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Cytopathologic Features in Papillary Thyroid Cancer Arising From Benign Nodular Disease

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The presence of papillary thyroid carcinoma (PTC) arising from benign nodular disease (PTCAB) is a rare condition. Our study evaluates the clinicopathologic features of PTCAB. PTCAB is extremely rare, and its characteristics have not been well described. From April 2007 through March 2014, 323 patients with PTC were treated at Kangdong Sacred Heart Hospital. During this period, 10 cases of PTCAB were found. We also randomly selected 15 cases each of benign and papillary thyroid microcarcinoma (PTMC) for controls. We reviewed the medical records and the cytomorphologic features of fine-needle aspiration cytology and postoperative specimens. There was a significant difference in the rates of capsular invasion ($P = 0.003$) and lymphovascular invasion ($P = 0.040$) between the PTCAB and PTMC groups. Hashimoto's thyroiditis was more prevalent in the PTCAB group (62.5%, $P = 0.026$). The PTCAB group had a more even and variable distribution from category II to VI by the Bethesda Systems for Reporting Thyroid Cytopathology ($P < 0.001$). The most common cytomorphologic features of PTCAB were nuclear grooves (90%), pale chromatin (90%), and follicles (60%). Moderate to high cellularity and anisonucleosis were absent in 90% and 80%, respectively, of PTCAB cases. The only cytomorphologic feature significantly different between PTCAB and PTMC group was cellularity. Clinical characteristics were similar between PTCAB and PTMC. PTCAB has an overlapping pattern of cytomorphologic features between benign nodules and PTMC. However, most PTCAB cases contained a nuclear groove, pale chromatin, numerous follicles, and low cellularity, and these features help to establish a new diagnostic point for PTCAB.

Key words: Cytopathology — Fine-needle aspiration — Papillary thyroid carcinoma

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Thyroid cancer is one of the most common cancers in Korea.[1] In 2011, the age-adjusted incidence rates per 100,000 persons were 20.2 and 79.6 in men and women, respectively. Papillary thyroid cancer (PTC) accounts for about 97% of all cases.[2]

The only clear risk factor for PTC is radiation exposure. There are many studies about factors that may increase the risk of PTC. However, none of these factors has sufficient evidence to prove its involvement yet. It is thought that benign nodular thyroid disease is not a risk factor for PTC. However, several studies have shown the incidence of thyroid cancer to be 9%–17% in this population.[3,4] Interestingly, the presence of PTC foci in benign nodular thyroid disease has been noted. Ono *et al* reported that less than 0.9% of all PTC cases arise in follicular adenoma.[5]

PTC arising from benign nodular disease (PTCAB) is an uncommon histologically defined subtype of PTC that exists with the presence of PTC foci in benign nodular thyroid disease. It is extremely rare, and its characteristics have not been well described.

Pathologists have had difficulty determining whether the entire lesion in cases of PTCAB should be interpreted as malignant and whether they should classify PTCAB within the broader category of "well-differentiated tumor of uncertain malignant potential." Fusco *et al* asserted that it is possible that foci indicative of PTC in a hyperplastic or adenomatous nodule precede the development of the invasive form.[6] In terms of diagnosis, aspirates of PTCAB often exhibit features intermediate between those of a benign thyroid nodule and PTC, frequently resulting in their inclusion into the recently defined "atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)" category by the Bethesda System for Reporting Thyroid Cytopathology (BSRTC).[5–7]

The purpose of this study was to evaluate the clinicopathologic features of the rare PTCAB category. We sought to identify specific cytomorphologic features that could help distinguish PTCAB from pure benign nodules and pure PTC.

Methods

From April 2007 through March 2014, 323 patients with PTC underwent operations at OOO Hospital. PTCAB is histologically defined as PTC foci arising within benign nodular disease. Ten cases of PTCAB were found during this period (Fig. 1). We defined

