

The World's Smallest Papillary Thyroid Microcarcinoma: A 1.9 Millimeter-Diameter

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ABSTRACT

This study investigated the usefulness of the Sonography, Superb Micro-Vascular Imaging and FNAC for the risk papillary thyroid microcarcinoma (PTMC). We report a case of a 30 -year-old Caucasian man affected by a papillary thyroid microcarcinoma (PTMC) of the right lobe of the thyroid gland with very tiny size of a 1.9-mm-diameter. The characteristics with the Diagnostic Imaging using Ultrasonography (US), Superb Micro-Vascular Imaging (SMI) and fine-needle-aspiration cytology (FNAC) are discussed. Ultrasonography, (SMI) and FNAC have proven to be the most sensitive diagnostic combination for the early detection of thyroid cancer. Despite tiny size of this nodule, associated with malignant cytology at FNAC represents an important biological risk factor and could predict possible for neck lymph node metastases (LNM).

Keywords: Ultrasonography; Papillary Thyroid Microcarcinoma; Fine Needle Aspiration Cytology; Lymph Node Metastasis; World Health Organization

ABBREVIATIONS

PTMC: Papillary Thyroid Microcarcinoma; FNAC: Fine-Needle -Aspiration Cytology; WHO: World Health Organization; SEER: National Cancer Institute's Surveillance, Epidemiology and End Results Program; LNM: Lymph Node Metastasis; Total Extracapsular Thiroidectomy (TT); Enlarged Lymph Node (ENL); Lateral Lymph Node Metastasis LLNM; Central Lymph Node Metastasis CLNM

INTRODUCTION

Papillary thyroid microcarcinoma (PTMC) is defined by the World Health Organization (WHO) as papillary thyroid carcinoma that is <1 cm in the maximum diameter of the lesion [1].

In recent years, its incidence has gradually increased, attracting more attention from clinical physicians and researchers. The data from the United States National Cancer Institute's Surveillance, Epidemiology and End Results Program (SEER) show that, from 1975 to date, the

incidence of thyroid cancer has been on the rise, and of all malignancies, it has the fastest rate of increase [2].

Malignant behavior has been proven by several authors [3-4-5].

METHODS

Ultrasonography represents the most sensitive imaging method for early diagnosis of thyroid lesion [6-7].

The SMI (Superb Micro-Vascular Imaging) can underline the vessel flow of the newly formed tortuous vessels around tumors [8].

The FNAC (Fine Needle Aspiration Cytology) allows the selection of cases that require surgery with a 92-95% diagnostic accuracy (very high positive predictive value) based mainly on the nuclear features of cancer cells [9].

Clinical-pathological features and prognosis of this neoplasm, have been discussed in a previous studies. [10,11,12].

RESULTS

A 30 year-old Caucasian man with no personal history of thyroid disease presented herself to perform a thyroid ultrasound examination. Routine laboratory tests results were normal. BMI result was 31 kg/m².

Sister and mother had previously been diagnosed with papillary thyroid microcarcinoma.

Bi-dimensional ultrasonography (DUS 2) performed using high frequency 5 - 18 MHz linear probes and real-time US system (Canon i800 Prism, Canon Medical System Corp., Otawarashi, Japan) highlighted a nodule in the right thyroid lobe, radial shape with markedly hypoechoic echostructure, irregular margins, very tiny size (Ø 1.9 mm).

We label this nodule found on US as suspicious image and classify them TI-RADS 5, very high risk lesion according to ATA guidelines (Fig. 1) with the following descriptive images: solid thyroid nodule with marked hypoechogenicity, an irregular margin and a radial shape located in the right lobe, size of a 1.9 mm-diameter (Fig 1A); papillary thyroid microcarcinoma (PTMC) (Fig 1B); the SMI, was performed in combination with grayscale sonography for improved detection of thyroid malignancy (Fig 1C) and showed a clear flow through newly formed tortuous vessels specifically at the periphery of the micronodule. (Fig 1D).

FNAC procedure was proposed to the patient and after that informed consent had been obtained, it was fulfilled under ultrasound guidance.

