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Ultrasonographic features and clinicopathologic characteristics of macrofollicular variant papillary thyroid carcinoma

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Abstract

Macrofollicular variant papillary thyroid carcinoma (MFV-PTC) is defined as papillary thyroid carcinoma with macrofollicles of >200 μm in more than 50% of the cross-sectional area of the specimen. The aim of this study was to evaluate the clinicopathologic characteristics of the MFV-PTC treated in the Yonsei University College of Medicine.

Between September 2007 and July 2012, 18,697 patients with PTC were treated in our institution. Of these, 10 patients (0.05%) were diagnosed as the MFV-PTC in final pathologic report.

Mean age of 10 patients were 42.5 years old, ranging from 26 to 69 years. Twelve lesions were found in 10 patients. On preoperative ultrasonographic examination, most of tumors looked like benign nodules. The tumor nodules varied in size from 0.3 to 3.5 cm in greatest dimension. Microscopically, the macrofollicles were surrounded by cuboidal cells with hyperchromatic nuclei and occupied entire nodule.

MFV-PTC showed the benign appearance in ultrasonography. To avoid misdiagnosis of MFV-PTC, clinicians should be aware of the characteristics of MFV-PTC and perform ultrasonography with fine needle aspiration biopsy appropriately.

Abbreviations: ATA = American Thyroid Association, CCND = central compartment node dissection, KTA = Korean Thyroid Association, PTC = papillary thyroid carcinoma, PTC, MFV-PTC = macrofollicular variant.

Keywords: marcrofollicualr variant, papillary thyroid carcinoma, ultrasonography

1. Introduction

Macrofollicular variant is one of the variant of papillary thyroid carcinoma (PTC), which was first reported in 1991.[1] Macrofollicular variant papillary thyroid carcinoma (MFV-PTC) is a well-differentiated thyroid carcinoma with large, follicular architecture and with nuclear characteristics of PTC including enlarged, ground glass clear nuclei, and nuclear grooves.[2,3]

MFV-PTC is clinically important as it as a differential diagnosis for a thyroid nodule. The differential diagnosis for thyroid nodules include MFV-PTC and benign disease which include goiter, macrofollicular adenoma, follicular neoplasm, and hyperplastic nodule.[4,5]

The aim of this study was to evaluate the clinicopathologic characteristics of the MFV-PTC treated in our institution.

2. Materials and methods

Between January 2007 and June 2012, of 18,697 patients with PTC were treated in the Department of Surgery, Yonsei University College of Medicine, Seoul, Korea. Around 10 patients (0.05%) were diagnosed as the MFV-PTC in final pathology report. In the same period, 926 patients (4.95%) were diagnosed as the follicular variant papillary thyroid carcinoma.

Extent of thyroidectomy was performed based on the American Thyroid Association (ATA) and Korean Thyroid Association (KTA) guidelines.[6,7] Central compartment node dissection (CCND) was performed in ipsilateral side routinely and contralateral CCND was performed on patients with suspicious metastatic node on contralateral side.

All pathology slides were reviewed and MFV-PTC was confirmed by the specialized pathologist (HSW). Demographic feature of patients, preoperative ultrasonography, and final pathology results were reviewed retrospectively.

Approval to conduct a retrospective review of the images and medical records of patients was obtained by the Institutional Review Board of our institution (IRB No. 3-2012-0156). The institutional review board approved this retrospective observational study and required neither patient approval nor informed consent for the review of their records.

3. Results

The clinicopathologic characteristics of the patients are listed in Table 1. There were 2 men and 8 women, with a mean age of 42.5 ± 13.6 years. The preoperative ultrasonographic findings of MFV-PTC are summarized in Table 2.

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Table 1

The clinicopathologic characteristics of macrofollicular variant papillary thyroid carcinoma*.

Patient no.	Gender	Age	FNAB (Bethesda classification)	Frozen pathology	Size, cm	Multiplicity	Margin	Extrathyroidal extension	Surgical procedure	Lymph node metastasis	RAI, mCi	Disease free survival duration, months
1	F	49	5	PTC	1.4	Single	Expanding	Yes	Bilateral total thyroidectomy with CCND	No	130	36
2	F	69	3		1.5	Multiple	Expanding	No	Bilateral total thyroidectomy with CCND	No	30	32
3	M	38	Rt.5/Lt.2	Rt. Lt. MFV-PTC	Rt. 1.4 Lt. 1.1	Bilateral	Expanding	No	Bilateral total thyroidectomy with CCND	No	30	27
4	F	45	Rt.2/Lt.5	Lt. PTC	Rt. 0.4 Lt. 0.8	Bilateral	Expanding	No	Bilateral total thyroidectomy with CCND	No	No	2
5	F	42			0.3	Single		No	Completion total thyroidectomy with CCND	Central 3/4	30	50
6	F	32	5	Deferred	0.5	Single		No	Rt. hemithyroidectomy with CCND	No	No	50
7	M	37	3		1.5	Single		No	Rt. hemithyroidectomy with CCND	No	No	47
8	F	69	6		1.5	Multiple	Expanding	No	Bilateral total thyroidectomy with CCND	No	30	21
9	F	28	5	Favoring adenomatous hyperplasia	3.5	Single	Expanding	No	Rt. hemithyroidectomy with CCND	No	No	13
10	F	26	6	PTC	2.7	Single		No	Bilateral total thyroidectomy with CCND	No	100	18

