

## Cribriform-morular variant of papillary thyroid carcinoma: an indication to screen for occult FAP

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**Abstract** Cribriform-morular variant (CMV) is a rare subtype of papillary thyroid carcinoma (PTC) that is associated with familial adenomatous polyposis (FAP). Given the high likelihood for multi-organ malignancies in FAP patients, this study explores the yield of diagnosing occult FAP among CMV-PTC patients. Institutional database was searched in order to identify patients with pathologically-confirmed CMV-PTC from 2000 to 2012. Medical records were reviewed, and clinical and pathological features were analyzed. Eleven cases of CMV were identified from 6,901 patients with PTC, for a prevalence of 0.16 %. All 11 patients were female. The median age at CMV-PTC diagnosis was 36 years (range 18–46). Two patients had pre-existing FAP at the time of PTC diagnosis. The other nine patients were referred for colonoscopy and/or genetic testing. Six patients underwent colonoscopy and one (17 %) was diagnosed with FAP based on polyposis phenotype and

genetic testing. The mean age of patients at the time of CMV-PTC diagnosis was younger in the FAP group (23 years, range 18–34) than in the sporadic group (37 years, range 25–46). All three patients with FAP-associated CMV-PTC had multicentric tumors, while all five sporadic patients did not. Our study found that approximately one-sixth of patients with CMV-PTC may have occult FAP. Patients with FAP-associated CMV-PTC appear to be younger and more likely to have multicentric tumors than those with sporadic CMV-PTC. Due to the increased risk of malignancy in patients with FAP, patients with CMV-PTC should be referred for colonoscopy and/or genetic evaluation for FAP.

**Keywords** Familial adenomatous polyposis · Cribriform-morular variant · Papillary thyroid carcinoma · Hereditary colorectal cancer

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### Introduction

Cribriform-morular variant (CMV) is a rare subtype of papillary thyroid carcinoma (PTC) that is often associated with familial adenomatous polyposis (FAP) [1, 2]. Since FAP, which is inherited in an autosomal dominant fashion, is characterized by multiple adenomatous polyps in the colon and rectum and a near certainty of developing colorectal cancer unless a risk-reducing prophylactic colectomy is performed, early identification and intervention in FAP patients is essential. FAP is also associated with several extracolonic malignancies, including malignancies of the upper gastrointestinal tract, hepatobiliary tract, central nervous system, and endocrine system [3]. While many individuals are diagnosed with FAP due to the discovery of colorectal polyps, the identification of CMV

histology in patients with PTC provides clinicians with a unique opportunity to diagnose occult cases of FAP.

The prevalence of PTC among individuals with FAP has been reported to be 0.4–12 % [1, 4–11], and several institutions have recently implemented prospective thyroid ultrasound (US) screening programs to increase early detection of thyroid abnormalities in the FAP population [10, 12, 13]. Forty-five years after the relationship between FAP and PTC was first identified [14]. Harach et al. discovered that many cases of FAP-associated PTC had distinct pathological features, including a cribriform pattern [2]. Although CMV accounts for only approximately 0.16 % of all PTC cases [15], reports suggest that up to 90 % of FAP-associated PTC have CMV histology [4]. One of seven (14.3 %) FAP patients with PTC in our institution's Hereditary Colorectal Cancer Family Registry has CMV morphology [13].

The purpose of this study is to evaluate the yield of diagnosing occult cases of FAP among patients with CMV-PTC at a specialized cancer care center over a 12-year period, and to enhance the small body of literature on this topic by further clarifying any clinical or pathological features that could possibly distinguish FAP-associated CMV-PTC from sporadic CMV-PTC.

## Methods

The medical records of patients with pathologically-confirmed diagnoses of CMV-PTC between 2000 and 2012 were retrospectively reviewed within a specialized cancer care center. Demographic and clinical data including age, sex, and personal and family history of polyps and/or thyroid disease were extracted. Pathology reports were analyzed for clinical features of CMV-PTC. Referrals for colonoscopy and/or genetic testing for FAP and subsequent test results were recorded. Fisher's exact and the Mann–Whitney U tests were used to detect statistical differences for categorical and continuous variables, respectively.

