

## Clinical and sonographic characteristics of Warthin-like variant papillary thyroid carcinomas

Chun-ping Ning<sup>1</sup>, Ja Seung Koo<sup>2</sup>, Eun-Kyung Kim<sup>3</sup>, Suji Lee<sup>4</sup>

<sup>1</sup>The Affiliated Hospital of Qingdao University, Medical College, Ultrasound Department, <sup>2</sup>Severance Hospital, College of Medicine, Yonsei University, Department of Pathology, <sup>3</sup>Severance Hospital, College of Medicine, Yonsei University, Department of Radiology, <sup>4</sup>College of Medicine, Yonsei University, Department of Diagnostic Radiology, Seoul, Korea

### Abstract

**Aim:** To summarize the clinical, ultrasonographic (US) and pathological characteristics of Warthin-like variant papillary thyroid carcinomas (WVPTC). **Material and methods:** Medical records and US images of 32 cases of WVPTCs diagnosed between December, 2006 and September, 2018 were reviewed. Clinical, pathological and US characteristics of these cases were collected and summarized. ACR TI-RADS was followed during the analysis of the US features of the lesions. **Results:** Totally, 32 patients with 33 WVPTC nodules were reviewed. WVPTC was more often seen in female patients (27/32, 84.4%) with a relatively high age (mean age, 51.0±10.8 years old). Hyperthyroidism was observed in 14 patients; 2 patients were diagnosed as subclinical hyperthyroidism and 1 patient as subclinical hypothyroidism. Abnormal thyroglobulin antibody was detected in 22 patients. Mean size of the nodule was 1.2±0.5 cm (range, 0.5~2.99 cm) on US. Pathologically, tumor margin of 63.6% carcinomas were infiltrative but most (72.9%) of the enrolled carcinomas were intra-thyroidal. Lymphocytic thyroiditis was detected in 87.5% (28/32) patients. On US, most WVPTCs were solid or almost complete solid (32/33, 97.0%) and very hypoechoic (26/33, 78.8%). Taller-than-wide shape (6/33, 18.2%) and punctate echogenic foci (9/33, 27.3%) were not popular. All the nodules were scored higher than 5 points according to the ACR TI-RADS, including 9 nodules that were classified into TR4 and 24 nodules as TR5. Follow-up information was available in 31 patients and no recurrence or distal metastasis was detected. **Conclusions:** WVPTC is a rare variant of PTCs with favorable outcomes. Very hypoechoic echogenicity, solid or almost complete solid composition are the vital indicators for biopsy, even though the nodule may be wider-than-tall and have a lack of punctuate echoic foci.

**Keywords:** Warthin-like variant; papillary thyroid carcinomas; ultrasound; TI-RADS

### Introduction

Several histopathologic variants are defined besides the conventional type of papillary thyroid carcinoma (PTC) [1]. Reports state that different histopathologic

carcinomas manifest distinctive biologic behavior and various clinical/prognostic features. For example, the tall cell, columnar cell and hobnail variants are widely considered associated with poor outcomes [2]. On the contrary, Warthin-like variant PTC (WVPTC) is classified into a subgroup with a favorable prognosis.

Proposed by Apel et al [3] in 1995, WVPTC got the name for the close histologic resemblance to Warthin's tumors, which were often encountered in the salivary gland. It is characterized by typical papillary foldings lined by tumor cells with oncocyctic cytoplasm and nuclear features of PTC, accompanied by prominent lymphocytic infiltration in the papillary stalks [4]. Prevalence of WVPTC is still unclear, ranging about 0.2~1.9% [4,5] of the PTC. Most of the publications are case reports.