CCND = prophylatic central compartment node dissection, F = female, FNAB = fine needle aspiration biopsy, M = male, MFV-PTC = macrofollicular variant of papillary thyroid carcinoma, PTC = papillary thyroid carcinoma.

* Central lymph node metastasis was not originated from macrofollicular variant PTC but from papillary thyroid microcarcinoma of left hemithyroidectomy before 6 years ago.

Internal content of MFV-PTC was predominantly solid, ovoid to round lesions. None of the 12 cancer lesions had suspicious malignant findings such as taller than wide shape, ill-defined margin, and microcalcification. On ultrasonography, 4 of the tumors were hypoechoic, while the rest were isoechoic.

Fine-needle aspiration cytology was performed in 11 of 12 tumors. Of these, 7 tumors were diagnosed as suspicious or carcinoma (Bethesda category V or VI) and the other lesions were benign and atypia (Bethesda category II or III). The tumor size varied from 0.3 to 3.5 cm (mean, 1.4±0.9 cm).

Microscopically, macrofollicles and microfollicles were observed synchronously and macrofollicles occupied almost the entire nodule (Fig. 1A, C, and E). Most macrofollicle of tumors were lined by cuboidal cell with irregular, ovoid and ground glass nuclei (Fig. 1B, D, and F).

Central lymph node metastasis was found in one patient with recurrent carcinoma. This patient was performed left hemithyroidectomy at 6 years ago (patient 5, T1aN0M0 stage I). After detection of recurrence in remnant thyroid gland, completion total thyroidectomy with central compartment node dissection was performed and the final pathologic result showed one MFV-PTC

Table 2

The ultrasonographic characteristics of macrofollicular variant papillary thyroid carcinoma.

Patient no Gender/Age	1 F/49	2 F/59	3 (Rt.) M/38	3 (Lt.) M/38	4 (Rt.) F/45	4 (Lt.) F/45	5 F/42	6 F/32	7 M/37	8 F/69	9 F/28	10 F/26
Internal content												
Predominantly solid >50%	+	−	+	+	+	+	+	+	+	+	+	+
Predominantly cystic>50%	−	+	−	−	−	−	−	−	−	−	−	−
Shape												
Ovoid to round	+	+	+	+	+	+	+	+	+	+	+	+
Taller than wide*	−	−	−	−	−	−	−	−	−	−	−	−
Irregular	−	−	−	−	−	−	−	−	−	−	−	−
Margin												
Well-defined smooth	+	+	+	+	+	+	+	−	+	+	+	+
Well-defined speculated	−	−	−	−	−	−	−	−	−	−	−	−
Ill-defined*	−	−	−	−	−	−	−	−	−	−	−	−
Echotexture												
Homogenous	+	−	+	+	+	+	+	−	−	−	+	+
Heterogenous	−	+	−	−	−	−	−	+	+	+	−	−
Echogenicity												
Hypoechogenecity*	−	−	−	−	+	+	+	−	+	−	−	−
Isoechogenecity	+	+	+	+	−	−	−	+	−	+	+	+
Hyperechoegecity	−	−	−	−	−	−	−	−	−	−	−	−
Calcification												
Microcalcification*	−	−	−	−	−	−	−	−	−	−	−	−
Macrocalcification	−	−	−	−	−	−	−	−	−	−	−	−
Rim calcification	−	−	−	+	−	−	−	−	−	+	−	−

* Suspicious finding for malignant thyroid nodules on ultrasonography.

