Cribiform-morular variant of papillary thyroid carcinoma: a distinctive type of thyroid cancer

Alfred King-yin Lam and Nassim Saremi

Cancer Molecular Pathology, School of Medicine and Menzies Health Institute Queensland, Griffith University, Gold Coast, Australia

Correspondence
should be addressed
to A Lam
Email
a.lam@griffith.edu.au

Abstract

The aim of this systematic review is to study the features of cribiform-morular variant of papillary thyroid carcinoma (CMV-PTC) by analysing the 129 documented cases in the English literature. The disease occurred almost exclusively in women. The median age of presentation for CMV-PTC was 24 years. Slightly over half of the patients with CMV-PTC had familial adenomatous polyposis (FAP). CMV-PTC presented before the colonic manifestations in approximately half of the patients with FAP. Patients with FAP often have multifocal tumours in the thyroid. Microscopic examination of CMV-PTC revealed predominately cribiform and morular pattern of cancer cells with characteristic nuclear features of papillary thyroid carcinoma. Psammoma body is rare. On immunohistochemical studies, β -catenin is diffusely positive in CMV-PTC. The morular cells in CMV-PTC are strongly positive for CD10, bcl-2 and E-cadherin. Pre-operative diagnosis of CMV-PTC by fine-needle aspiration biopsy could be aided by cribiform architecture, epithelial morules and β -catenin immunostaining. Mutations of *APC* gene are found in the patients with CMV-PTC associated with FAP. In addition, mutations in *CTNNB1*, *RET/PTC* rearrangement and *PI3K3CA* mutations have been reported. *BRAF* mutation is negative in all CMV-PTC tested. Compared to conventional papillary thyroid carcinoma, CMV-PTC had a lower frequency of lymph node metastases at presentation (12%) and distant metastases (3%) as well as lower recurrence rates (8.5%) and patients' mortality rates (2%). To conclude, patients with CMV-PTC have distinctive clinical, pathological and molecular profiles when compared to conventional papillary thyroid carcinoma.

Key Words

- cribiform-morular
- thyroid
- papillary carcinoma
- review

Endocrine-Related Cancer
(2017) **24**, R109–R121

Introduction

Cribiform-morular variant of papillary thyroid carcinoma (CMV-PTC) is an uncommon variant of papillary thyroid carcinoma. It is a variant of papillary thyroid carcinoma recognized in the current World Health Organization (WHO) classification of endocrine tumours (Lam 2017). However, when compared to other variants of papillary thyroid carcinoma, it was relatively recently characterized

in the literature. The first well-illustrated case was reported by Chan and Loo from Hong Kong in 1990 (Chan & Loo 1990). After this case, there were a few cases and a small series reported in the subsequent years (Yamashita *et al.* 1992, Harach *et al.* 1994, Hizawa *et al.* 1996, Mizukami *et al.* 1996, Perrier *et al.* 1998). Then, in 1999, Cameselle-Teijeiro and Chan coined the name of

this type of cancer and identified the unique pathological features of this variant of papillary thyroid carcinoma (Cameselle-Teijeiro & Chan 1999).

Methods

All the English literature that reported features of patients with CMV-PTC from PubMed database were analysed. Cases that had been presented in more than one study were counted only once to avoid duplication. Also, cases without demographic data were excluded. Overall, 129 CMV-PTC with well-documented characteristics were noted in the English literature (Chan & Loo 1990, Yamashita *et al.* 1992, Harach *et al.* 1994, Hizawa *et al.* 1996, Mizukami *et al.* 1996, Perrier *et al.* 1998, Cameselle-Teijeiro & Chan 1999, Iwama *et al.* 1999, Soravia *et al.* 1999, Chong *et al.* 2000, Cameselle-Teijeiro *et al.* 2001, 2009, Fenton *et al.* 2001, Kameyama & Takami 2001, Ng *et al.* 2003, Rohaizak *et al.* 2003, Rosen *et al.* 2003, Xu *et al.* 2003, Chikkamuniyappa & Jagirdar 2004, Kameyama *et al.* 2004, Kuma *et al.* 2004, Tomoda *et al.* 2004, Chuah *et al.* 2005, Dalal *et al.* 2006, Uchino *et al.* 2006, Subramaniam *et al.* 2007, Dong *et al.* 2009, Donnellan *et al.* 2009, Jung *et al.* 2009, Hirokawa *et al.* 2010, Baloch *et al.* 2011, Koo *et al.* 2011, Schaeffer *et al.* 2011, Crippa *et al.* 2012, Gronnier *et al.* 2012, Mogoş *et al.* 2012, Rossi *et al.* 2012, Boonyaarunnate *et al.* 2013, Chong *et al.* 2013, Nakazawa *et al.* 2013, Giannelli *et al.* 2014, Yeoh *et al.* 2014, Abdullah Suhaimi *et al.* 2015, Alikhan *et al.* 2015, Kwon *et al.* 2015, Liyanapathirana *et al.* 2015, Perea Del Pozo *et al.* 2015, Brehar *et al.* 2016, Casellas-Cabrera *et al.* 2016, Oh *et al.* 2016).

