feature for PTMCs [17, 18]. In our study, it was also a common sign in PTMCs group, and the proportion was as high as 59.56%. However, there was only 9 (19.57%) cases with a taller-than-wide shape in MTMCs, which indicated that it did not apply to MTMCs. Previous studies have shown that, regardless of size, the shape of MTCs was mostly round or ovoid rather than taller than wide [19, 20]. Similar results were also observed in our series. The MTMCs nodules were more likely to show ovoid to round comparing with PTMCs, and the difference was statistically significant (P = 0.000).

Calcifications, especially microcalcifications, had been regarded as a specific sign associated with thyroid malignancy. Kim et al [21] found that calcifications were not significantly different between PTCs and MTCs. The results of this study showed that calcifications were not common in MTMCs and PTMCs, and the incidence of calcification was similar (P = 0.674). However, the type of calcification was different between the two groups. We found that microcalcification was frequently seen in PTMCs, and macrocalcification appeared more commonly in MTMCs. This might be related to the different mechanisms of calcification formation in MTCs and PTCs. Calcification in MTCs was mainly due to the deposition of local calcium salts surrounded by amyloid substances, leading to the formation of coarse calcification. However, calcifications in PTCs are mainly caused by psammoma bodies with the smaller diameter of 10~100 μm, which are commonly manifested in round or concentric under the light microscope.

To the best of our knowledge, there were very limited literatures reported the blood supply of MTCs. Trimboli et al [22] reported that the percentage of intranodular vascularization in MTCs (25%) was higher than that in PTCs (15%), but with no significant difference. However, in the present study, MTMCs were more likely to show hypervascularity than PTMCs (p = 0.000). PTMCs were predominantly characterized by reduced blood supply, which might be due to the incompletely developed neoangiogenetic vascular bed in comparison with the uncontrolled cell proliferation typical of carcinoma [23]. In the present series, 80.15% of PTMCs were deficient in vascularity. According to the study reported by Lai et al [24], 72.4% of MTCs showed hypervascularity, which might be induced by the rapid division and growth of MTCs cells in patients, resulting in a faster rate of proliferation than PTCs. In this study, abundant blood supply was also commonly detected in MTMCs (58.70%), but the proportion was not as high as reported in the literature. This may be due to the small size of the tumor and its relatively small number of blood vessels.

There were some limitations in our study. First, this was a retrospective study with statistical bias. Second, due to the low incidence of MTCs and the collection of case take too much time, the development of ultrasound technology may have an impact on the evaluation of certain ultrasound features. In addition, although the sample size had increased compared with previous studies, it still belonged to small sample studies, and the error is unavoidable. The larger series is very useful to define the US presentation of MTMCs.

**Conclusions**
MTMCs had overlapping sonographic features with PTMCs, but MTMCs usually tended to be ovoid to round nodules with macrocalcifications and hypervascularity. Ultrasound couldn’t accurately distinguish the pathological types of thyroid cancer, but it could provide a certain degree of consciousness for radiologists, and provide some help for the early identification of MTCs.

**Availability Of Data And Materials**

All data in this study are available from the corresponding authors upon reasonable request.

**Abbreviations**

MTC: medullary thyroid carcinoma

MTMC: medullary thyroid microcarcinoma

PTMC: papillary thyroid microcarcinoma

PTC: papillary thyroid carcinoma

US: ultrasound

MEN: multiple endocrine neoplasia

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Declarations

Acknowledgments

None.

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Contributions

XYL collected and analyzed data, XYL and WZ wrote the paper; WZ and WWZ revised the paper. All authors read and approved the final manuscript.

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Funding

None.

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. The procedures of reviewing the research were in line with the ethical standards of the institutional and national research committees.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.
Tables

Table 1. Clinic of the MTMCs and PTMCs

|                      | MTMC       | PTMC       | P       |
|----------------------|------------|------------|---------|
| No. of nodules       | 46         | 136        |         |
| No. of patients      | 41         | 104        |         |
| Age                  |            |            |         |
| Mean                 | 41.78±16.39| 44.07±10.43| 0.323   |
| Range                | 14-80      | 24-71      |         |
| Sex                  |            |            | 0.205   |
| Male                 | 18 (43.90%)| 34 (32.69%)|         |
| Female               | 23 (56.10%)| 70 (67.31%)|         |
| Size                 |            |            |         |
| mean                 | 6.30±2.27  | 6.06±2.16  | 0.605   |
| Range                | 2.0-9.91   | 1.5-10     |         |
| Multiplicity         |            |            | 0.027   |
| Single               | 36 (87.80%)| 73 (70.19%)|         |
| Multifocality        | 5 (12.20%) | 31 (29.81%)|         |
| Lymph node metastasis|           |            | 0.040   |
| None                 | 26 (63.41%)| 83 (79.81%)|         |
| Present              | 15 (36.59%)| 21 (20.19%)|         |