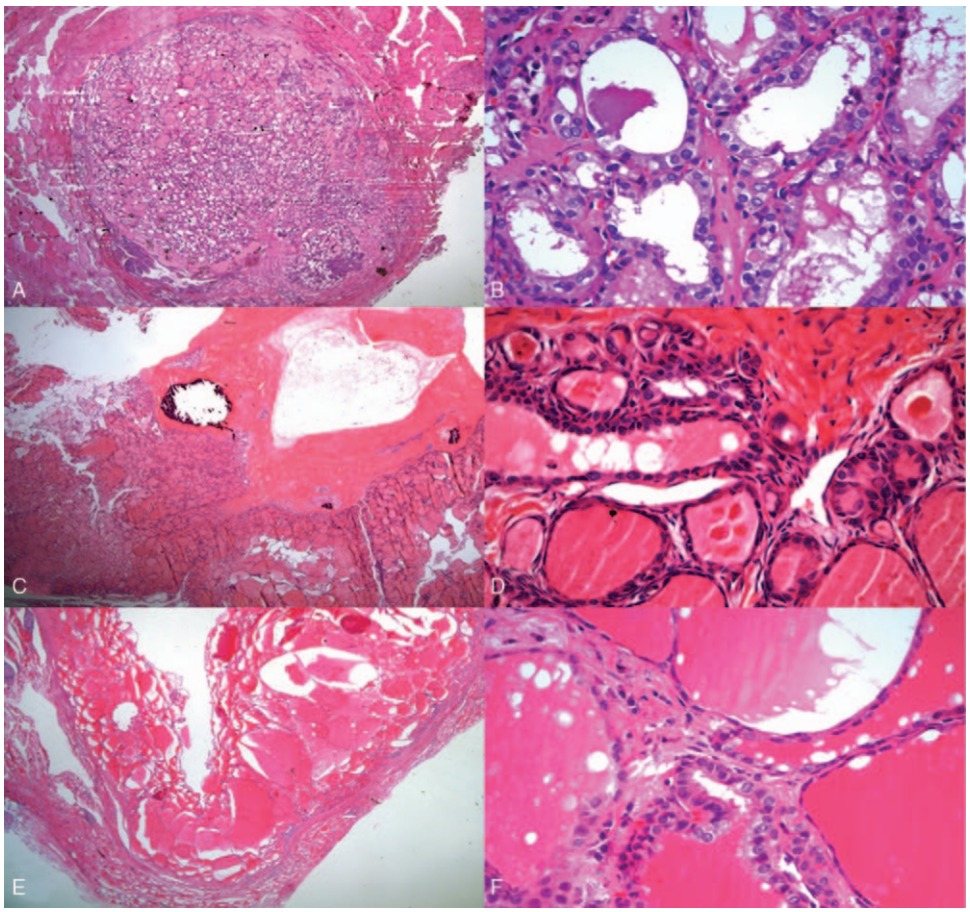

Figure 1. Histologic appearance of the tumor, which shows numerous macrofollicles>200 μm with various sized follicles in thyroid (A, C, E; hematoxylin-eosin stain ×12.5), and shows ground glass appearance, hyperchromatin nuclei in lining cuboidal cell around of macrofollicles (B, D, E; hematoxylin-eosin stain ×400). (A, B—patient 3; C, D—patient 1; E, F—patient 2).

on remnant thyroid gland and central lymph node metastasis (3 of 4) which might be originated from conventional PTC treated at 6 years ago.

On follow-up duration from 2 to 50 months (median 29.5 months), recurrence was not observed in all patients (Fig. 2).

4. Discussion

The MFV-PTC is a rare entity, which was first reported in 1991.[1] Albores-Saavedra et al[1] described 17 cases of macrofollicular variant of an encapsulated papillary carcinoma of the thyroid, which can be easily confused and misdiagnosed as benign nodules.

The follicular-patterned lesions of the thyroid gland are a spectrum of lesions spanning from hyperplastic nodules to follicular variant of PTC and follicular thyroid carcinoma. Follicular variant of PTC is characterized by follicular architecture and cytomorphologic features of PTC. The follicles are small in size and are associated with thick dense colloid.[2] MFV-PTC is a well-differentiated thyroid carcinoma with large, follicular architecture and with nuclear characteristics of papillary thyroid carcinoma including enlarged, ground glass clear nuclei, and nuclear grooves.[3] The major difference of macrofollicular variant and follicular variant of PTC is the size of follicles. The follicle size of follicular variant is 20–40 μm, and that of macrofollicular variant is various, predominantly macrofollicle larger than 250 μm.

Macrofollicles lined by cells with clear nuclei are found in goiter and adenomas and in this variant of PTC. However, in goiter and adenomas the nuclei are not enlarged and do not overlap as they do in MFV-PTC.[3] According to the definition, the PTC must have macrofollicles of >200 μm in more than 50% of the cross-sectional area of the specimen to diagnose MFV-PTC.[4,5] Because of its histologic features, the differential diagnosis with benign diseases including goiter, follicular adenoma, or hyperplastic nodule may be challenging.

Preoperative diagnosis of this variant is very difficult. Suspicious features for malignancy on thyroid ultrasonography are taller than wide shape, speculated margin, marked hypoechogenicity, and the presence of calcification.[8–10] Ultrasonographic findings of MFV-PTC show the pattern of benign thyroid nodules. They demonstrated ovoid to round, well-defined smooth margined, homogenous nodules (Table 2).