Epidemiology

The new edition of the World Health Organization (WHO) classification of endocrine tumours classified the papillary thyroid carcinoma into 15 variants (Lam 2017). Table 1 summarized the prevalence of the different variants of papillary thyroid carcinoma noted in surgical series.

CMV-PTC is one of the 15 variants and is very uncommon. In the English literature, only 3 larger populations of CMV-PTCs were reported. The first population was from Japan. This group of authors have reported CMV-PTC in different overlapping periods in a few publications. The largest series from this group was reported by Ito and coworkers in 2011 who had found 32 CMV-PTCs in the period 1991–2010 (Ito *et al.* 2011). However, no detailed information or prevalence of the disease was recorded in the publication. In 2015, authors

Table 1 Relative prevalence of different variants of papillary thyroid carcinoma in surgical biopsy series.

Variants of papillary thyroid carcinoma	Relative prevalence
1. Conventional/classical	~40%*
2. Papillary microcarcinoma	~25%
3. Encapsulated	~10%*
4. Follicular	~15%*
5. Diffuse sclerosing	~2%
6. Tall cell	~4%
7. Columnar cell	Rare, not known
8. Cribiform-morular	~0.2%
9. Hobnail	Rare, not known*
10. Papillary thyroid carcinoma with fibromatosis/fasciitis-like stroma	Rare, not known
11. Solid/trabecular	1–3%
12. Oncocytic	Rare, not known*
13. Spindle cell	Not known
14. Clear cell	Rare, not known
15. Warthin like	Rare, not known*

*The proportion of these variants is estimated as the fourth edition of World Health Organization of endocrine tumours has updated the definitions of these variants.

from the same hospital reported a 0.3% (22 of 7228) prevalence of CMV-PTC in papillary thyroid carcinoma in the period 2005–2011 (Fujimoto *et al.* 2015). Also, in 2010, Hirokawa and coworkers from this hospital reported a prevalence of 0.22% (18 of 8583) of CMV-PTC in papillary thyroid carcinoma in the period 1991–2008 (Hirokawa *et al.* 2010). More recently, in 2004, Tomoda and coworkers presented 7 patients from the same hospital and noted a prevalence of 0.16% (7 of 4194) of CMV-PTV in papillary thyroid carcinoma in the period 1991–2003 (Tomoda *et al.* 2004). The other large population of CMV-PTCs were reported by Perrier and coworkers from Mayo Clinic and Cleveland Clinic in the USA who reported 11 cases of CMV-PTC (Perrier *et al.* 1998). However, the authors did not present the prevalence of CMV-PTC. The third large series of CMV-PTC was reported by Levy and coworkers in Memorial Sloan Kettering Cancer Centre in the USA in 2014 (Levy *et al.* 2014). The authors identified 11 patients with CMV-PTC of 6901 patients with papillary thyroid carcinoma in the period from 2001 to 2012. The prevalence of CMV-PTC was 0.16%. Thus, CMV-PTC accounts for approximately 0.2% of all papillary thyroid carcinoma.

CMV-PTCs were more commonly reported in patients from either Japan ($n=47$) or the USA ($n=27$). Geographically, the reported cases in Asia comprised approximately 63% of the cases ($n=81$). They were reported in Japan ($n=47$), South Korea ($n=19$), Singapore and Malaysia ($n=8$), China (including Hong Kong ($n=6$) and Sri Lanka ($n=1$)). It appears that CMV-PTC was more

Figure 1

Bar chart showing the distribution of cases of CMV-PTC in different age groups, separated into decades of life.

common in Asian populations. The other cases were reported in America ($n=33$; 26%) and Europe ($n=15$; 11%).

