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Ultrasonographic features and clinical characteristics of Warthin-like variant of papillary thyroid carcinoma

Ga Ram Kim[1)], Jung Hee Shin[1)], Soo Yeon Hahn[1)], Eun Young Ko[1)] and Young Lyun Oh[2)]

[1)] *Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[2)] *Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*

Abstract. Warthin-like variant of papillary thyroid carcinoma (WVPTC) is a rare entity recently characterized. We evaluated ultrasonographic (US) features and clinical characteristics of WVPTC. Nine patients were diagnosed with WVPTC through surgery in our institution from May 2005 to January 2015. Eight of nine patients had available preoperative US images. A retrospective review of the US and clinical characteristics was performed. WVPTC compromised of 0.06% of 14,071 PTCs surgically confirmed. A mean age of nine patients was 53.2 years (range, 32-75 years). The mean nodule size of nine WVPTCs was 0.9 cm (range, 0.5-1.5 cm). Two patients showed central nodal metastasis and one patient with conventional PTC as an index tumor underwent central and lateral neck dissection. No one showed recurrence or distant metastasis during the follow-up period (mean, 4.6 years; range, 0.6-10 years). The most common US features of WVPTCs were solid composition (62.5%), hypoechogenicity (75%), and wider-than-tall shape (100%), respectively. Four (50%) of eight nodules showed well-defined margin and three (37.5%) of them had cystic component. One of eight resembled focal thyroiditis. Three nodules were considered as probably benign with US. All nine cases demonstrated underlying heterogeneous parenchymal echogenicity and accompanied chronic lymphocytic thyroiditis in permanent sections. Thyroid function tests in all patients were normal except for one with subclinical hypothyroidism. WVPTC is an uncommon subtype of PTC and has favorable prognosis, which can be misdiagnosed as a probably benign nodule or focal thyroiditis with US. All cases are associated with heterogeneous parenchyma in the background.

Key words: Papillary thyroid carcinoma, Warthin-like variant, Ultrasonography

A RECENT study has reported that different histopathologic variants of papillary thyroid carcinoma (PTC) can have different clinical courses and prognosis [1]. The Warthin-like variant of PTC (WVPTC), which is very rare and recently recognized, is characterized by papillary architecture and oncocytic cells, often in a background of lymphocytic thyroiditis showing lymphocystic stroma in the papillary stalks; the origin of its name was that this morphological appearance is similar to that of Warthin's tumor of the salivary gland [2-6]. WVPTC is known to have a similar clinical representation and prognosis to conventional PTC or to have a more favorable prognosis with a lower incidence of nodal metastasis [5, 7, 8].

An accurate preoperative diagnosis with only fine-needle aspiration (FNA) may be difficult even though histological characters of WVPTC are so particular [2, 3, 9]. Meanwhile, preoperative ultrasonographic (US) features of PTC would allow clinicians to predict the biologic behavior of PTC, and some US features would help to suggest certain PTC variants [1, 10]. Understanding the US features of WVPTC might be helpful for making an appropriate treatment plan. The clinical, cytological and histopathological features of WVPTC had been demonstrated [8, 11]. However, to our knowledge, there were no reports about the imaging characteristics of WVPTC, in that this is a recently described histological subtype. Therefore, we evaluated the US features and clinical characteristics of WVPTC, and whether this variant could be diagnosed using well-known malignant US criteria.

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Correspondence to: Jung Hee Shin, M.D., Ph.D., Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-Ro, Gangnam-gu, Seoul 135-710, Republic of Korea. E-mail: jhshin11@skku.edu, helena35@hanmail.net

Materials and Methods

Patients

Institutional review board approval was obtained

and informed consent was waived for this retrospective study. From May 2005 to January 2015, nine (0.06%) patients out of a total of 14,071 patients with PTC were histopathologically diagnosed with WVPTC through surgery in our institution. Of nine patients, two were included in a study by Lee *et al* [1]. We retrospectively evaluated their clinical characteristics such as their age or sex and their cytopathological results from their electronic medical records. One out of the nine patients had only undergone neck computed tomography (CT) scans before surgery and had no available thyroid US images in the picture archiving and communications system (PACS) because the US was performed at outside hospital. Eight of the nine patients had preoperative US images available.