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Corresponding author: Eun-Kyung Kim MD

Severance Hospital, College of Medicine,  
Yonsei University, Department of Radiology  
250 Yonse-Ro, Seodaemun-gu,  
Seoul, Korea 120-752  
Email: ekkim@yuhs.ac  
Phone: 82-2-2228-7400

High-resolution ultrasound (US) examination is the first-line preoperative modality in evaluating thyroid lesions [2,6]. Taller-than-wide shape, irregular/spiculated margin, microcalcifications, extremely hypoechoic and solid composition are universally considered as the malignant indicators of thyroid cancers. The largest study about the US features of WVPTC was conducted by Kim et al in 2016 [7]. They concluded that WVPTCs did not sufficiently meet the typical suspicious findings mentioned above. However, only 9 patients were enrolled in the study. Here, we summarized the clinical, US and pathological characteristics of WVPTCs detected during 11 years in our hospital. We believe this is the largest study about the sonographic features of WVPTC along with the follow-up information up to now.

### Material and methods

This is a retrospective study. The protocol was approved by the Institutional Review Board of the Severance Hospital of Yonsei University. Informed consents were waived because of the retrospective designation.

#### *Patients and clinical data*

Two radiologists were invited to search the database of surgical pathology and to retrieve all the records of WVPTCs. Criteria for diagnosing WVPTC were as follows [8]: 1) papillary growth pattern, 2) oncocytic cytoplasm, 3) nuclear feature of PTC and 4) heavy lymphoplasmacytic infiltration. Between 2006 December and 2018 September, 35 records were hit among 25659 surgeries for papillary carcinomas, representing 0.14%. Preoperative US images were not available in three cases, so we included 32 patients in this study. Clinical information, including the age, sex and complaints of the patients together with the date and methods of the surgery were collected when reviewing the medical records. Results of thyroid function tests were also collected, including total T3, free T4, TSH and thyroglobulin antibody. Normal range of the thyroid function indexes were 0.61~1.16 ng/ml for total T3, 0.80~1.23 ng/dl for free T4, 0.41~4.30 uIU/ml for TSH and 0~130.6 IU/ml for thyroglobulin antibody. Mean age of the enrolled 32 patients (5 male and 27 female) was 51.0±10.8 years old (range, 30~74 years old). Among these, 12 patients were younger than 45 years old when surgeries were conducted.

#### *US data*

US examinations were performed by one of 16 radiologists (with 1~34 years' experiences in thyroid US scanning) according to the working shift. Two high-resolution US equipment, IU22 (Philips Medical Systems, USA) and E9 (GE Medical Systems, Milwaukee, WI, USA),

were used during the examinations. Clear ultrasonic images, including both longitudinal and transversal views of the thyroid gland and the nodules, were stored in a picture archiving and communication system (PACS). Color Doppler parameters were adjusted to optimal to illustrate the blood signals in the nodule.

#### *Image analysis*

Two radiologists (with 9 and 29 years' of experience in thyroid US examinations, respectively) were invited to review the stored images according to the white paper of ACR thyroid imaging, reporting and data system (TI-RADS) [6]. All the US features, including composition, echogenicity, shape, margin and echogenic foci were described and scored following the instruction of TI-RADS. The final level was determined according to the sum of the scores, ranging from TR1 (benign) to TR5 (high suspicion of malignancy). Besides, location, size, vascularity of the nodule (none/minimal/abundant) and parenchyma of the surrounding thyroid tissue (homogeneous/heterogeneous) were also recorded.

#### *Pathological data*

All the surgeries were performed by one of the two groups of surgeons after a careful evaluation of the patients' status. All pathological data were extracted directly by a radiologist from the pathological records. The records were made by one group of experienced pathologists according to the criteria of the World Health Organization International Classification of Thyroid tumors [9]. An experienced pathologist was invited to re-review the pathology slides and verify the records if necessary. Collected data were list as follows: the location (left lobe/right lobe/isthmus), margin (infiltrative/expanding/partially infiltrative), involvement (intra-thyroidal/involve the capsule of the gland/extra-thyroidal soft tissue involved), psammomatous calcifications of the lesion (absent/present), associated benign lesions (adenomatous hyperplasia/lymphocytic thyroiditis) and affected lymph nodes (yes/no).

#### *Statistical analysis*

Measurement data were recorded with the decimal kept to one place. Count variables were described in ratio.

