Age- and Gender-Specific Risk of Thyroid Cancer in Patients with Familial Adenomatous Polyposis

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Context: The cribriform-morula variant of papillary thyroid carcinoma (CMV-PTC) is a rare variant of papillary thyroid carcinoma (PTC) and is associated with familial adenomatous polyposis (FAP). However, the incidence and the nature of CMV-PTC among FAP patients have not been well characterized.

Objective: The aim of this study was to determine the incidence and characteristics of thyroid cancer screened by neck ultrasonography for FAP patients.

Design, Patients and Intervention: A total of 129 FAP patients were included in this study. Neck ultrasonography was performed using a 12.0 MHz transducer probe. Germline *APC* gene mutation was examined for by the protein truncation test (PTT) or DNA sequencing methods.

Results: Twenty-one patients (16.3%) had solid nodules, and 24 patients (18.6%) had benign cystic nodules. In total, PTC was found in 11 patients (16% of the women and 0% of the men), 8 of which were CMV-PTC and the rest were classical PTC. In 17 female patients with thyroid nodules, CMV-PTC occurred in 8 of 9 patients who were 35 years age or younger, but in none of the 8 patients who were older than 36 ($p=0.0004$ by Fisher's exact test). The *APC* germline mutations in 8 patients with CMV-PTC were present at the 5′ side of the profuse type of FAP region (codons 1249–1330).

Conclusions: The prevalence of CMV-PTC in FAP patients was higher than previously reported and this type of tumor was found preferentially in younger (under age 35) female patients with FAP in this cohort.

Familial adenomatous polyposis (FAP) is an autosomal dominant polyposis syndrome that is characterized by hundreds of colorectal adenomatous polyps. The major causative gene for FAP is the *APC* gene, which is located in the 5q21 region. Individuals with a germline *APC* gene mutation have an almost 100% risk of developing colorectal cancer during their life time. Gastric or duodenal polyps, desmoid tumors, congenital hypertrophy of retinal pigmentation, and thyroid cancer are other well-known extracolonic manifestations of FAP. Crail (1) was the first to publish a case report of brain and thyroid carcinomas in a patient with FAP. Since this report, many papers have further documented this interesting association; however, the histological characteristics of thyroid cancer in FAP patients were not described until the 1990's. Harach et al (2) first described the histological characteristics as a cribriform pattern with solid areas and a spindle cell component. This specific tumor subtype is known as the cribriform-morula variant of papillary thyroid carcinoma (CMV-PTC).

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Abbreviations: FAP: familial adenomatous polyposis; CMV-PTC: cribriform-morula variant of papillary thyroid carcinoma; PTC: papillary thyroid carcinoma; H&E: Hematoxylin and Eosin; FNABC: fine-needle aspiration biopsy cytology; ER: estrogen receptor; PgR: progesterone receptor

In young female FAP patients, the incidence of thyroid cancer before age 35 is 160 times higher than in the general population (3). This figure is based on the clinical incidence of thyroid cancer, ie, cancers that are discovered due to the presence of clinical symptoms or a palpable neck nodule in FAP patients. The prognosis of FAP patients once depended on colorectal cancer outcomes, but recent advances in the management of colorectal cancer have successfully improved colorectal cancer survival. Now that deaths due to colorectal cancer can be prevented, the early discovery and treatment of the extracolonic manifestations of FAP have becomes increasingly important.

Thyroid carcinoma in FAP patients is thought to be relatively rare; with an approximate rate of 0.4–1.3%, according to a retrospective review of large registries (4–7). However, the results of these studies were based on retrospective observations, mainly in symptomatic patients. Thyroid cancer in FAP patients is generally indolent and has few clinical symptoms. Recent progress in high-resolution ultrasonographic devices for imaging has made ultrasonography the first choice for detecting thyroid nodules even if the nodules are too small to palpate. The incidence of thyroid cancer in FAP patients may be underestimated in the absence of ultrasonographic screening; the true incidence of thyroid cancer among FAP patients therefore unknown. The aim of this study was to use systematic ultrasonographic screening to investigate the incidence of thyroid cancer and its association with *APC* gene mutations in FAP patients.