US examinations

Thyroid US examinations were performed by one of 11 radiologists with HDI 5000, or iU22 scanners (Philips Medical Systems, Bothell, WA) equipped with a commercially available 7- to 12-MHz linear transducer. The US findings for eight thyroid nodules of the eight patients were retrospectively reviewed by two radiologists who determined consensus between them. The nodule size was determined according to US reports in which the maximal dimension seen on US was written. US features were identified as follows: composition (solid, solid portion < 50%, or solid portion ≥ 50%), echogenicity (hyper-, iso-, or, hypoechogenicity compared with the surrounding thyroid gland, or marked hypoechogenicity compared with the strap muscle), margin (well-defined, microlobulated, or irregular), calcifications (microcalcifications [hyperechoic foci < 2mm sized with or without acoustic shadows], macrocalcifications, or no calcifications), shape (taller-than-wide [greater in the anteroposterior dimension than in the transverse dimension], or wider-than-tall), and underlying parenchymal echogenicity (homogeneous, or heterogeneous). Echogenicity was evaluated for the remaining solid portion if solid and cystic components are mixed. Color Doppler US was not routinely performed since vascularity of thyroid nodules is not a major predictor of malignancy [12]. In our study, two of eight nodules had available Doppler US images. Marked hypoechogenicity, irregular or microlobulated margin, presence of microcalcifications, and a taller-than-wide shape were regarded as suspicious US features and thyroid nodules showing one or more US features mentioned above were assessed as "malignant" and those without suspicious features were assessed as "probable benign" [13-15]. Homogeneous or heterogeneous categories were classified based on underlying parenchymal echogenicity and heterogeneous parenchymal echogenicity with coarse echotexture was regarded as underlying thyroiditis [16].

US-FNA, thyroid surgery, and cytopathological analyses

Six of nine patients underwent preoperative US-guided FNA either in our institution (n=5) or in outside clinics (n=1). US-guided FNA was done by the same radiologist who performed the US examination with a 23-gauge needle connected with a 2-mL disposable plastic syringe. Two patients underwent preoperative US-guided core needle biopsy (CNB) in our institution (n=1) or outside clinics (n=1). US-guided CNB was performed with two or three passes using a spring-activated, short-throw (1.1 cm excursion) 18-gauge needle (Acecut, TSK Laboratory, Tochigiken, Japan). Slides from US-guided FNA or CNB performed in outside clinics were reviewed by the pathology department of our institution. In the case of the one patient among the nine who did not undergo preoperative FNA or CNB, WVPTC was incidentally found in permanent sections because preoperative FNA was performed for an index tumor confirmed as conventional PTC. Our institution routinely performed prophylactic central compartment neck dissection for surgery of PTC before 2013. All patients underwent total thyroidectomy (n=6), or hemithyroidectomy (n=3). Modified lateral neck dissection (n=1) was performed only when lateral neck lymph node (LN) metastasis was diagnosed at preoperative US and US-guided FNA. During the study period, cytopathological diagnosis was performed by one of seven pathologists dedicated in thyroid cytopathology, who was arbitrarily assigned according to the hospital schedule. Chronic lymphocytic thyroiditis was pathologically reported as an accompanied finding if lymphocytic and plasma cell infiltrates, oxyphilic cells, or formation of lymphoid follicles with germinal centers with or without atrophic changes of thyroid tissue are noted.

Results

The baseline and clinical information and pathological results of the nine patients with WVPTC are sum-

marized in Table 1. No patients had palpable nodule or a family history of thyroid cancer. The median age of the patients was 50 years (range, 32-75 years) and six patients (66.7%) were older than 45 years. There is only one male patient in our study (11.1%). The median size of the nodule was 1.1 cm (range, 0.5-1.5cm). Five patients had PTCs in the right lobe and four had PTCs in the left lobe. Six out of nine patients underwent total thyroidectomy and the other three underwent hemithyroidectomy. Two of nine patients had multiple PTCs in the ipsilateral lobe, but none had bilateral cancer. Both of the patients with multiple cancers had conventional PTCs accompanied by one WVPTC. All nine patients underwent central compartment neck dissection: two of them had nodal metastases of central neck. One of the nine underwent modified lateral neck dissection and had nodal metastases in the ipsilateral central and lateral neck; extrathyroidal extension was observed in this patient associated with the main 1.2 cm conventional PTC, not with the 0.5cm WVPTC. In all nine patients, chronic lymphocytic thyroiditis was found associated with WVPTCs in permanent sections. The median period of follow-up US was 6 years (range, 1-11 years): no patients showed recurrence or distant metastasis during the follow-up period. Thyroid function tests in all patients were normal with the exception of one with subclinical hypothyroidism.