Cytologic examination using Cell Block preparation (3 4µm sections Ematoxilin/Eosin stain) allowed clear-cut recognition of malignancy resulting in cytologic diagnostic category TIR5 according to Italian Consensus for the classification and reporting of thyroid cytology corresponding to category VI according to The Bethesda System for Reporting Thyroid

Cytopathology (Fig 1E) with a cytologic pattern pointedly very suspicious for papillary carcinoma.

The patient became candidate for thyroidectomy and subsequently underwent a Total Extracapsular Thyroidectomy procedure (TT). Some enlarged lymph node (ENL) were evaluated ultrasonography previous to surgical exploration and found and removed close to the right inferior thyroid pole at the time of thyroidectomy.

Histopathological tissue examination of the thyroidectomy showed that lesion was made of epithelial cells forming only differentiated follicular structures devoid of content or containing hypereosinophilic colloid with general contours were thorny and irregular, overtly infiltrating thyroid parenchyma. The neoplasm was solitary and showed no relationship to thyroid capsule (contained in thyroid) no evidence of vascular or lymphatic invasion and no metastasis to the lymph node received (final TNM 8th eds. staging pT1, pN0) (Fig 1F) inasmuch Radioiodine-I131 therapy (RIT) was not administered.

Patient underwent hormonal and tumor markers evaluation plus ultrasonographic re-evaluation of the neck after 3 months and showed no sign of recurrence.

DISCUSSION

Papillary thyroid carcinoma (PTC) is usually a non-encapsulated tumor mass sharply circumscribed from the adjoining thyroid parenchyma and its margins may be bosselated or scalloped. It is not uncommon for this neoplasm to extend to the thyroid capsule which usually is not violated.

Papillary thyroid microcarcinomas (non-incidental PTMC inferior to 1 cm) can have aggressive features and disease recurrence somewhat similar to conventional PTC, therefore it would be appropriate them to be managed like any other papillary thyroid malignancy [13] nonetheless many studies have shown that lymph node metastasis is associated with tumor size. Kasai and Sakamoto claim that the size of PTMC is a risk of lymph node metastasis and vascular invasion and have given great importance to the size and the location of the tumor [14]. Tuttle et al., believe that papillary thyroid microcarcinomas whose diameter is >0.5 cm have significantly higher rates of central lymph node metastasis, and are often multifocal (35%) [15]. Hunt and collaborators suggested that the location of the tumor is closely related to lateral neck lymph node metastasis (LLNM) [16]. Zhang and colleagues found that tumors in the upper third of the thyroid were at greater risk of LLNM, but at lower risk of central lymph node metastasis (CLNM) [17].

The sonographic nodule identified in the present study was found in the right thyroid lobe, presenting a radial shape, markedly hypoechoic echostructure, irregular margins, characteristics that even with a maximum size 1.9 mm still keep a high predictive score/value/index for malignancy ($p < 0.001$) [18].

Anyway it must be also said that hyperplasia and inflammation that can take place around cancer nests, resulting in indistinct borders may render ultrasound somewhat incapable of definitively distinguish the cancer nest from the surrounding tissue.

Folkman first reported a hypothesis that tumors would be unable to grow beyond a microscopic size of 1 to 2 mm³ without continuous recruitment of new capillary blood vessels [19].

The SMI allows detection of microvascularization at the periphery of the micronodule with accuracy [20] and showed 91.2% specificity and 75.9% sensitivity, which were superior to Power Doppler Flow Imaging (PDFI), at 82.3% and 41.8%, respectively ($P < .01$) [21] therefore peripheral vascularization was independent risk factor for thyroid malignancy and can be useful for detecting thyroid carcinoma. We are also convinced that it is very important to discuss the value of the tumor size a predictor of lymph node involvement and to predict the stage and the aggressiveness and prognosis of microcarcinomas in order to choose the right treatment as this is still controversial.

Lim et al., (2009) [22] indicated it to be 0.7 cm, Zhang et al., (2012) [23] indicated it in 0.6 cm, and Chang et al., (2015) [24] suggested 0.5 cm. Wang argue the cut-off value of tumor size to predict the risk of CLNM in papillary thyroid microcarcinoma is 0.575 cm (area under the curve 0.721) according to the ROC curves [25].