Materials and Methods

Patients

One hundred twenty-nine Japanese patients belonging to 95 families with FAP who treated between May 2008 and October 2010 at the Ishikawa Clinic, Osaka, Japan were entered in this study. The patients included 60 males and 69 females. Thirty-nine of the patients had undergone colorectal surgery; specifically ileo-anal anastomosis (IAA) in 7 patients, ileo-anal canal anastomosis (IACA) in one patient, ileo-rectal anastomosis (IRA) in 26 patients, right colectomy in two patients, left colectomy in one patient and colostomy in two patients. The remaining 90 patients had not undergone colorectal surgery and were followed up with periodic colonoscopies, with or without extensive polypectomy. Two female patients had previously undergone thyroidectomy for thyroid cancer at another hospital prior to this study. Hematoxylin and Eosin (H&E)-stained specimens from these thyroid carcinomas were requested by our study group and examined by Dr. Hirokawa, an expert pathologist. Another 127 patients had not previously undergone thyroid screening.

This study was approved by the ethics committee of Noguchi Thyroid Clinic and Hospital Foundation, Oita, Japan and Kyoto Prefectural University of Medicine, Kyoto, Japan. The ethical review for protocol performing this study in Ishikawa Clinic and Kuma Hospita l was delegated to the review boards in Noguchi Thyroid Clinic c and Hospital Foundation, and the protocol was approved. All patients provided written informed consent for neck ultrasonographic screening. The *APC* gene was analyzed in 120 patients, who gave written informed consent for the gene study.

Ultraosonographic thyroid screening

Thyroid ultrasonography was performed using a LOGIQ e Expert with a 12.0 MHz 12L-RS transducer probe (GE Health Care Japan Inc. Japan) at the Ishikawa Clinic. An expert ultrasonographer at Kuma Hospital, Osaka, Japan reexamined patients in whom the first ultrasonographic screening had identified a thyroid nodule. For solid thyroid nodules that were larger than 5 mm in diameter, fine-needle aspiration biopsy cytology (FNABC) was performed. When the thyroid nodule shows entirely cystic and there are no solid components in ultrasonographic imaging, the nodule is diagnosed as cyst. In patients with cystic thyroid nodule(s) (whether single or multiple), FNABC was deferred, and the patients were observed. When the FNABC findings were suspicious for malignancy, surgery was recommended. Thyroid operations consisted of total thyroidectomy with central compartment dissection of the neck and were performed at Kuma Hospital.

Immunohistochemical evaluation

In tumors that were diagnosed as CMV-PTC, immunohistochemical analyses of β-catenin, the estrogen receptor (ER), progesterone receptor (PgR) and Ki-67 (MIB1) were also performed

Table 1. Age of patients and results of neck ultrasonographic screening

		All (n = 129)	Men (n = 60)	Women (n = 69)
Age	Average	40.0 +/- 15.4	41.2 +/- 15.5	39.0 +/- 15.3
	Median	37.0	38.5	36.0
	Range	17–83	17–83	17–83
Previous thyroid surgery		2	0	2
Solid tumor(s)		21	6	15
	Solitary	12	6	6
	Multiple	9	0	9
Cyst(s)		24	7	17
	Solitary	12	4	8
	Multiple	12	3	9

using 4-μm-thick, formalin-fixed, paraffin-embedded tissues. Immunostaining was performed using the automated Leica Bond-Max system and Bond Refine detection kit (Leica Microsystems, Wetzlar, Germany) according to the manufacturer's instructions. The antibodies used were as follows; β-catenin (β-catenin1, mouse monoclonal antibody, 1:200 dilution, Dako, Carpinteria, CA), ER (clone 6F11, mouse monoclonal antibody, 1:400 dilution, Novocastra, Newcastle, UK), PgR (clone PgR636, mouse monoclonal antibody, 1:200 dilution, DAKO), and Ki-67 (clone MIB-1, mouse monoclonal antibody, 1:200 dilution, Dako) (8).

Genetic analysis

APC germline mutation was investigated with the protein truncation (PTT) assay or DNA sequencing from peripheral blood leukocytes according to a previously published method (9–11). The PTT assay was performed at Otsuka assay company, Tokushima, Japan. Dr. T. Yoshida and M. Ushiama, of the Genetics Division of the National Cancer Center Research Institute, Japan performed DNA sequencing.

Statistical analysis

Statistical analyses were performed with the χ^2 test or Fisher's exact test, using SAS JMP software version 9 (SAS Institute Inc.).