US features of eight nodules are provided in Table 2. The common US features of WVPTC were solid composition (62.5%), hypoechogenicity (75%), and

Table 1 Baseline and clinical information and pathological results of nine patients with Warthin-like variant of papillary thyroid carcinoma

Case	Age (yr)/ sex	Tumorsize/ location	Thyroid function test	Type of operation	TNM staging	Extra-thyroidal extension	Accompanied chronic lymphocytic thyroiditis	Multiplicity/ Bilaterality/ Recurrence	Follow-up period (year)
1	47 / F	1.5cm / Right	Normal	Total thyroidectomy	T1N0M0	No	Yes	No/No/No	11
2	50 / F	1.1cm / Left	Normal	Total thyroidectomy	T1N1aM0	No	Yes	Yes*/No/No	7
3	75 / F	1.2cm / Right	Normal	Total thyroidectomy	T1N0M0	No	Yes	No/No/No	7
4	37 / F	0.6cm / Left	Subclinical hypo-thyroidism	Hemi-thyroidectomy	T1N0M0	No	Yes	No/No/No	6
5	44 / F	0.6cm / Right	Normal	Hemi-thyroidectomy	T1N0M0	No	Yes	No/No/No	6
6	32 / M	1.5cm / Right	Normal	Total thyroidectomy	T1N1aM0	No	Yes	No/No/No	4
7	74 / F	1.1cm / Left	Normal	Total thyroidectomy	T1N0M0	No	Yes	No/No/No	2
8	67 / F	0.5cm / Left	Normal	Hemi-thyroidectomy	T1N0M0	No	Yes	No/No/No	1
9	56 / F	0.5cm / Right	Normal	Total thyroidectomy	T3N1bM0	Yes†	Yes	Yes*/No/No	1

* Accompanied with additional conventional papillary thyroid carcinoma, not with the Warthin-like variant of papillary thyroid carcinoma.
† Associated with the main 1.2 cm conventional papillary thyroid carcinoma.

Table 2 Ultrasonographic features of eight (1 and 3-9 cases) thyroid nodules diagnosed as Warthin-like variant of papillary thyroid carcinoma

Case	Age (yr)/ sex	Tumor size	Composition	Echogenicity	Margin	Calcification	Shape	Underlying echogenicity	Final US assessment	FNA or CNB* result
1	47 / F	1.5cm	Solid < 50%	Hypoechoic	Well-defined	No	Wider-than-tall	Heterogeneous	Probable benign	PTC in background of cystic degeneration
2	50 / F	1.1cm	–	–	–	–	–	–	–	PTC*
3	75 / F	1.2cm	Solid < 50%	isoechoic	Well-defined	No	Wider-than-tall	Heterogeneous	Probable benign	PTC
4	37 / F	0.6cm	Solid	Hypoechoic	Irregular	Microcalcifications	Wider-than-tall	Heterogeneous	Malignant	PTC in background of lymphocytic thyroiditis
5	44 / F	0.6cm	Solid	Hypoechoic	Irregular	Microcalcifications	Wider-than-tall	Heterogeneous	Malignant	Suspicious for PTC
6	32 / M	1.5cm	Solid	Hypoechoic	Irregular	Microcalcifications	Wider-than-tall	Heterogeneous	Malignant	PTC
7	74 / F	1.1cm	solid ≥ 50%	Hypoechoic	Well-defined	No	Wider-than-tall	Heterogeneous	Probable benign	Suspicious for malignancy*
8	67 / F	0.5cm	Solid	Hypoechoic	Microlobulated	No	Wider-than-tall	Heterogeneous	Malignant	PTC
9	56 / F	0.5cm	Solid	Marked hypoechoic	Well-defined	No	Wider-than-tall	Heterogeneous	Malignant	Not done

US, Ultrasonography; FNA, US-guided fine-needle aspiration; CNB, US-guided core needle biopsy; PTC, Papillary thyroid carcinoma.
* The result was diagnosed by CNB.

wider-than-tall shape (100%), respectively. Irregular or microlobulated margin and microcalcifications, the well-known, typical suspicious findings suggestive of PTC, mentioned above, were present in four (50%) of eight nodules (Fig. 1, case 5). Three WVPTCs contained cystic components; these well-defined nodules had been assessed as probable benign based on their US morphologies (Fig. 2, case 1). One of eight nodules was considered as malignant based on the US features but resembled focal thyroiditis with an irregular, elliptical or flat shaped hypoechoic lesion (Fig. 3, case 4). All eight nodules demonstrated heterogeneous parenchymal echogenicity, which may indicate underlying diffuse thyroid disease. Color Doppler US was performed in two patients (case 3, and Fig. 4, case 7) and the targeted Doppler US scan showed little or no definite internal vascularity.