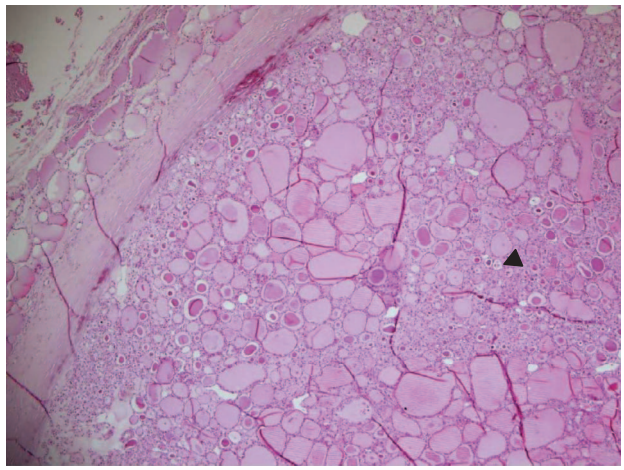

Fig. 1 Histology of papillary thyroid carcinoma arising from benign nodular disease (PTCAB). PTCAB was surrounded by nodular hyperplasia. Arrow shows fine chromatin with anisonucleosis. (H&E, x40)

the tumor size as the size of the PTC foci. There were no multifocal foci within benign nodular disease. We also collected cytological data from 15 randomly selected cases of pure benign nodules and 15 randomly selected cases of pure papillary thyroid microcarcinoma (PTMC) for comparison. Only PTMC was selected randomly as a control group and PTC, in which the size is more than 1 cm, was not selected as a control group because the size of the PTC foci in PTCAB is generally less than 1 cm.

All patients had undergone preoperative ultrasonography-guided fine needle aspiration (FNA) cytology. Samples were prepared by the liquid-based method.

The liquid-based method was as follows: The aspiration material was rinsed into a collection medium (CytoLyt solution, Cytyc Inc., MA, USA), and the cell suspensions were spun down at 600 g for 10 minutes. Then the supernatant was poured off, and the cell pellet was transferred to a second buffered fixative (PreservCyt solution, Cytyc). Next, the vials were placed into a processor (ThinPrep Processor 2000, Cytyc) in accordance with the instructions in the operator's manual and stained with hematoxylin and eosin.

The slides were sent to an experienced pathologist who reviewed cytologic and histologic slides to evaluate the features of the cases as well as to confirm the histologic diagnosis. The slides were systemically evaluated for 17 cytomorphologic features: cellularity, follicles, papillae, monolayers, small clusters, oncocytes, nuclear grooves, nuclear

Table 1 Cytomorphologic features evaluated in PTCAB and control groups

Cytomorphologic feature	Evaluation
Cellularity	Low to scant, medium to high
Follicle	Absent, present
Papilla	Absent, present
Monolayer	Absent, present
Small cluster	Absent, present
Oncocytes	Absent, present
Nuclear groove	Absent, present
Nuclear inclusion	Absent, present
pale chromatin	Absent, present
Dense chromatin	Absent, present
Anisonucleosis	Absent, present
Cytoplasm	Absent, present
Cystic fluid	Absent, present
Macrophage	Absent, present
Colloid	Absent, present
Giant cell	Absent, present
Psammoma body	Absent, present

PTCAB, papillary thyroid cancer arising from benign nodular disease.

inclusions, pale chromatin, dense chromatin, anisonucleosis, cytoplasm, cystic fluid, macrophages, colloids, giant cells, and psammoma bodies (Table 1, Fig. 2).

We reviewed the medical records of the patients, including sex, age, operative method, tumor size, lymph node metastasis, multifocality, presence of Hashimoto's thyroiditis, capsular invasion, and extrathyroidal extension.

We analyzed the statistical differences in each cytomorphologic feature among the three groups by Fisher's exact test. For the statistically different cytomorphologic features, we also evaluated the differences between each 2-group pair. Other continuous variables among the 3 groups were analyzed nonparametrically by the Kruskal–Wallis test. A P value of < 0.05 was considered statistically significant. Calculations were performed with the SPSS software package v. 18.0 (SPSS Inc., Chicago, IL, USA).

Results

The PTCAB group showed a female predominance (n = 9, 90%) and a mean age of 49 years (range, 34–70), for which there was no statistical difference among the 3 groups ($P = 0.410$). The PTC foci in the PTCAB group ranged in size from 1–10 mm in maximum diameter (mean 3.5 mm), and the entire tumor with the benign nodular lesion in the PTCAB group ranged from 4–41 mm in diameter (mean 15.6 mm). Interestingly, Hashimoto's thyroiditis was more prevalent in the PTCAB group (62.5%, $P = 0.026$).