Table 2. US characteristics of the MTMCs and PTMCs on Univariate Analysis
| Feature                        | MTMC (N=46) | PTMC (N=136) | P     |
|-------------------------------|-------------|--------------|-------|
| **Location**                  |             |              | 0.86  |
| Upper pole                    | 24/52.17%   | 73/53.68%    |       |
| Lower pole                    | 22/47.83%   | 63/46.32%    |       |
| **Shape**                     |             |              | 0     |
| Ovoid to round                | 25/54.35%   | 13/9.56%     | 0     |
| Taller than wide              | 9/19.57%    | 81/59.56%    | 0     |
| Irregular                     | 12/26.09%   | 42/30.88%    | 0.538 |
| **Boundary**                  |             |              | 0     |
| Clear                         | 26/56.52%   | 19/13.97%    |       |
| Unclear                       | 20/43.48%   | 117/86.03%   |       |
| **Margin**                    |             |              | 0.101 |
| Smooth                        | 17/36.96%   | 37/27.21%    | 0.211 |
| Spiculated                    | 10/21.74%   | 53/38.97%    | 0.034 |
| Poorly defined                | 19/41.30%   | 46/33.82%    | 0.36  |
| **Peripheral halo ring**      |             |              | 0.595 |
| Absent                        | 41/95.65%   | 133/97.79%   |       |
| Present                       | 2/4.35%     | 3/2.21%      |       |
| **Echogenicity**              |             |              | 0.727 |
| Marked hypoechoicity          | 10/21.74%   | 33/24.26%    |       |
| Hypoechoicity                 | 36/78.26%   | 103/75.74%   |       |
| Hyperechoicity and isoechoicity | 0          | 0            | 0.004 |
| **Composition**               |             |              |       |
| Solid                         | 40/86.96%   | 134/98.53%   |       |
| >50% solid                    | 6/13.04%    | 2/1.47%      |       |
| **Presence of calcification** |             |              |       |
| Absent                        | 31/67.39%   | 87/63.97%    | 0.674 |
| Present                       | 15/32.61%   | 49/36.03%    |       |
| Microcalcification             | 5/10.87%    | 40/29.41%    | 0.001 |
| Macrocalcification             | 10/21.74%   | 9/6.62%      |       |
| **Vascularity**               |             |              | 0.000 |
| Avascularity                  | 19/41.30%   | 109/80.15%   |       |
| Hypervascularity              | 27/58.70%   | 27/19.85%    |       |

Table 3. US characteristics of the MTMCs and PTMCs on Multivariate Logistic Regression Analysis
| Variable                        | B         | Wals $\chi^2$ | Odds Ratio | 95% CI       | P        |
|--------------------------------|-----------|---------------|------------|--------------|----------|
| Composition                    | -2.043    | 4.579         | 0.13       | 0.020-0.842  | 0.032    |
| Shape                          |           | 16.876        |            |              | 0        |
| Ovoid to round vs Irregular    | 1.391     | 5.792         | 4.018      | 1.295-12.473 | 0.016    |
| Taller than wide vs Irregular  | 2.602     | 16.869        | 13.488     | 3.897-46.681 | 0        |
| Calcification                  |           | 8.808         |            |              | 0.012    |
| Microcalcification vs absent    | -0.829    | 1.543         | 0.436      | 0.118-1.615  | 0.214    |
| Macrocalcification vs absent    | -2.465    | 8.314         | 0.085      | 0.016-0.454  | 0.004    |
| Vascularity                    | 2.377     | 21.434        | 10.778     | 3.939-29.488 | 0        |
| Boundry                        | -0.623    | 1.735         | 0.536      | 0.212-1.356  | 0.188    |

**Figures**

**Figure 1**

The sonographic features of MTMCs and PTMC. A. The transverse sonographic image of MTC in 68-year-old male showed hypoechogenicity, ovoid to round shape, and macrocalcifications. B. The sonographic features of marked hypoechogenicity, solid composition, and smooth margin were shown on a transverse ultrasound image from a 40-year-old female with MTC. C. The MTC nodule transverse sonographic image of 76-year-old female displayed taller than wide shape, poorly defined margin, and
A 31-year-old female with PTC. The transverse sonographic image showed a taller than wide shape, solid composition, hypoechogenicity, poorly defined margin and microcalcifications.