## Results

Eleven pathologically-confirmed cases of CMV-PTC were identified from a total of 6,901 patients with PTC who were treated at our institution during the study period, for an estimated prevalence of 0.16 %. All 11 (100 %) patients with CMV-PTC were female. The median age at diagnosis of CMV-PTC was 36 years (range 18–46). One (9 %) patient had a personal history of benign thyroid disease. Five (46 %) patients had personal or family histories of colonic polyps. The patients in the study cohort underwent

**Table 1** PTC-CMV features and treatment

	Patients with CMV-PTC (%) n = 11
<i>Tumor location</i>	
Right lobe	2 (18)
Left lobe	5 (46)
Both lobes	4 (36)
<i>Thyroid cancer features</i>	
Median diameter of largest tumor per patient (cm)	2.05 (range 1–5.8)
Lymph node metastases	1 (9)
Capsular invasion	8 (73)
Extrathyroid extension	2 (18)
Tumor multicentricity	3 (27)
Aberrant $\beta$ -catenin staining	8 (73)
<i>Surgical treatment</i>	
Total thyroidectomy	9 (82)
Left thyroidectomy with isthmusectomy	1 (9)
Partial followed by completion thyroidectomy	1 (9)
<i>Radioactive iodine ablation</i>	
	5 (46)

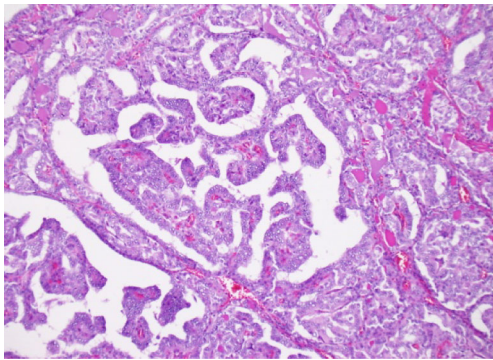
thyroid evaluation for various reasons. Five (46 %) patients were found to have an enlarged thyroid on routine physical examination. Three (27 %) patients sought medical workup due to symptoms of lethargy, neck pain, dizziness and vertigo. One (9 %) patient self-detected a thyroid mass, while the reasons for thyroid evaluation of two (18 %) patients are unknown.

The clinical and pathological features and treatment of the 11 cases of CMV-PTC are summarized in Table 1. Photomicrographs of PTC and CMV-PTC are displayed in Fig. 1. To the best of our knowledge, no patient has had PTC recurrence. One patient, who also had FAP, died 1.9 years after CMV-PTC diagnosis due to progressive peritoneal carcinomatosis from an ovarian cancer.

Two of the 11 (18 %) patients had pre-existing diagnoses of FAP at the time of PTC diagnosis. The other nine patients were all referred for colonoscopy and/or genetic testing by their physicians because of a CMV-PTC diagnosis. Three of the nine referred patients were lost to follow up and did not, according to available records, undergo a colonoscopy or genetic testing. Of the six patients who did undergo colonoscopy, one (17 %) was diagnosed with FAP based on polyposis phenotype and subsequent confirmation with genetic testing. The remaining five patients had negative colonoscopies; two of those patients also underwent genetic counseling due to a family history of colorectal polyps. Of these two patients, one underwent genetic testing which was negative for an *APC* gene