Results

Ultrasonographic thyroid screening and diagnosis of PTC

The average age of the 129 patients in the present study was 40.0 +/- 15.4 years, with a median age of 37 years (range; 17–83 years old). There were no significant differences in the age of the male and female patients (Table 1). Ultrasonographic screening identified thyroid nodules in 45 patients (34.9%). Twenty-one patients (16.3%) had solid nodules (solitary in 12 and multiple in 9), and 24 patients (18.6%) had benign cysts (solitary in 12 and multiple in 12, Table 1). During follow-up, cystic nodule(s) had not enlarged and no thyroid nodule suspected for cancer had been emerged in all patients with cystic nodule(s).

In 6 male patients who had a solitary solid nodule (5–22 mm in diameter on ultrasonography), cytology was benign; these patients were closely followed and did not receive therapy (Table 2 and Figure 1A). None of the male patients had multiple solid nodules.

Table 2. Association of neck ultrasonography with cytological/histological diagnosis

Diagnosis of Neck Ultrasonography	Number of Patients	Benign Tumor	typical PTC	CMV-PTC
Solid tumor(s)	21	12	3	6
Solitary (Men)	6	6	0	0
Multiple (Men)	0	0	0	0
Solitary (Women)	6	3	2	1
Multiple (Women)	9	3	1	5

In 6 female patients who had a solitary solid nodule (7–46 mm in diameter on ultrasonography), PTC was diagnosed by FNABC in 3 patients (classical PTC in 2 and CMV-PTC in one). In one 24-year-old patient with classical PTC (Patient A in Table 3), the nodule was 7 mm in diameter and was located in the isthmus; this patient underwent total thyroidectomy with central compartment dissection. Microscopic lymph node metastases were present (2/6). Patient B is a 36-year-old with a 6-mm classical PTC; the patient refused surgery and is presently under close observation. Patient J, aged 32 years, had an 8-mm CMV-PTC; this patient also opted to not have surgery and is being observed as well.

In 9 female patients with multiple solid nodules (6–30 mm in diameter according to ultrasonography), PTC was diagnosed cytologically in 6 patients; classical PTC was found in 1 patient, and CMV-PTC was diagnosed in 5 patients (Figure 1B, 1C and 1D). One 47-year-old patient with classical PTC (Patient C) had multiple cancers in the left lobe, with a maximum tumor diameter of 10 mm. This patient underwent total thyroidectomy with central compartment dissection. Microscopic lymph node metastases were absent (0/13). Five patients aged 18, 22, 25, 27 and 35 years (Patients D, G, H, I and K, respectively), had CMV-PTC and underwent total thyroidectomy with central compartment dissection. The maximum tumor diameters were 7, 5, 32, 12 and 10 mm, respectively. None of these patients had invasion outside the thyroid gland or lymph node metastases (0/0, 0/12, 0/4, 0/5, and 0/7, respectively). Immunohistochemistry for β-catenin, estrogen receptor and progesterone receptor was positive in all CMV-PTCs (Figure 1E and 1F) and negative in all classical PTCs. The tumor cells of CMV-PTCs demonstrated nuclear and cytoplasmic expression of β-catenin, strong nuclear positivity for estrogen receptor and strong nuclear positivity for PgR. The MIB-1 labeling index was also positive in all CMV-PTCs (5%–10% in 4 patients and 0%–5% in 1). The 2 female patients who had undergone previous thyroid surgery had CMV-PTC upon further pathologic examination (Patients E and F).

In total, PTC was found in 11 patients (16% of females); 8 of these nodules were CMV-PTC. In 17 female patients with solid thyroid nodules, including 2 patients who had previous thyroid surgery (aged 37.9 $\pm$ 16.3 years, range 18–79 years), CMV-PTC was found in 8 of 9 patients aged 35 years or younger, and in none of the 8 patients who were older than 36 years ($P = .0004$ by Fisher's exact test). The average age of the patients with CMV-PTC was 24.8 +/- 6.2 years old.