Nowadays, focusing on the percentage of biological risk factors due to very small tumors, the cut-off could drop to 0.3 cm [11].

This value is of great importance because the dimensions of PTMC in ultrasound images are fundamental data to predict the stage and the aggressiveness and prognosis of microcarcinomas and can help us choose the right treatment. Noguchi et al., they state in their study that the important goal is to determine the measure of appropriate surgery for the small thyroid carcinomas [26].

The diagnosis of tumors less than 0.5 cm in diameter requires very careful cytopathological evaluation. If an accurate diagnosis can be made before surgery, physicians will then be able to select and propose to the patient a reasonable surgical approach, nonetheless they will still debate on whether or not to perform prophylactic central lymph node dissection. We also suggest this shall be carefully tailored for each patient according to multiple risk factors and ultrasonography clinical data instead that on the sole malignancy on cytology report [27].

Based on nuclear crowding and presence of prominent nuclear grooves and pseudoinclusions FNAC was classified TIR5 according to the Italian consensus [28] corresponding to Category VI according to the Bethesda Classification [29].

Familiarity, age and gender, for this patient with these characteristics of high risk of long-term recurrence, total extracapsular thyroidectomy (TT), following the technique described by Lahey [30] and dissection of some enlarged lymph node (ELN), close to the right inferior thyroid pole, was considered to avoid reoperation (Hwangbo et al., 2017) [31].

CONCLUSION

We have described a case of a 30-year-old man with a nodule 1.9-mm-diameter, submitted to FNA for cytology, treated with total extracapsular thyroidectomy with a subsequent histological report of invasive papillary thyroid microcarcinoma follicular variant. US-FNAC and SMI have

proven to be the most sensitive diagnostic combination for the early detection of thyroid cancer.

Nowadays, focusing on biological risk factors for very small tumors, the cut-off of ultrasonography recognizable tumors could even dropped to 0.3 cm. This value is of great importance because the dimensions of PTMC in ultrasound images are still fundamental data to predict the stage and the aggressiveness of tumors and they can also become an advantageous tool for the prognosis of microcarcinomas and play their role in helping physicians wisely choose a tailored treatment.

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References

- 1.Hedinger C, Williams ED, Sobin LH. The WHO histological classification of thyroid tumors: a commentary on the second edition. *Cancer*. 1989; 63:908–11
- 2.Howlader N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975–2013, National Cancer Institute.2016
- 3.Lastra RR, LiVolsi VA, Baloch ZW. Aggressive variants of follicular cell-derived thyroid carcinomas: a cytopathologist's perspective. *Cancer Cytopathol*. 2014; 122:484–503
- 4.Gikas PW, Labow SS, Di Giulio W et al. Occult metastasis from occult papillary carcinoma of the thyroid. *Cancer*. 1967; 20:2100–04
- 5.Silver CE, Owen RP, Rodrigo JP et al. Aggressive variants of papillary thyroid carcinoma. *Head Neck*. 2011; 33:1052–59
- 6.Li QS, Chen SH, Xiong HH et al. Papillary thyroid carcinoma on sonography.*Clin Imaging*. 2010; 34:121–126
- 7.Kim GR, Kim MH, Moon HJ et al. Sonographic characteristics suggesting papillary thyroid carcinoma according to nodule size. *Ann Surg Oncol*. 2013; 20:906–913
- 8.Lu R, Meng Y, Zhang Y et al. Superb microvascular imaging (SMI) compared with conventional ultrasound for evaluating thyroid nodule.*BMC Med Imaging*.2017; 28:17(1):65
- 9.Berker D, Aydin Y, Ustun et al. The value of fine-needle aspiration biopsy in subcentimeter thyroid nodules. *Thyroid*. 2008; 18:603–608
- 10.Trapanese E, Agrusta M, D'Arco E et al. Insidious rare thyroid microcarcinoma “Black Ink”. *Indian J Appl Res*. 2017; 7:67
- 11.Trapanese E, De Bartolomeis C, Angrisani B, Tarro G. Papillary thyroid microcarcinoma (Black Ink). *Oncotarget*. 2018.29275-29283
- 12.Trapanese E, Angrisani B, Angrisani A et al. “Black Ink” Sonographic Pattern as a Predictor for Invasive Papillary Thyroid Microcarcinoma.*JAMMR*. 2019/v30i130162
- 13.Arora N, Turbendian HK, Kato MA et al. Papillary thyroid carcinoma and microcarcinoma: is there a need to distinguish the two?. *Thyroid*. 2009; 19(5):473-7
- 14.Kasai N., Sakamoto A. New subgrouping of small thyroid carcinomas. *Cancer*.1987;15;60(8):1767-70
- 15.Tuttle RM, Haddad RI, Ball DW et al. Thyroid carcinoma, version 2.2014. *J Natl Compr Canc Netw*. 2014;12:1671–80. 1680