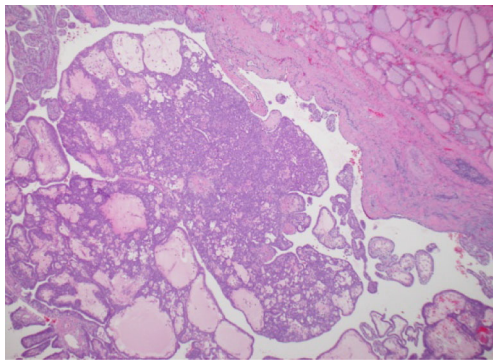
**PTC**

**(A)**

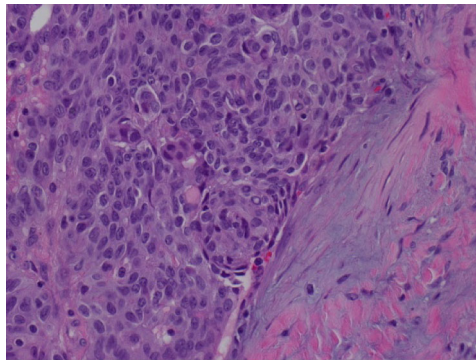


**CMV-PTC**

**(B)**

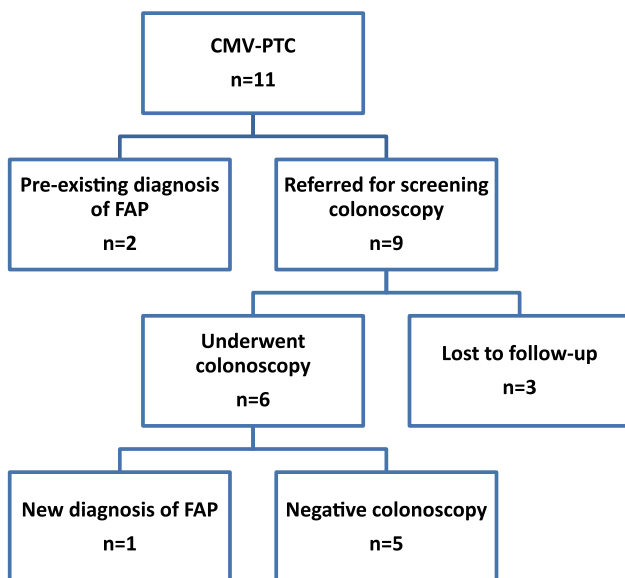


**(C)**



**Fig. 1** Histology of PTC versus CMV-PTC. Hematoxylin and eosin sections of PTC and CMV-PTC cases, courtesy of Nora Katabi, MD. PTC-classical type is characterized by papillary architecture (a),

while CMV-PTC shows focal papillary architecture and is characterized by cribriform pattern (b) and squamoid morules (c)



**Fig. 2** Referral of patients with CMV-PTC for FAP workup

mutation, while the other was precluded from testing due to insurance issues. A schematic of the referral of patients with CMV-PTC for genetic workup is displayed in Fig. 2. In sum, the overall prevalence of FAP among patients with CMV-PTC in our institution is 27 % (3 of the 11).

Our cohort contains three patients with FAP-associated CMV and five patients with sporadic CMV-PTC, as determined by colonoscopy and/or genetic testing (excluding the three patients who were lost to follow up from either group). The mean age of patients in the FAP group at the time of CMV-PTC diagnosis was 23 years (range 18–34), while the mean age of patients in the sporadic group was 37 years (range 25–46) ( $p = 0.03$ ). In addition, all three patients with FAP-associated CMV-PTC had multicentric tumors, while the five patients without FAP did not ( $p = 0.04$ ). All three patients with FAP had PTC located in both the right and left lobes, while four of the five patients without FAP had PTC located in only one lobe, though no statistical significance was noted. Though

**Table 2** Characteristics of FAP-associated versus sporadic CMV-PTC

	FAP-associated CMV-PTC (%) (n = 3)	Sporadic CMV-PTC (%) (n = 5)	<i>p</i> value
Mean age at diagnosis of CMV-PTC (years)	23	37	0.03
Tumor multicentricity	3 (100)	0	0.04
Tumor bilaterality	3 (100)	1 (20)	NS
Mean diameter of largest tumor per patient (cm)	1.8	1.89	NS
Capsular invasion	3 (100)	2 (40)	NS
Extrathyroid extension	1 (33)	0	NS
Aberrant $\beta$ -catenin staining	3 (100)	3 (60)	NS

NS not significant

no other striking differences between the two groups were identified, all patients with FAP had aberrant B-catenin staining, consistent with the theory that the loss of function of the adenomatous polyposis coli (APC) gene causes B-catenin to accumulate in the nuclei of syndrome-related carcinomas (Table 2) [16, 17].