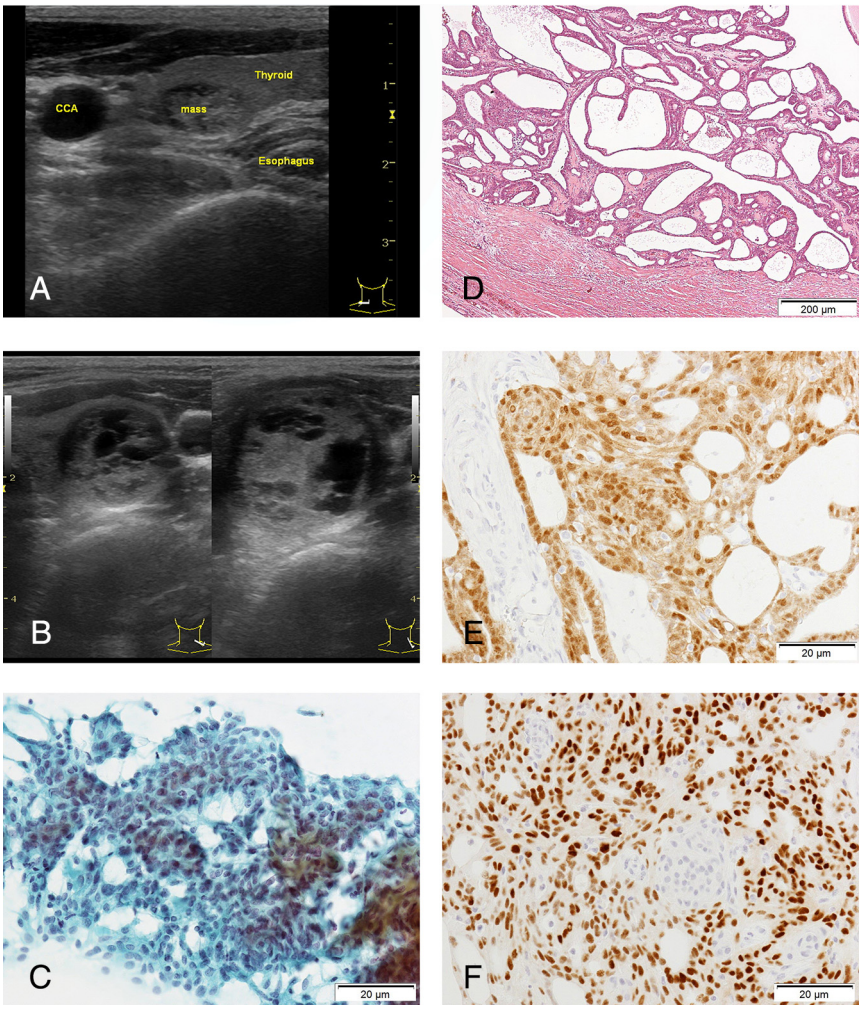

Figure 1. Ultrasonographic, Cytopathological and Histopathological Findings of Thyroid Nodules in FAP Patients. A, Ultrasonography shows an iso- to low echoic solid nodule in a 63-year-old-man. The nodule was located in the left lobe, with a maximum diameter of 11 mm. FNABC showed a benign nodule, and the patient is now being followed. Mass: thyroid nodule, CCA: common carotid artery. B, Ultrasonography shows an iso- to low echoic solid nodule with multiple small cystic changes in patient H. The nodule was located in the left lobe, with a maximum diameter of 30 mm. FNABC showed CMV-PTC, and total thyroidectomy was performed. C, The photograph shows the cytopathologic findings of CMV-PTC in patient H (x40). The tumor cells show hypercellularity, a cribriform pattern, morules, peculiar nuclear clearing and the absence of colloid in the background. The findings are typical for CMV-PTC. D, The photograph shows the histopathology of hematoxylin-eosin-stained CMV-PTC in patient H (x10). The cribriform pattern without colloid content, formed by the carcinoma cells, is a special feature of the tumor. E, Immunohistochemical staining for β-catenin demonstrates nuclear and cytoplasmic accumulation due to an *APC* germline mutation in patient I (x40). F, Immunohistochemical staining for the estrogen receptor in patient I (x40). Strong nuclear accumulation is noted in the tumor cells.