## Results

### *Clinical and surgical results*

Clinical and surgical results of the enrolled patients were listed in Table I. Only three patients visited a hospital seeking medical advice because of a palpable mass in the neck. Other patients, with no specific complaints, were diagnosed during a routine check-up. Most patients (31/32, 96.9%) had unifocal WVPTC except one, who had two focal of WVPTCs (size, 1.1 cm and 0.5 cm) lo-

cating in the isthmus and the lower pole of the left lobe, respectively. So, the total number of enrolled nodules was 33. Five patients were found having two PTCs, which are one nodule of WVPTC and another nodule of different subtype of PTC (including four cases of classic PTCs and one case of follicular PTC). Moreover, one patient was found to have multifocal PTCs, including two classic type PTCs, one WVPTC and one follicular type PTC. Information about the TNM stage was also listed in table I. Pathologically, about 87.5% (28/32) patients were diagnosed as lymphocytic thyroiditis. Results of thyroid function test were available in 30 patients.

According to the pathological results (listed in table II), 63.6% of the WVPTCs have infiltrative margins, expanding margin was observed only in 7 (21.2 %) patients. However, most of (72.7%) the lesions were still

Table I. Clinical results of the WVPTC patients

Characteristics	Number (%)
Age	32
<45	12 (37.5%)
≥45	20 (62.5%)
Mean and range	51.0±10.8 (30~74)
Sex	32
Female	27 (84.4%)
Male	5 (15.6%)
Location	33
Left lobe	13 (39.4%)
Right lobe	16 (48.5%)
Isthmus	4 (12.1%)
Thyroid Function	30
Normal	13 (43.3%)
Hyperthyroidism	14 (46.7%)
Subclinical hyperthyroidism	2 (15.4%)
Subclinical hypothyroidism	1 (3.3%)
Abnormal thyroid antibody	22 (73.3%)
TNM staging	32
T1aN0M0	7 (21.9%)
T1aN1M0	4 (12.5%)
T1bN0M0	16 (50.0%)
T1bN1M0	3 (9.4%)
T2N0M0	1 (3.1%)
T2N1M0	1 (3.1%)
Surgery	32
Total thyroidectomy with central compartment dissection	20 (62.5%)
Total thyroidectomy with modified lymph dissection	2 (6.3%)
Subtotal thyroidectomy with central compartment dissection	3 (9.4%)
Hemithyroidectomy with central compartment dissection	4 (12.5%)
Hemithyroidectomy without central compartment dissection	3 (9.4%)

Table II. Pathological characteristics of the WVPTC patients

Characteristics	Number (%)
Tumor margin	
Infiltrative	21 (63.6%)
Expanding	7 (21.2%)
Partially infiltrative	2 (6.1%)
Not mention	3 (9.1%)
Tumor involvement	
Intra-thyroidal	24 (72.7%)
Extra-thyroidal soft tissue involved	9 (27.3%)
Lymphatic metastasis	
Yes	8 (25.0%)
Only central LN involved	6 (75.0%)
Central and lateral LN involved	2 (25.0%)
No	24 (75.0%)
Psammomatous calcification	
Absent	16 (48.5%)
Present	14 (42.4%)
Not mention	3 (9.1%)
Lymphocytic thyroiditis	
Yes	28 (87.5%)
No	4 (12.0%)

intrathyroidal. Lymphatic metastasis was detected in 8 patients (including 6 cases in the central part and 2 cases in both central and lateral parts). Among the six patients with other subtype of PTCs, only one patient, who had a nodule of WVPTC and another nodule of conventional PTC, had a lymphatic metastasis in level VI. However, it is difficult to decide the origin of the metastasis. About half (16/33, 48.5%) of the WVPTCs had psammomatous calcifications. Prognoses of the cases were evaluated by follow-up. Only one patient was missed during the follow-up. The mean period of follow-up was 67.4±25.2 months (range, 4-138 months). No recurrence or distal metastasis was found.