Seven of eight patients who underwent preoperative US-guided FNA (n=6) or CNB (n=1) were diagnosed with PTC (n=6) or suspicious for PTC (n=1). The other one patient underwent US-guided CNB in our institution after she had been diagnosed with follicular lesion of undetermined significance through US-guided FNA at an outside clinic: this well-defined nodule with solid composition more than 50% was reported as suspicious for malignancy having chronic lymphocytic thyroiditis with necrosis and squamous metaplasia on US-guided CNB (case 7).

The identification of $BRAF^{V600E}$ mutation was performed in three out of nine patients (case 3, 4, and 8), but none with $BRAF^{V600E}$ mutations was identified.

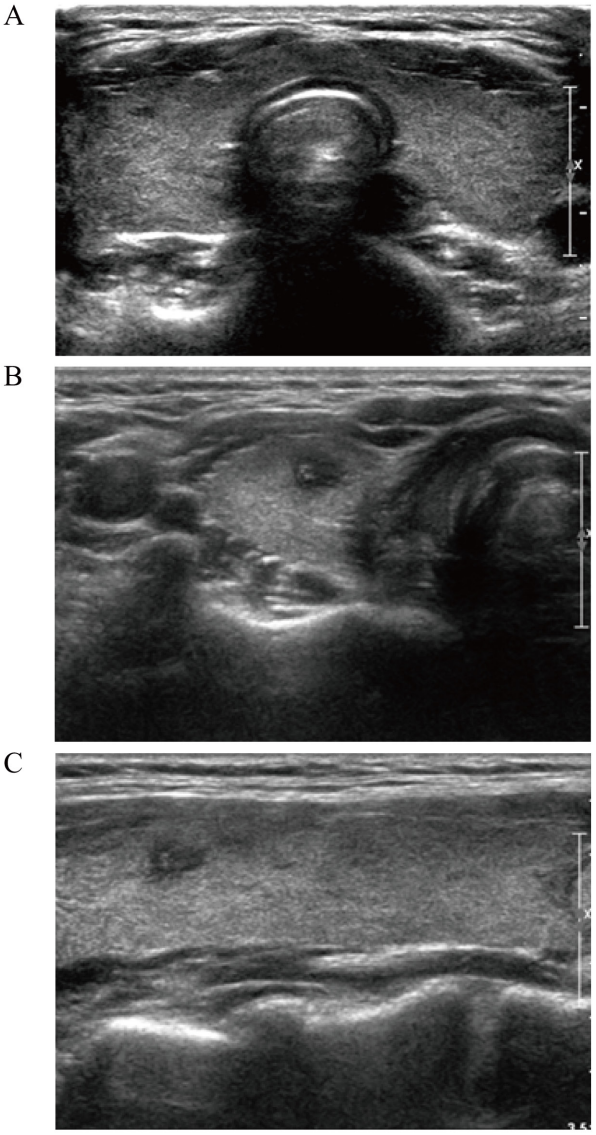

Fig. 1 Case 5: Warthin-like variant of papillary thyroid carcinoma in a 44-year-old woman who was diagnosed with suspicious for papillary thyroid carcinoma on fine-needle aspiration cytology. Transverse ultrasonography (**A**) of the thyroid gland demonstrates underlying diffuse heterogeneous parenchymal echogenicity. Transverse (**B**) and longitudinal (**C**) ultrasonography show a 0.6-cm solid, hypoechoic, parallel nodule with irregular margin and microcalcifications in the right lobe of the thyroid gland.

Discussion

Similarly to previous studies, female predominance was observed in our study: eight out of nine were female (88.9%). Our patients were somewhat older than those reported in previous studies, but showed similar wide range of age distribution [5, 6, 8, 11]. The mean nodule size was smaller than previous studies [5, 6], but similar to the recent studies [8, 11]. No $BRAF^{V600E}$ mutation was detected in patients with WVPTCs although three of nine had undergone $BRAF^{V600E}$ mutation analysis in this study: this trend is comparable to the findings of a previous study in which WVPTCs showed fewer mutations than conventional PTCs [11].