Association between PTC development and mutations

PTT and/or DNA sequencing was performed in 120 patients. A PTT assay was performed in 100 patients and DNA was sequenced in 32 patients. Both PTT and sequencing were performed in 12 patients. Table 4 summarizes the results of the PTT and sequencing analyses. The sites of the mutations were divided into regions A-F of the *APC* gene based on the PTT assay. Ninety-one of the 120 (75.8%) patients had *APC* germline mutations. Patients with CMV-PTC had mutations at region A (codons 2–479) in 4 patients, region B (codons 348–758) in 1 patient, and region C (codons 658–1283) in 3 patients. Patients with classical PTC had mutations at region A in 1 patient, region C in 1 patient and deletion at the *APC* locus in 1 patient. DNA sequencing showed *APC* germline mutations at codons 159 (n = 2), 161, 302, 689, 964, 1068, and 1157, Table 3).

Discussion

The risk of developing thyroid cancer has been known to be much higher in FAP patients than in the normal population but previous studies have reported that the incidence of thyroid cancer among FAP patients was only approximately 1%. Plail et al (3), in an analysis of 998 FAP patients from the FAP registry at St. Mark's Hospital in London, reported a 160-fold increased risk of developing a thyroid carcinoma before the age of 35 years in FAP patients compared to the normal population. Of special note is that thyroid cancer was first reported being very common in younger patients, especially before the age of 35. However, the incidence of thyroid cancer in Plail's report was only 0.7% (7/998). Many other studies have also observed that the incidence of differentiated thyroid carcinoma in FAP patients is between 0.4–1.3% (4–7, 12). However, these data were retrospective reviews of registry data that depended on the presence of clinical symptoms (such as neck swelling) for diagnosis, and did not perform systematic thyroid screening tests. Because most FAP patients die from colorectal cancer and the prognosis of thyroid cancer is favorable, little attention has been paid to detecting occult thyroid nodules in FAP patients (13).

Some investigators have recommended careful palpation of the thyroid gland and cervical lymph nodes, especially in young women, to screen FAP patients for thyroid nodules (3). Recent advances in high-resolution ultra-