#### US findings

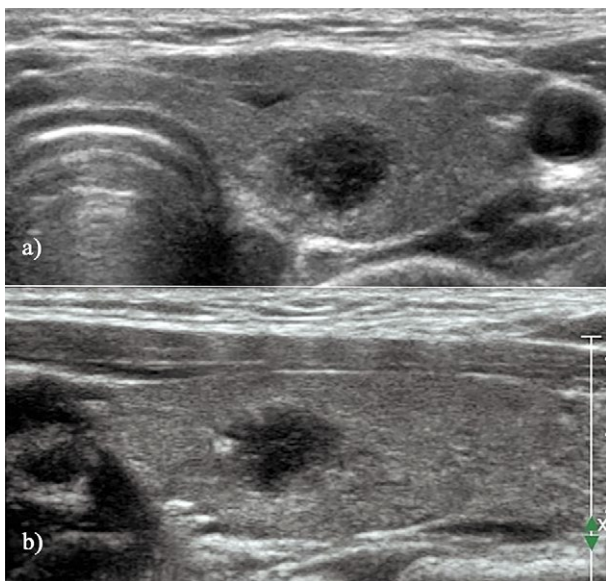
Among the 32 patients, 30 patients accepted ultrasound guided FNA before the operation. One patient underwent ultrasound guided core biopsy examination and the other accepted surgery directly. All the patients who underwent biopsy were preoperatively diagnosed as “papillary carcinoma” (9/31, 29.0%) or “suspicious for papillary carcinoma” (22/31, 71.0%). US findings of the enrolled cases were summarized in Table III. The mean diameter of the nodules was 1.2±0.5 cm (range, 0.5~2.99 cm). All the cases were scored higher than 5 points according to the ACR TI-RADS, including 7 cases were classified into TR4 and 26 cases were graded as TR5. Most of the lesions were solid or almost complete solid (32/33, 97.0%), very hypoechoic (26/33, 78.8%) and wider-than-tall shape (27/33, 81.8%) (fig 1 and 2). Only

one case was mixed cystic and solid. Regarding the margin, 11 cases were considered to be smooth/ill-defined, 18 cases were classified into lobulated or irregular, and 4 cases were suspicious for extra-thyroidal extension. Echogenic foci were detected in 11 cases, including 2 cases with macrocalcifications and 9 cases with punctate echogenic foci. Color Doppler images were available in 26 cases, most (18/26, 69.2%) cases were classified into none blood flow signal group. Among the 28 cases with lymphocytic thyroiditis confirmed by pathological results, parenchyma of the thyroid gland was described as “heterogeneous” in 22 cases and “homogeneous” in 10 cases.