Detailed evaluation and preparation for FNA cytology of WVPTC are critical to avoid misdiagnosis such as benign lymphocyte-rich disease of the thyroid gland [17]. US evaluation as well as cytological diagnosis of WVPTC can be challenging; our results demonstrated that all WVPTCs did not sufficiently meet the typical suspicious US findings such as marked hypoechogenicity, microlobulated or irregular margin, presence of microcalcifications, and taller-than-wide shape [13, 18]. Relatively more benign-looking US features of WVPTC

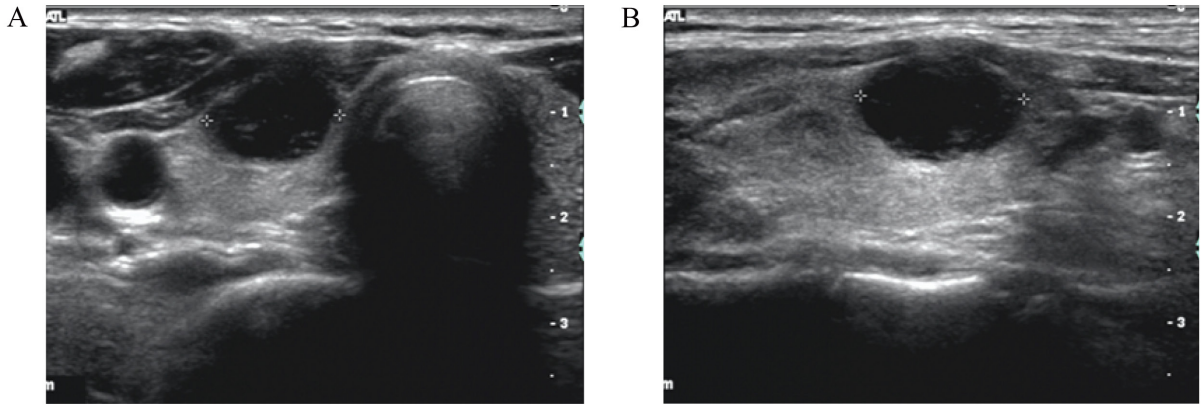

Fig. 2 Case 1: Warthin-like variant of papillary thyroid carcinoma in a 47-year-old woman who was diagnosed with papillary thyroid carcinoma in a background of cystic degenerationon at fine-needle aspiration cytology. Transverse (**A**) and longitudinal (**B**) ultrasonography show a 1.5-cm well-defined, hypoechoic, wider-than-tall nodule with internal cystic component in the right lobe of the thyroid gland.

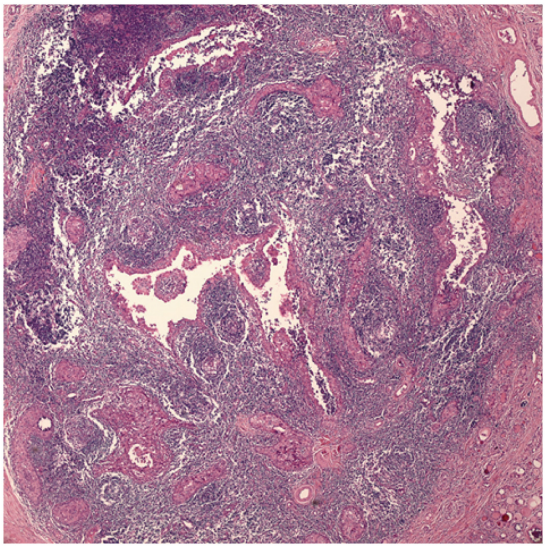

Fig. 3 Case 4: High-power photomicrograph (hematoxylin-eosin, original magnification ×40) showing papillary, centrally cystic thyroid carcinoma with oncocytic cytoplasm and abundant lymphoplasmacytic infiltration.