- 16.Hunt JP, Buchmann LO, Wang L et al. An analysis of factors predicting lateral cervical nodal metastases in papillary carcinoma of the thyroid. *Arch Otolaryngol Head Neck Surg*. 2011;137:1141–1145
- 17.Zhang L, Wei WJ, Ji QH et al. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. *J Clin Endocrinol Metab*. 2012;97:1250-1257
- 18.Gu W, Yan H, Luo Y,W et al. Characterization of Papillary Thyroid Microcarcinomas Using Sonographic Features in Malignant Papillary Thyroid Cancer: A Retrospective Analysis. Tian. C, ed. *Medicine*. 2015;94(21):841
19. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med*. 1971; 285:1182–1186
- 20.Machado P, Segal S, Lyshchik A et al. Novel Microvascular Flow Tecnique: Initial Results in Thyroids. *Ultrasound Q*. 2016;32 (1) 67-74
- 21.Kong J, Li JC, Wang HY et al. Role of Superb Micro-Vascular Imaging in the Preoperative Evaluation of Thyroid Nodules: Comparison With Power Doppler Flow Imaging. *J Ultrasound Med*. 2017 Jul;36(7):1329-1337
- 22.Lim YC, Choi EC, Yoon YH et al. Central lymph node metastases in unilateral papillary thyroid microcarcinoma. *Br J Surg*. 2009; 96(3):253-7
- 23.Zhang L, Wei WJ, Ji QH et al. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. *J Clin Endocrinol Metab*. 2012; 97, 1250-57
- 24.Chang YW, Kim HS, Kim HY et al.Should central lymph node dissection be considered for all papillary thyroid microcarcinoma. *Asian J Surg*. 2015;02.006.
- 25.Wang M, Wu WD, Chou SL et al. Could Tumor Size Be A Predictor for Papillary Thyroid Microcarcinoma: a Retrospective Cohort Study. *Asian Pac J Cancer Prev*.2015;16 (18):8625-8
- 26.Noguchi S, Yamashita H, Murakami N et al. Small carcinomas of the thyroid. A long-term follow-up of 867 patients. *Arch Surg*. 1996;131(2):187-91.
- 27.Zhao C, Jiang W, Gao Y et al. Risk factors for lymph node metastasis (LNM) in patients with papillary thyroid microcarcinoma (PTMC): role of preoperative ultrasound. *J Int Med Res*. 2017;45(3):1221-1230.
- 28.Nardi F, Basolo F, Crescenzi A et al. Italian Consensus for the classification and reporting of thyroid cytology. *J Endocrinol Invest*. 2014; 37(6):593-9.
- 29.Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*. 2009;19(11):1159-65.
- 30.Campana FP, Marchesi M, Biffoni M et al. Total thyroidectomy techniques: suggestions and proposals of surgical practice. *Ann Ital Chir*.1996;67:627-35
- 31.Hwangbo Y, Kim JM, Park YJ et al. Long-term recurrence of small papillary thyroid cancer and its risk in a korean multicenter study. *J Clin Endocrinol Metab*.2017;102:625-33