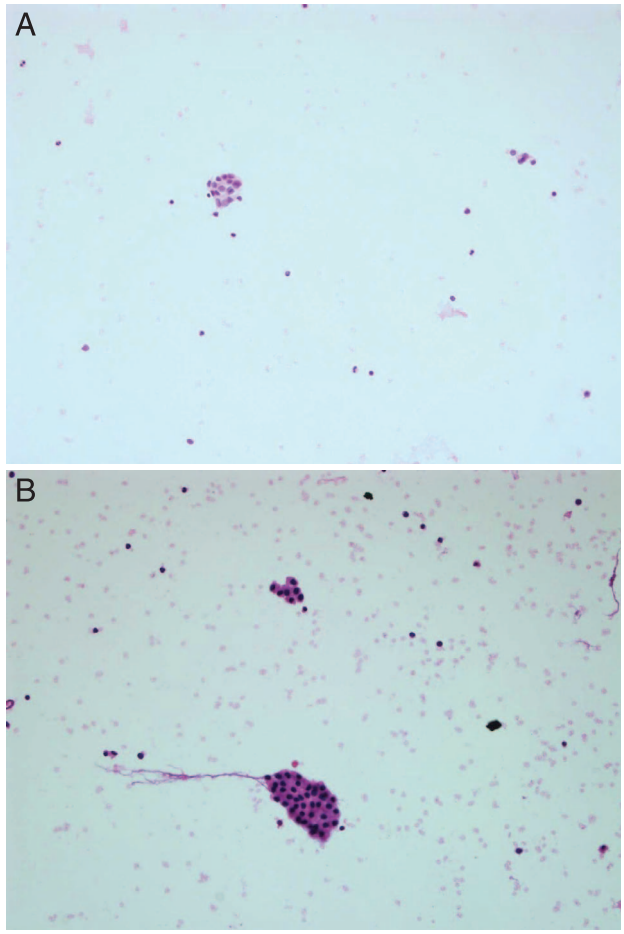

Fig. 2 Cytomorphologic features of papillary thyroid cancer arising benign nodular disease (PTCAB) and control groups. (a) PTCAB (b) nodular hyperplasia (c) papillary thyroid carcinoma (a–c, H&E, x200).

In the PTCAB group, the background benign nodular lesions of PTC were found to be follicular adenoma (n = 6, 60%), nodular hyperplasia (n = 3, 30%), and oncocytic adenoma (n = 1, 10%).

There was a significant difference in the rates of capsular invasion and lymphovascular invasion associated with the PTCAB and PTMC groups (Table 2). These features were less frequent in the PTCAB group than in the PTMC group (capsular invasion 0 versus 9, $P = 0.003$; lymphovascular invasion, 1 versus 8, $P = 0.040$). No other significant differences were observed between the 2 groups.

Based upon a blinded BSRTC review, the majority of cases in the pure benign and cancer groups were classified as Categories I and II and Categories V

Table 2 Pathologic features associated with PTCAB and PTMC group

	PTCAB (n = 10)	PTC (n = 15)	*P* value
Histologic variant			0.426
Conventional	8	14	
Follicular variant	1	1	
Oncocytic variant	1	0	
Capsular invasion			0.003
(+)	0	9	
(−)	10	6	
Extrathyroidal extension			0.500
(+)	0	2	
(−)	10	13	
Multifocality			0.653
(+)	3	3	
(−)	7	12	
Lymphovascular invasion			0.040
(+)	1	8	
(−)	9	7	
LN metastasis			0.397
(+)	5	4	
(−)	5	11	
Dissected LN (number)	7 ± 11.35	10 ± 9.71	0.520

Values are presented as number or mean ± standard deviation.

PTCAB, papillary thyroid cancer arising benign nodular disease; PTMC, papillary thyroid microcarcinoma.

and VI, respectively. The PTCAB group had more even and variable BSRTC distribution from Categories II to VI ($P < 0.001$) (Table 3).

Among the 17 cytomorphologic features evaluated, 7 features showed statistical differences between the benign and PTMC groups: nuclear groove, pale chromatin, dense chromatin, cellularity, follicles, monolayers, and anisonucleosis. Other features showed no differences.