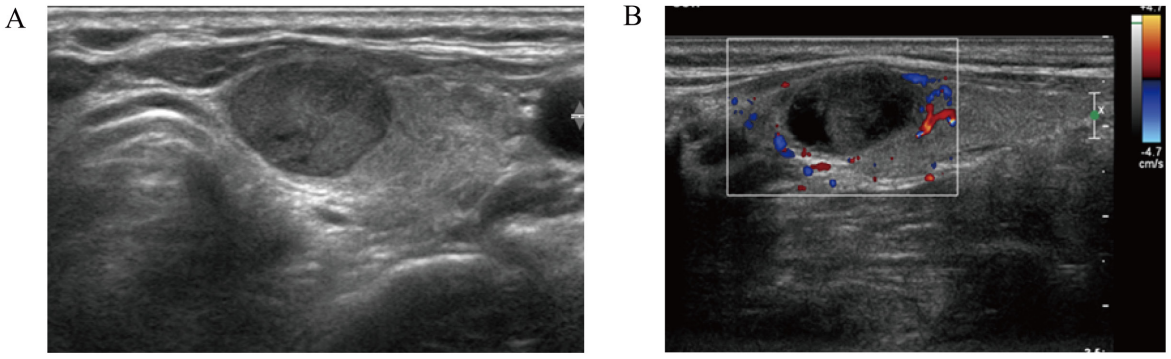

Fig. 4 Case 7: Warthin-like variant of papillary thyroid carcinoma in a 74-year-old woman who was diagnosed with suspicious for papillary thyroid carcinoma at fine-needle aspiration cytology. Transverse (**A**) and longitudinal ultrasonographic image with color Doppler (**B**) show a 1.1-cm well-defined, hypoechoic nodule with cystic change in the left lobe of the thyroid gland.

compared to conventional PTC could be missed if the US performer did not decide to do US-guided FNA of the target. Well-defined, oval-shaped nodules (case 1, 2, 7) containing cystic component proved to be WVPTCs and the seemingly cystic components which were seen as anechoic or markedly hypoechoic portions on US images turned out to be cystic degeneration, background lymphocytic thyroiditis, or lymphocytic inflammation with necrosis through FNA cytology. In addition, the US features of an irregular, elliptical or flat shaped hypoechoic lesion (case 4) resembled to those of focal thyroiditis. Therefore, the seemingly anechoic or marked hypoechoic part itself in the nodule may be correlated with lymphocytic stroma of WVPTC, which is a distinct histological feature distinguishing WVPTC from other types or subtypes of thyroid cancer or cysts which were observed accompanied with lymphocystic stroma in the papillary stalks [5-7].

Generally, WVPTC is said to behave like conventional PTC showing good long-term overall survival and rare extrathyroidal extension, nodal metastasis, recurrence or distant metastasis [2, 5, 6, 8, 11]; our findings were similar to previous reports showing favorable prognosis. All WVPTCs in our study were assigned as T1 stage except the last case (case 9) in which conventional PTC larger than 1 cm were accompanied in the ipsilateral lobe with extrathyroidal extension and nodal metastases. Six out of nine patients had no regional nodal metastasis in our study and this result is consistent with previous trend with a lower incidence of nodal metastasis of WVPTC than conventional PTC [7, 8]. Coexistences of WVPTC and other variants of PTC might cause worse prognosis because of the unfavorable side among the variants [5, 19]; in our study, all two patients who had additional conventional PTCs showed nodal metastases. Curiously enough, the other patient with nodal metastases demonstrated irregular nodules with mutliple microcalcifications, which had the closest US features to conventional PTC among our cases (case 6). Consequently, we may infer WVPTCs with suspicious malignant US features seem to behave in a more aggressive fashion than those without malignant features.

Associated lymphocytic thyroiditis is common in WVPTC according to previous studies [2-4, 6]. Likely, all of nine patients had chronic lymphocytic thyroiditis, which had been anticipated based on their underlying heterogeneous parenchyma of the thyroid gland. Even though the prognostic effect of lymphocytic thyroiditis accompanying PTC has been controversial [11, 20, 21], meticulous care is required in the evaluation of focal lesion with underlying lymphocytic thyroiditis [22]. It is difficult to differentiate WVPTC from dominant lymphocytic infiltration on FNA cytology and the background of lymphocytic thyroiditis may give rise to false negative reports [5, 6, 17]. Equally, heterogeneous parenchymal change which may be caused by lymphocytic thyroiditis lowers the diagnostic performances of US in the differentiation of thyroid nodules, thus thyroid nodules which do not meet the typical suspicious US findings suggestive of PTC might be missed [23, 24]. US features of focal thyroiditis and PTC can be confused, especially in the background of thyroiditis, such as in the present case.

Several limitations of our study are as follows. First, the study sample size is relatively small since WVPTC is a very rare disease. Second, our study is of a retrospective design and there is a lack of long-term follow-up of all patients to assess their prognosis. Further long-term follow-up studies with larger sample size are necessary to confirm the biological and clinical behavior and prognosis of WVPTC.

In conclusion, WVPTC is one of the uncommon subtypes of PTC, with a favorable prognosis, and it can be misdiagnosed by US as a probably benign nodule or focal thyroiditis. All cases are associated with heterogeneous parenchyma in the background.

Disclosure Statement

No competing financial interests exist.

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