Fine-needle aspiration cytology is the main diagnostic method for diagnosing the thyroid carcinoma, 7 of 11cases was diagnosed by cytology in this study.[6,7] But preoperative cytology result also confused between PTC and benign lesions. The left-sided tumor of patient 3 and right-sided tumor of patient 4 were diagnosed as

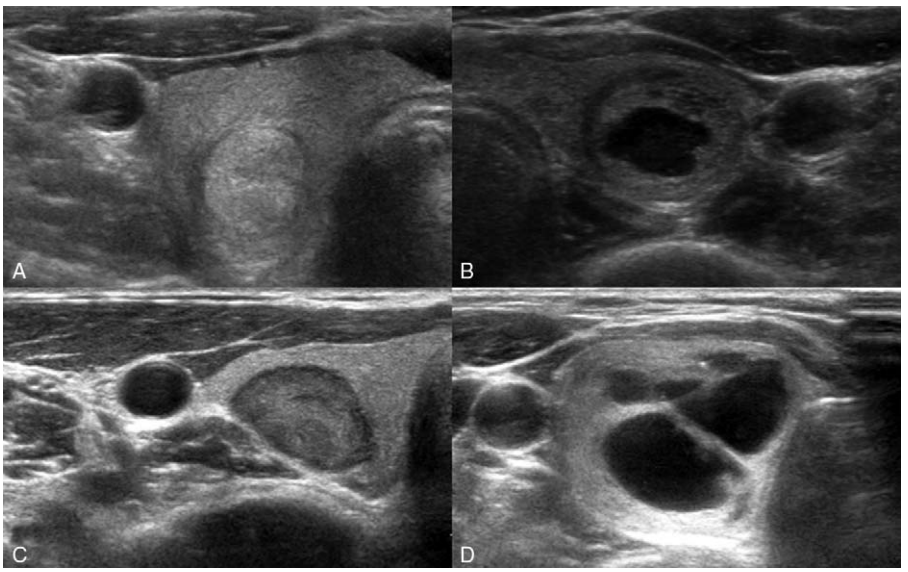

Figure 2. Transverse ultrasound image of macrofollicular variant of PTC, which has well-defined smooth margin, ovoid to round shape (A–D), and which shows isoechogenic solid nodule (A) or hypoechogenic nodule (C), or mixed echogenic nodule (B, D). (A—patient 2; B—patient 3; C—patient 6; D—patient 9). PTC= papillary thyroid carcinoma.

benign nodule in preoperative fine-needle aspiration cytology. MFV-PTC lesion of patients 3 and 5 were discovered accidentally in the course of surgery for another cancer lesion. These cases were not be with ipsilateral or contralateral cancer lesion, the MFV-PTC lesion is missed out and not operated.

Elastography is used in the evaluation of thyroid nodules for distinguishing benign from malignant by comparing tissue elasticity.[11] Strain and shear-wave elastography (SWE) are 2 types of elastography in clinical practice.[11,12] Two kinds of elasticity can be assessed by strain elastography. First, colors around and within the nodules were evaluated and visually scored according to the 4–5-scale scoring systems. Second, regions of interest are specified as the target region and the adjacent reference region. Later, elastograph calculates strain ratio automatically. Higher strain ratio leads to a high probability of malignancy.[11,12]

Although elastography is beneficial to distinguish benign and malignant thyroid nodules, elastography was not used in the present study. Due to this why our institution has set elastography examination lately and radiologists in our institution were not familiar to perform elastography in thyroid nodules.

In gross findings of the specimens, they also look like the benign thyroid lesions. On frozen section the tumors, composed predominantly of macrofollicular structures often lined with low cuboidal or flat cells with small, hyperchromatic nuclei, are likely to be confused with goiter or macrofollicular adenoma.[3,13]

There have been few articles reporting the clinical presentation and the prognosis of MFV-PTC.[1,4,14] It has been described as an indolent disease with a good prognosis and a moderate risk of metastasis as compared with conventional PTC.[4] This is probably due to the presence of a capsule, the well-differentiated character of the neoplastic cells, and the low proliferative activity of the tumor.

Limitations of this study are small cases and single institutional experience. Generalizing to small cases and single institutional experience can be a big mistake. Next step for us is to confirm these clinicopathologic characteristics of this rare variant of PTC.

5. Conclusion

Although MFV-PTC is rare entity, with 0.06% of incidence at our institution, the differential diagnosis on preoperative evaluation modalities is important because of its benign looking characteristics on ultrasonographic examinations. Clinicians should be aware of the characteristics of MFV-PTC and do not miss the possibility of MFV-PTC in preoperative examinations.

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