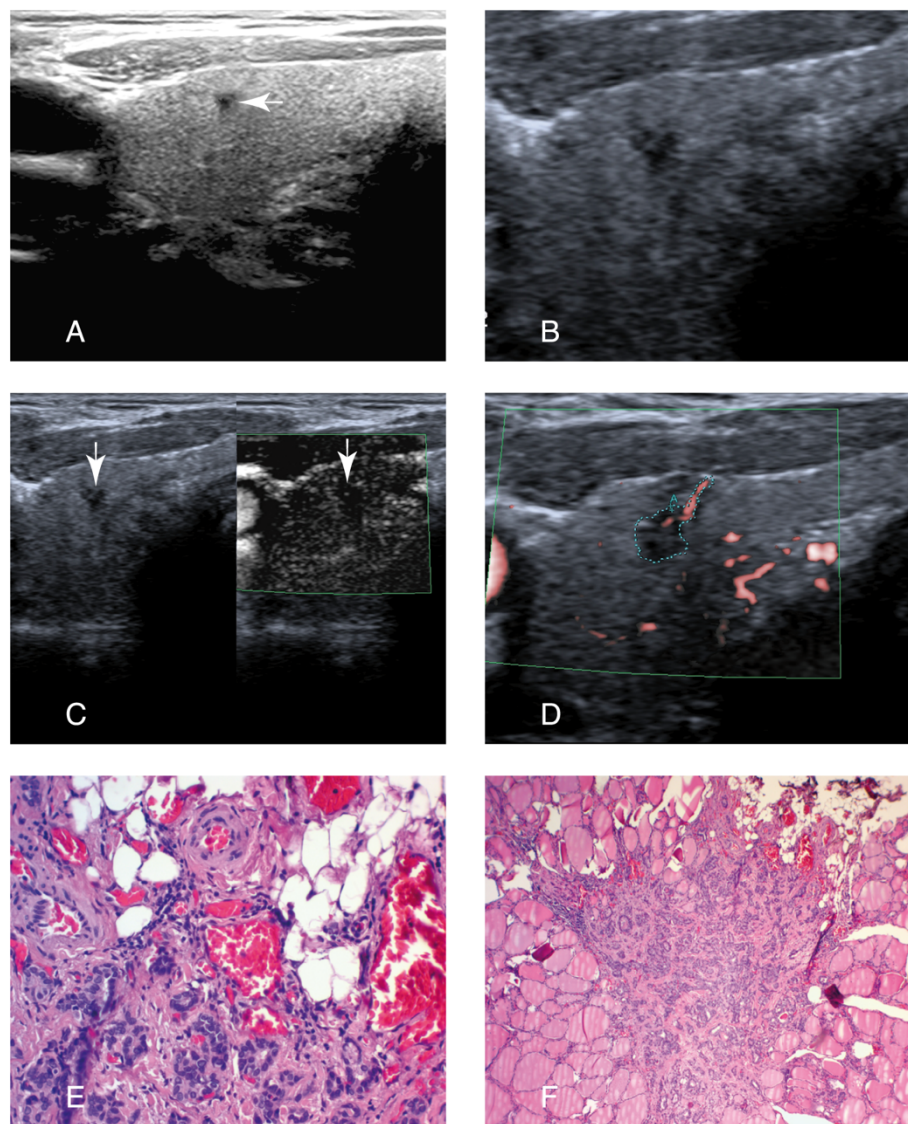


Figure 1. A, A transverse sonogram shows a 1.9 mm-diameter solid thyroid nodule with marked hypoechogenicity, an irregular margin and a radial shape located in the right lobe “Highly Suspicious” (white arrow). B, Zoom image, PTMC detected in the right thyroid lobe. C, SMI, Superb Micro-Vascular Imaging (arrows). D, Zoom image, SMI Test, shows a clear flow through newly formed tortuous vessels at the periphery of the specific micronodule. E, This picture highlights the overtly malignant behavior of this microcarcinoma. In spite of its very small full size (maximum 1.9-mm-diameter), this follicular variant of papillary carcinoma shows clearly infiltrating borders at which the tumor cells evoke a definite stromal reaction with fibrosis and desmoplastic response. Copious small vessels cram the space between the spikes. The neoplasm is contained in the resection (note the thyroid capsule ink layer at top-right) nevertheless, follicular cells are about to invade the fat lobules that lay around gland parenchyma contour. Hematoxylin-Eosin 400X). F, Numerous small vessels thrive at the infiltrative border of the neoplasm. Arteries are readily identified by the thick wall while veins are by thin endothelial lining. Small capillaries penetrate the tumor outline. Hematoxylin-Eosin 200X).