The overall percentages of the cytomorphologic features of the PTCAB and control groups exhibited an overlapping pattern. The most common cytomorphologic features of PTCAB were a nuclear groove (90%), pale chromatin (90%), and follicles (60%), whereas moderate-to-high cellularity and anisonucleosis were absent in 90% and 80% of PTCAB cases, respectively (Fig. 3).

The only cytomorphologic feature different between the PTCAB and PTMC groups was cellularity. Ten cases (66.7%) showed moderate to high cellularity in the PTMC group; however, only 1 case (10%) had that feature in the PTCAB group ($P = 0.001$).

Discussion

PTCAB is an uncommon histologically defined subtype of PTC that exists in the presence of PTC foci in benign nodular thyroid disease. In our study, the incidence of PTCAB was low, only 3% of all PTC cases. There are no reports on the incidence of PTCAB, although Ono *et al*[5] reported that 0.9% of PTC cases arise in follicular adenoma, and at our institution, this figure was 1.8%. We suspect that this discrepancy is due to the small sample sizes of both studies (Ono *et al*, 17 cases; our institution, 6 cases).

In this study, the clinical characteristics of PTCAB and PTMC were similar. PTCAB had almost typical characteristics of thyroid cancer (extrathyroidal extension, multifocality, and cervical lymph node metastasis). However, there were several differences between PTCAB and PTMC. Capsular invasion and lymphovascular invasion were less frequent in the PTCAB group than in the PTMC group. That is why less invasive procedures were more frequently performed in the PTCAB group. It is also assumed that this is why there was a lower incidence of infiltrating adjacent tissue in PTCAB because the PTCAB was surrounded by benign cells.

Most malignancies appear to arise by a multistep process, including alterations in cell morphology and architecture. However, PTC has no known progression model. The association between Hashimoto's thyroiditis and PTC was first proposed by Daily *et al*[8] in 1955. The relationship between Hashimoto's thyroiditis and PTC has been studied

Table 3 Bethesda System for Reporting Thyroid Cytopathology review associated with PTCAB and control groups

	Nondiagnostic	Benign	AUS/FLUS	FN	Suspicious PTC	*P* vlaue
PTCAB	0	2	3	2	3	<0.001
Benign	3	7	1	4	0	
PTMC	0	0	0	1	14	

Benign versus PTCAB : $P = 0.046$

PTCAB vs PTMC : $P = 0.002$

PTCAB, papillary thyroid cancer arising benign nodular disease; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN, follicular neoplasm or suspicious for follicular neoplasm; PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma.

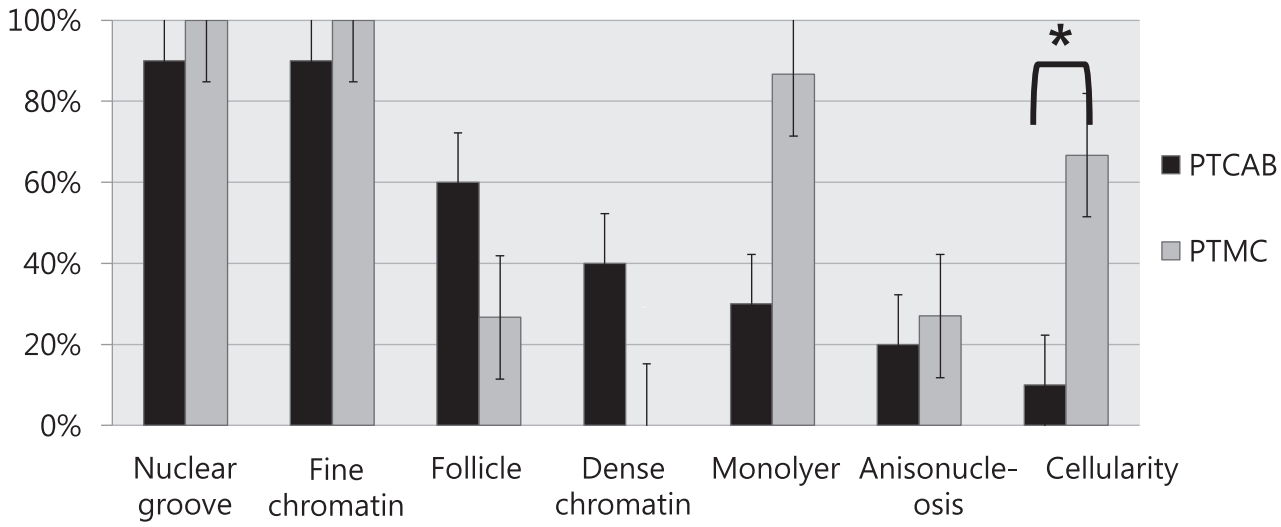

Fig. 3 Cytomorphologic features associated with PTCAB and PTMC groups. *P value < 0.05 PTCAB, papillary thyroid cancer arising from benign nodular disease; PTMC, papillary thyroid microcarcinoma.