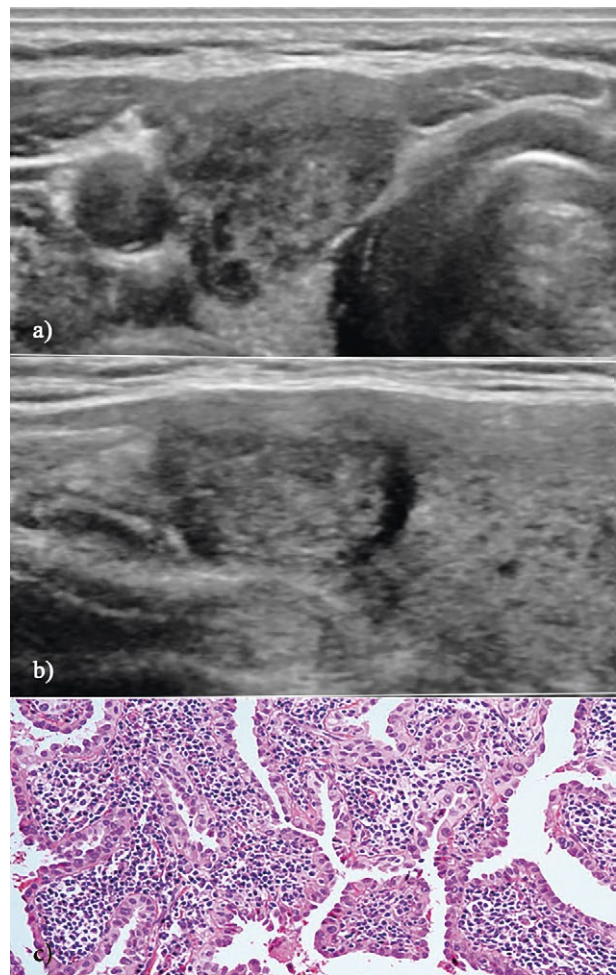
### Discussions

Thyroid cancer is one of the most commonly seen diseases in clinical practice. Rates for new thyroid cancers have been rising on average 3.1% each year over the last 10 years [10]. A similar tendency is found both in China and Korea [11,12]. Several studies reported that, prognosis of patients with PTCs may be associated with both clinical features and pathological variants [13-15]. However, US characters of various PTC subgroups are still insufficient [15,16], even though the method was widely used as the primary method in evaluating thyroid lesions.

WVPTC is a rare subgroup of oncocyctic variant [1] PTC, with about 162 cases reported in the English lit-



**Fig 1.** Transverse (a) and longitudinal (b) views of a 30-year-old woman with a solid thyroid nodule in the left lobe. The nodule was very hypoechoic with ill-defined margins. Three punctate echogenic foci were noticed on the edge of the nodule. It was confirmed as WVPTC.



**Fig 2.** Transverse(a) and longitudinal (b) sonographic images of a WVPTC in a 41-year old woman. The nodule was solid, hypoechoic and wider-than-tall shape. Surrounding thyroid parenchyma was heterogeneous, indicating the underlying diffuse thyroiditis; c) the pathological image of the nodule ( $\times 200$ ). Tumor cells showed oncocytic epithelium and dense lymphocytic infiltration in the stroma.

erature up to now [4,5,7,8]. Similar to previous reports, we found that WVPTC were more often seen in female patients (27/32, 84.4%) with a relative high age (mean age,  $51.0 \pm 10.8$  years old). Thyroid function test showed that, though plenty of patients had lymphatic thyroiditis and WVPTC simultaneously, incidence of hypothyroidism was not as high as expected; only one patient was detected as subclinical hypothyroidism.

After a thorough literature searching, we found that most of the articles published were about the pathological characteristics of WVPTCs [8,17-19]. It is widely accepted that WVPTC is morphologically characterized by a papillary architecture with an oncocytic epithelial lining and lymphoplasmacytic core infiltrate. In this study,

we summarized some pathological information regarding WVPTC, including tumor margin, involvement and lymph metastasis. Results showed that the tumor margin was infiltrative in 63.6% nodules and partially infiltrative in 2 nodules. Regarding the involvement, 71.8% carcinomas were intra-thyroidal. During the follow-up, neither local recurrence nor distal metastasis was detected. Thus, we agree with the statement that WVPTCs is a kind of variant with a favorable prognosis [5,18,20] though there was one fatal case reported [21]. It is also widely accepted that Hashimoto's thyroiditis usually presents in the nonneoplastic thyroid tissue in patients with WVPTC [20,22]. In our case series, 87.5% patients were diagnosed as lymphatic thyroiditis simultaneously. Preoperative abnormal thyroglobulin antibody was detected in 22 patients. So, it is important to differentiate WVPTC with other thyroid diseases with lymphocytic infiltration, such as Hashimoto thyroiditis, malignant lymphoma, the tall cell variant of PTC, etc. Fortunately, previous

studies reported that PTCs with Hashimoto's thyroiditis (HT)/ chronic lymphocytic thyroiditis (CLT) are less aggressive than those without HT/CLT [19,23,24]. However, we are not sure about the relationship between the prognosis of WVPTC and HT due to the limited sample size.