Papillary thyroid carcinoma was often noted in adult in the fifth decade of life (mean age=45 years) (Lam *et al.* 2005). From the literature, CMV-PTC was most often seen in patients in the third decade of life (Fig. 1 and Table 2). The mean age and median age of patients with CMV-PTC were 28 and 24, respectively. The age range of patients with CMV-PTC was from 8 to 69 years, and 89% ($n=115$) of the cancers were noted in patients aged younger than 40 years. It is worth noting that among the different variants of papillary thyroid carcinoma, diffuse sclerosing variant of papillary thyroid carcinoma also noted most often in patients at third decade of life (Pillai *et al.* 2015). Thus, both CMV-PTC and diffuse sclerosing variant of papillary thyroid carcinoma should be considered in thyroid cancer detected in young adults. From the accumulated data in the literature, CMV-PTC occurs in a slightly younger age than diffuse sclerosing variant of papillary thyroid carcinoma ($P=0.0001$) (Pillai *et al.* 2015).

Table 2 Clinical and molecular differences between conventional papillary thyroid carcinoma and cribriform-morular variant of papillary thyroid carcinoma.

Features	Conventional	Cribriform-morular
Mean age	45	28
Female to male ratio	3:1	31:1
Mean diameter (mm)	26	30
Association with FAP	Occasional	Noted in 53%
Lymph node metastases (%)	43	12
Cancer recurrence (%)	16	9
Mortality (%)	2.5	2
<i>Braf</i> mutation (%)	~60	0
<i>Ras</i> mutation	Uncommon	Uncommon
Non- <i>Braf</i> -non- <i>Ras</i> mutation	Uncommon	Common in the Wnt signalling pathway

In patients with papillary thyroid carcinoma, the female-to-male ratio is 3 to 4:1 (Lam *et al.* 2005). On the other hand, CMV-PTC occurred almost exclusively in females. Of the 129 patients, 97% were females ($n=125$) and 3% were males ($n=4$). The female-to-male ratio was thus 31:1 (Table 2). The 4 male patients with CMV-PTC were of ages 34, 40, 42 and 55, respectively (mean age=43 years). Male patients with CMV-PTC were found in similar age group as conventional papillary thyroid carcinoma. The difference of age at diagnosis of CMV-PTC between the genders was significant ($P=0.03$).

Clinical features

Patients with CMV-PTC mostly present with a mass lesion in the neck discovered incidentally on palpation or on imaging. All the cases were euthyroid. Alikhan and coworkers had reported a case with ectopic production of serum human chorionic gonadotropin (Alikhan *et al.* 2015).

The most unique clinical feature of CMV-PTC is related to its relationship with familial adenomatous polyposis (FAP). FAP is an autosomal dominant polyposis syndrome characterized by hundreds of adenomas in the large intestine as well as in the upper gastrointestinal tract (Leoz *et al.* 2015, Waller *et al.* 2016). It is due to germline mutations in *APC* gene located on long (q) arm of chromosome 5 at position 22.2. The *APC* gene plays a role in *Wnt* signalling pathway. The *APC* protein functions as a tumour suppressor by negatively regulating the β -catenin oncoprotein. The individuals with FAP have almost 100% chance to develop colorectal cancer. The colorectal carcinoma in the setting of FAP could occur at young age and could be multiple. FAP accounted for 4% of patients with synchronous colorectal carcinoma (Lam *et al.* 2011, 2014).

There are 2 major types of FAP with extracolonic manifestations of FAP, namely Gardner syndrome and type 2 Turcot syndrome. Gardner syndrome is a subtype of FAP that has colonic lesions as well as lesions in many different organs (Gómez García & Knoers 2009). The lesions are mostly benign such as epidermoid cyst, fibroma, desmoid tumour (fibromatosis), osteoma and congenital hypertrophy of the retinal pigment epithelium (CHRPE), etc. The pathogenesis of the lesions is postulated to be a ciliary dysfunction as both *APC* and the cilia have degradation of β -catenin as the common downstream target in the *Wnt* signalling pathway. Apart from colorectal cancer, patients with Gardner syndrome most often have small bowel cancer. The other cancers included pancreatic

cancer, hepatoblastoma, gastric cancer, bile duct cancer, adrenal cancer, central nervous system tumour as well as papillary thyroid carcinoma (Leoz *et al.* 2015).