because the concept of chronic inflammation leading to malignancy is well known for other tissues: inflammatory bowel disease to colorectal cancer, chronic esophagitis to esophageal cancer, and primary biliary cirrhosis to hepatocellular carcinoma.[9,10] However, there are still arguments as to whether Hashimoto's thyroiditis causes PTC or not. Interestingly, Hashimoto's thyroiditis was more frequent in the PTCAB group in our study. Although we cannot reach a definitive conclusion, our study may support the theory that Hashimoto's thyroiditis might play a role in causing an inflammatory environment that contributes to the development of PTCAB.

Until now, FNA has been the primary and most effective diagnostic tool for patients with thyroid nodules, with a high sensitivity and specificity. Thyroid aspirates are usually divided into 6 diagnostic categories by the BSRTC, including benign, AUS, FLUS, follicular neoplasm or suspicious for follicular neoplasm, suspicious for malignancy, malignant, and nondiagnostic.[7]

The necessary cytomorphologic criteria for a definitive diagnosis of PTC include large monolayer sheets of follicular epithelial cells with pale chromatin, intranuclear inclusions and nuclear grooves, and papillary structures.[11]

In this study, the cytomorphologic features of PTCAB exhibited an overlapping pattern between benign nodules and PTMC, and PTCAB lacked sufficient cytomorphologic features to be diagnostic of PTC. Thus, the PTCAB group had a variable BSRTC distribution from Categories II to VI, and only 30% of the PTCAB cases were diagnosed as PTC. More seriously, 20% of these lesions may be misdiagnosed as pure benign lesions. Although PTC has been known to have a favorable prognosis, the survival rate decreases in advanced stages. Therefore, misdiagnosis in this PTCAB group can result in deteriorating outcomes.

One of the limitations of FNA is the reliance of this technique on adequate sampling of the lesion. The diagnostic accuracy of thyroid FNA is affected by nodule heterogeneity.[12] Therefore, we evaluated the cytomorphologic features of FNA specimens from PTCAB and compared these features with those of pure PTMC to establish a new diagnostic point for PTCAB. Most PTCAB cases contained nuclear grooves, pale chromatin, and numerous follicles, and these cytomorphological features are typical in PTC. However, only 10% of PTCAB cases had moderate to high cellularity, which was close to the value for benign nodules.

Despite the positive finding as it evaluated clinicopathologic features of PTCAB, which is a very rare type of PTC, our study is limited by its small sample size and low statistical power. An additional limitation arises from the short duration of follow-up. A significantly longer follow-up duration would be necessary to determine whether the prognosis of PTCAB is similar to that of pure PTC.

We did not evaluate molecular and genetic markers. However, Fusco *et al* reported that accord-

ing to evaluations of RET/PTC oncogene activation and clonality of microscopic foci of PTC in a hyperplastic or adenomatous nodule, RET/PTC rearrangements are restricted to the focal areas containing nuclear features of PTC and are absent from the surrounding benign-appearing nodule.[3] Although the role of genetic markers in identifying PTCAB is unclear, this shows that the use of genetic markers can help in diagnosing PTCAB.

In conclusion, our study evaluated the clinical and cytomorphologic features of a rare type of PTC, PTCAB. PTCAB had almost typical thyroid cancer characteristics, such as extrathyroidal extension, multifocality, and cervical lymph node metastasis, and the clinical characteristics of PTCAB and PTMC were similar. The cytomorphologic features of PTCAB exhibited an overlapping pattern between benign nodules and PTMC, and PTCAB lacked sufficient cytomorphologic features to be diagnostic of PTC by the BSRTC. However, most PTCAB cases contained nuclear grooves, pale chromatin, numerous follicles, and low cellularity, and these features will help to establish a new diagnostic point for PTCAB.

Acknowledgments

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