We analyzed the WVPTCs enrolled in this study according to the ACR TI-RADS system. All the cases were scored higher than 5 points. Though 78.8% cases were categorized as highly suspicious (TR5), further analysis showed that 11 cases scored 7 and only 6 cases manifesting typical US malignant characteristics (such as solid, very hypoechoic echogenicity, taller-than-wide shape with punctate echoic foci) scored 10~13. So, we believe that US appearance of WVPTC is quite non-specific and the final diagnosis relies on pathologic examinations. FNA was a recommendable way for the preoperative diagnosis. According to the ACR TI-RADS, FNA should be suggest to 20 patients including 3 cases in TR4 with a nodule larger than 1.5 cm and 17 cases in TR5 with a nodule larger than 1.0 cm, and follow-up should be suggested to the other 12 patients. In our series, 11 more patients underwent FNA because they were worried about adverse consequences during the follow-up. Though all the biopsies resulted as "papillary carcinoma" (9/31, 29.0%) or "suspicious for papillary carcinoma" (22/31, 71.0%), none of them were diagnosed as WVPTC directly. We assume the reason was that the nuclear feature of classical PTC was easily detected in cytological samples as well as the lymphatic infiltration. However, the papillary growth pattern and the dense lymphoplasmacytic infiltration in the cores of the papillae were more obvious in surgical specimen. Similar results were also reported previously by Chong et al and Vallonthaiel et al [17,25].

Similar with conventional variant PTCs, most of WVPTCs enrolled in our study were solid or almost complete solid and very hypoechoic. This feature was the main suspicious indicator for FNA. In accordance with Kim et al findings [7], we found that taller-than-wide shape in our case series was not popular (18.2%). Besides, punctate echoic foci were detected in 9 cases only. So, we assumed that wider-than-tall shape and lack of punctate echoic foci were the most important confusing factors during the detection of WVPTCs.

As far as we know, this is the largest study concentrated on the sonographic characteristics of WVPTC until now. However, there are still four limitations in our study. Firstly, this is a retrospective study performed in a single tertiary hospital. Further studies with a larger sample from multi medical centers are expected to confirm our conclusion. Secondly, cases enrolled in our study were all surgically removed, though the pathological re-

Table III. Ultrasonographic findings of the enrolled WVPTCs

Composition	
Cystic/almost complete cystic	0
Spongiform	0
Mixed cystic and solid	1 (3.0%)
Solid or almost complete solid	32 (97.0%)
Echogenicity	
Anechoic	0
Hyperechoic or isoechoic	1 (3.0%)
Hypoechoic	6 (18.2%)
Very hypoechoic	26 (78.8%)
Shape	
Wider-than-tall	27 (81.8%)
Taller-than-wide	6 (18.2%)
Margin	
Smooth/ill-defined	11 (33.3%)
Lobulated or irregular	18 (54.5%)
Extra-thyroidal extension	4 (12.1%)
Echogenic foci	
None or large comet-tail artifacts	22 (66.7%)
Macrocalcifications	2 (6.1%)
Peripheral calcifications	0
Punctate echogenic foci	9 (27.3%)
Color Doppler	
None	18 (69.2%)
Minimal	8 (30.8%)
TI-RADS level	
TR1-3	0
TR4	7 (21.2%)
TR5	26 (78.8%)
Parenchyma of the thyroid gland	
Homogeneous	10 (31.2%)
Heterogeneous	22 (68.8%)

sults were explicit, selective bias was inevitable. Thirdly, only nodules of WVPTC were included in this study; no control group or differential diagnosis was designed. Fourth, the detection of BRAF<sup>V600E</sup> was not a routine test in our hospital. Among the enrolled cases, only one patient accepted the detection test of BRAF<sup>V600E</sup> and the result was positive. So we did not include the result in the manuscript.

In **conclusion**, WVPTC is a rare variant of PTCs with favorable outcomes. Sonographic appearance of WVPTC is quite non-specific and the final diagnosis relies on pathologic examinations. However, very hypoechoic echogenicity, solid or almost complete solid composition still are the vital indicators for FNA, even though the nodule may be wider-than-tall and without punctuate echoic foci.

**Conflict of interest:** none

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