## Discussion

In our study, one of six (17 %) patients with CMV-PTC who underwent colonoscopy was found to have occult FAP. This incidence is slightly lower than that of a Japanese study in which two of six (33 %) patients with CMV-PTC were found to have colonic polyps and a mutation of the *APC* gene [15]. However, the overall prevalence of FAP in our CMV-PTC cohort is three of 11 (27 %). Other studies include a few case reports of patients who were screened for FAP after being diagnosed with CMV-PTC, and are therefore not able to comment on incidence or prevalence [18–20].

Several recent studies have tried to determine clinical or pathological features that may distinguish FAP-associated CMV-PTC from sporadic CMV-PTC. The Japanese group found that patients with FAP-associated CMV-PTC tended to have multiple tumors compared to the sporadic group. Patient age and tumor size were not statistically different between the two groups [21]. Another retrospective study describes 11 female patients with CMV-PTC and one male with typical PTC histology and noted trends toward young age (average 23.5 years for CMV-PTC), multicentricity (66 %), and bilateral tumors (42 %) [4]. Our data confirms these observations and suggests that patients with FAP-associated CMV-PTC are more likely to be younger and

have bilateral and multicentric tumors than patients with sporadic CMV-PTC. While some studies have found that CMV-PTC is generally indolent regardless of whether or not it is associated with FAP [4, 18, 21–23], several of our cases had aggressive histological findings such as lymph node metastases, capsular invasion, and extrathyroid extension.

A major limitation of our study is the small cohort, particularly in the FAP-associated CMV group. However, since FAP and CMV are both rare, amassing a large cohort of patients is challenging for a single institution. In a recent analysis of characteristics that may be associated with FAP-associated versus sporadic CMV-PTC, the Japanese group reported only 12 patients with FAP-associated CMV-PTC in 19 years. However, their cohort of patients may have been enhanced due to their relatively loose inclusion criteria. Patients in their study were considered to have FAP if they had family histories of colonic polyposis or colorectal cancer, regardless of whether they themselves underwent evaluation for FAP. Our study did not consider a family history alone to be sufficient for a diagnosis of FAP, since individuals with FAP transmit the condition to only 50 % of their offspring. In addition, it is possible that some cases of colonic polyposis from the Japanese group may be attributed to other forms of adenomatous polyposis, such as attenuated FAP (AFAP) or MYH-associated polyposis (MAP), which has an autosomal recessive hereditary pattern with variations in penetrance and presumably differences in cancer risks. It is unknown whether patients with other polyposis syndromes are also at risk for CMV-PTC [21].

The Japanese study also designated patients who did not undergo workup for FAP as part of the sporadic group, even though up to 30 % of FAP cases can be attributed to *de novo* mutations and will not have a family history of polyposis or colorectal cancer [24–27]. Therefore, some cases of FAP may have been missed in the Japanese study CMV-PTC cohort. In contrast, our study was fairly conservative and excluded patients without colonoscopic and/or genetic evaluation from the analyses.

Given the rarity of both CMV-PTC and FAP, further studies are required to determine the prevalence of FAP among patients with CMV-PTC and to investigate whether clinical and/or pathological features, such as a younger age and/or multicentric tumors, can distinguish FAP-associated from sporadic CMV-PTC. Until then, we believe that since a significant proportion of patients with CMV-PTC may potentially harbor occult FAP, these patients should be referred for colonoscopy and/or genetic evaluation for FAP.

**Conflict of interest** The authors declare no conflicts of interest associated with this manuscript.



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