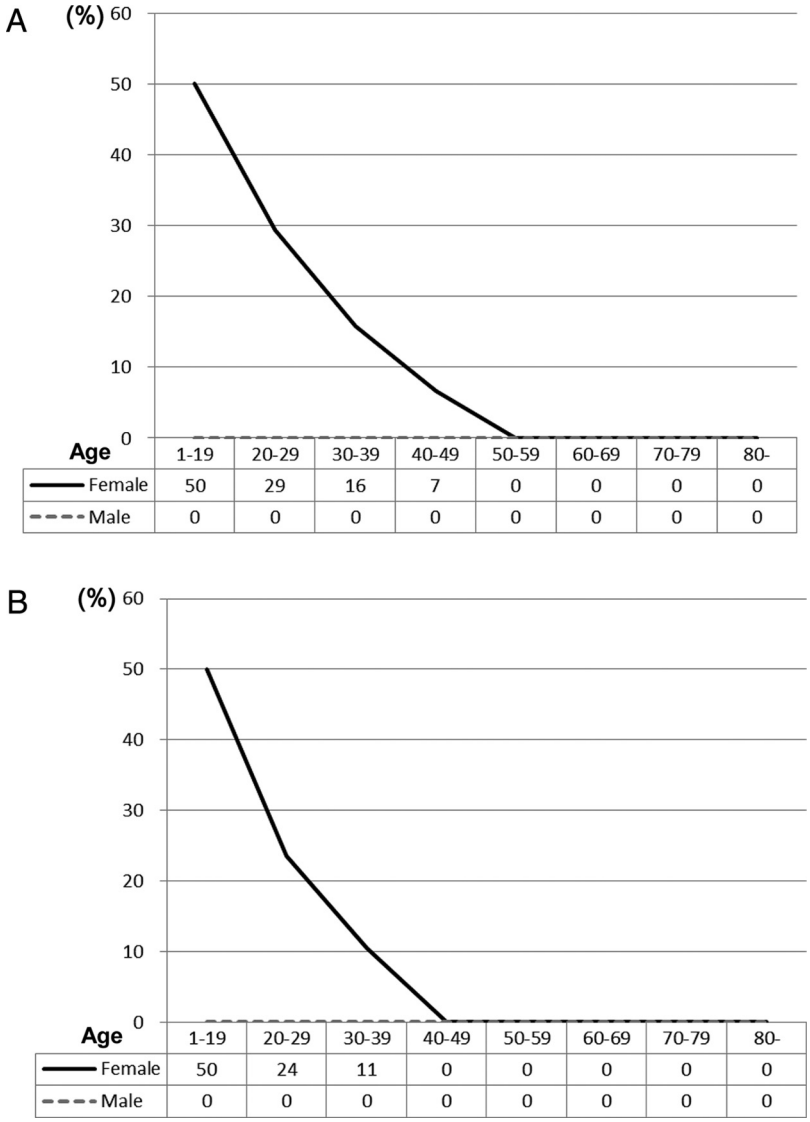

Figure 2. Incidence of Thyroid Cancer by Age and Sex in FAP Patients. A, Incidence of papillary thyroid cancer (both classical type and CMVPTC) by age and sex. Straight line denotes female and a dotted line denotes male. B, Incidence of CMVPTC by age and sex. Straight line denotes female and a dotted line denotes male.

sonography have enabled the detection of small, nonpalpable thyroid nodules and can distinguish benign from malignant nodules by the combined use of FNABC. Currently, thyroid ultrasonography is routinely used for patients with palpable nodules as well as for patients without clinical symptoms. In a retrospective chart review of the High-Risk Gastrointestinal Cancer Clinic, Herraiz et al (14) reported that PTC was diagnosed in 6 of 51 (12%) FAP patients. CMV-PTC was found in five female patients, and classical PTC was found in one female patient. In this series, ultrasonography was used in 28 of 51 patients, and detected thyroid nodules in 22 (79%) patients who had at least one ultrasonographic screening. PTC was found in 2 (7%) patients who underwent ultrasonography. Recently, Jarrar et al (15) also performed ultrasonographic screening for thyroid cancer in 192 patients with FAP. In this series, 72 (38%) had thyroid nodules, 5 (2.6%) had PTC, and only one had CMV-PTC. In their retrospective review of 664 FAP patients in a registry, 14 (2.1%) were found to have thyroid cancer. Eleven of the 14 were female. Although the incidence of thyroid cancer was slightly higher than previous estimates, these figures are much lower than our observation that PTC occurred in 16% of female FAP patients. One of the main reasons for the different incidence rates may be the criteria for performing FNABC. Jarrar et al performed FNABC for nodules that were larger than 10 mm in diameter. In contrast, we performed FNABC for solid nodules that were larger than 5 mm. In fact, the maximum tumor diameter in 7 of the 9 newly diagnosed PTC in our study was less than or equal to 10 mm. Another reason for the discrepancy may have been due to the difficulties of diagnosing CMV-PTC in cytological specimens. The cytological findings of CMV-PTC show unusual features, and expertise is needed to diagnose this disease (8). CMV-PTC is an extremely rare variant of papillary thyroid carcinoma, representing approximately 0.16% of all thyroid malignancies (16). Therefore, it is comparatively difficult, even for experienced cytologists, to diagnose CMV-PTC in cytological specimens because of its rarity.

With respect to genetic abnormalities in patients with CMV-PTC, Cetta et al (17) reported that 21 of 24 *APC* germline mutations were found in exon 18, the distribution of these mutations was associated with the CHRPE region (congenital hypertrophy of the retinal pigment epithelium, ie, codons 463–1387). Truta et al (18) reported that germline mutations were predominantly found proximally to the mutation cluster region (codons 1286–1514). In this study, only 4 of 8 (50%) mutations were located in the CHRPE area and no mutations were found in the mutation cluster region. In fact, the other 4 mutations were located in the 5′ side from the CHRPE region. All mutations were located in the 5′ side of the region specific for profuse type of FAP (codons 1249–1330) (19,

Table 3. Details of FAP patients with papillary thyroid carcinoma

			Histology or	Operation	Solitary or	Tumor		*APC* Germline
No.	Age	Sex	Cytology of PTC	Procedure	Multiple	Diameter (mm)	LN metastasis	Mutation
A	24	F	Classical	Total Tx	solitary	7	2/6	c.3593C>G, p.S1198X
B	36	F	Classical	not performed	solitary	6		c.508 9del2GA
C	47	F	Classical	Total Tx	multiple	10	0/13	Deletion at *APC* locus
D	18	F	Cribriform variant	Total Tx	multiple	7	0/0	codon964~966 TTAAATAGT>AAGT
E	19	F	Cribriform variant	op. before	solitary	NA	none	c.476dupA
F	20	F	Cribriform variant	op. before	solitary	NA	none	c.2065 2066del1GC
G	22	F	Cribriform variant	Total Tx	multiple	10	0/12	c.477C>A, p.Y159X
H	25	F	Cribriform variant	Total Tx	multiple	32	0/4	c.481C>T, p.Q161X
I	27	F	Cribriform variant	Total Tx	multiple	12	0/5	c.3469G>T, p.E1157X
J	32	F	Cribriform variant	not performed	slolitary	8		c.3202 3205del4TCAA
K	35	F	Cribriform variant	Total Tx	multiple	10	0/7	c904C>T, p.R302X(TGA)

Total Tx; total thyroidectomy, NA; not assessed.

Table 4. Association of thyroid tumor with *APC* germline mutation

		Women					Men				
Region of *APC* Mutation (codons) or Deletion	**Total Number of Patietns**	Number of Patients	Cyst	Benign Tumor	Classical PTC	CMV-PTC	Number of Patients	Cyst	Benign Tumor	Classical PTC	CMV-PTC
RegionA (2–479)	33	21	7	3	1	4	12	0	1	0	0
RegionB (348–758)	17	11	2	0	0	1	6	0	0	0	0
RegionC (658–1283)	28	20	6	2	1	3	8	0	0	0	0
RegionD (1099–1700)	4	3	0	0	0	0	1	0	0	0	0
Region E-F (1547–2843)	0	0	0	0	0	0	0	0	0	0	0
Region, unspecified	7	5	0	0	0	0	2	0	0	0	0
Deletion at the *APC* locus	2	1	0	0	1	0	1	0	1	0	0
No mutation	29	6	2	1	0	0	23	6	2	0	0
Not examined	9	2	0	0	0	0	7	1	2	0	0

20). We previously reported a case of 25-year-old woman with FAP-associated CMV-PTC who carried a germline mutation within the mutation cluster region (21). Six of the patient's 12 tumors contained *APC* somatic mutations that were concentrated in codons 308–935. Several papers also have described germline and somatic *APC* mutations in FAP-associated CMVPTC (22, 23). Five of 8 germline mutations found in this study were within codons 308–935, and the remaining 3 were outside from this area. Further examinations for somatic mutations in these tumors could resolve this question. Furthermore, we found nuclear and cytoplasmic accumulation of β-catenin in the tumor cells of CMV-PTC; β-catenin may accumulate because of the loss of the β-catenin binding site (codons 1020–1169) of the APC protein (which is truncated due to the 5′ side of the mutation) and the inability of β-catenin to bind to the APC protein. As a result, degradation of β-catenin cannot proceed, and β-catenin accumulates in the cell nucleus and cytoplasm. From our results of immunohistochemistry, we speculate that abnormal expression of ß-catenin, estrogen receptor and progesterone receptor is associated with the development of CMV-PTCs of patients with abnormal structure of APC protein.

It is well known that CMV-PTC is found in younger female FAP patients, especially in those younger than 35 years old. In this paper, systematic ultrasonographic screening confirmed the absence of CMV-PTC in all male FAP patients and female FAP patients who were over 35 years. It is difficult to determine why this phenomenon occurs in CMV-PTC. ERα was immunoreactive in the nucleus of CMV-PTC cases, unlike classical PTC. The different expression pattern of ERα may be the key to the female preponderance of this disease. Furthermore, CMV-PTC may spontaneously regress after the age of 35 years in women. There have been many reports of spontaneous tumor regression, including neuroblastoma, lymphoma, and others (24–28). Although the exact mechanism of spontaneous regression remains a mystery, various mechanisms have been proposed. Neuroblastoma is the best-known example of spontaneous regression of a tumor. Neuroblastomas expressing TrkA (tropomyosin receptor kinase A) are biologically favorable and prone to spontaneous regression of differentiation (29). TrkA plays an important role in the regulation of growth, differentiation and programmed cell death of neurons in the peripheral and central nervous systems. Interestingly, rearrangement of the *TrkA* gene is also found in some PTCs and is thought to activate the RAF-MEK-ERK pathway (30). The expression of TrkA may help explain this phenomenon in CMV-PTC.

In conclusion, the rate of CMV-PTC found in FAP pa-

tients by ultrasonographic screening was higher than previously reported. Careful follow-up without thyroid surgery may put into a strategy for these asymptomatic female FAP patients whose thyroid nodules are suspected for CMV-PTC.

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