Type 2 Turcot's syndrome is a very rare form of mutation of APC gene in which there is an association of intestinal polyposis and brain tumours – most often medulloblastoma (Gadish *et al.* 2005, Skomorowski *et al.* 2012). The occurrence of thyroid cancer in Turcot syndrome is extremely rare. In the literature, Crail reported a case of medulloblastoma, papillary thyroid carcinoma and colonic polyposis in 1949 (Crail 1949). The first and the only documented CMV-PTC and medulloblastoma was reported by Fenton and coworkers in 2001 (Fenton *et al.* 2001).

Devic and Bussy were first to recognize the association of colonic polyposis with thyroid mass in 1912 in French literature (Devic & Bussy 1912). In 1949, Crail reported a case of papillary thyroid carcinoma in a patient with FAP, which was the first report of thyroid cancer in patient with FAP (Crail 1949). Then, Gardner in 1951 recognized thyroid cancer as extra-colonic manifestation in FAP (Gardner 1951). In 1968, Camiel and coworkers reported two sisters with FAP having papillary thyroid carcinoma (Camiel *et al.* 1968). Moreover, in 1994, Harach and coworkers first described that CMV-PTC is a unique variant of papillary thyroid carcinoma that could occur in the setting of FAP (Harach *et al.* 1994). In 1997, Bülow and Bülow in the United Kingdom have reported in a large cohort of patients with FAP that the incidence of thyroid carcinoma in FAP is 1.2% (Bülow & Bülow 1997).

From the data in literature, around half of the reported patients with CMV-PTC ($n=69$; 53%) had FAP. In the 4 male patients with CMV-PTC, three had FAP. There was no difference in the age of presentation between patients with or without FAP. Of these patients with FAP, approximately half ($n=33$; 48%) of the patients had the thyroid cancer as the first presentation. A few cases ($n=3$) had the thyroid cancer detected 5 years before the presentation of the colonic lesions (polyposis or carcinoma) (Chong *et al.* 2000, Fenton *et al.* 2001, Jung *et al.* 2009). Jung and coworkers reported a patient with FAP having CMV-PTC detected 12 years before the presentation of the colonic lesions (Jung *et al.* 2009). On the other hand, the thyroid cancer could occur up to 38 years after the appearance of colonic lesions in FAP (Kameyama & Takami 2001). The median lag time for the CMV-PTC was 10 years after the colonic lesions.

Of the CMV-PTC associated with FAP, other features of Gardner syndrome are sometimes noted. The most

common lesion noted is desmoid tumour ($n=8$) (Chong *et al.* 2000, Dalal *et al.* 2006, Crippa *et al.* 2012, Giannelli *et al.* 2014, Abdullah Suhaimi *et al.* 2015, Alikhan *et al.* 2015, Perea del Pozo *et al.* 2015). In addition, one patient presented with osteoma (Soravia *et al.* 1999).

Macroscopic features

Many of the CMV-PTCs were lobulated tan masses with encapsulation or circumscription. There is lack of gritty appearance of calcium. The mean maximum dimension of CMV-PTCs was 30mm (range, 5–95mm). The dimension of the CMV-PTC is similar to conventional papillary thyroid carcinoma in which the mean dimension is 26mm (Lam *et al.* 2005). From the literature, there is no significant difference in size of CMV-PTC between patients with or without FAP.

The sites of the CMV-PTCs were mentioned in 81 cases documented in the literature. The distribution of the CMV-PTCs is different between patients with and without FAP ($P=0.0001$). In patients without FAP, CMV-PTC often appears as solitary nodule with no site predilection. Only 16% (5 of 32) of the CMV-PTC without FAP involved both lobes of the thyroid. The remaining 84% (27 of 32) of CMV-PTC had roughly equal distribution in either lobe of the thyroid (13 in the left lobe and 14 in the right lobe). On the other hand, in patients with FAP, more than half of the patients (28 of 49; 57%) had bilateral cancers with multinodular appearance. In the remaining patients with FAP having solitary lesion, it appeared that CMV-PTC was often located in the right lobe (15 in right lobe and 8 in left lobe).

Microscopic features

CMV-PTC had the characteristic nuclear features of papillary thyroid carcinoma (crowded, oval, optically clear, grooves and eosinophilic cytoplasmic pseudo inclusions and so forth) though the nuclei of them are not particular clear.

As the name of CMV-PTC implied, it is a papillary thyroid carcinoma with predominate cribriform and morular pattern of carcinoma cells. The cribriform pattern of CMV-PTC is represented by back-to-back follicles with anatomising bars and arches of cancer cells in the absence of intervening fibrovascular stroma (Fig. 2A). In some cases, the morular area may be difficult to be identified or non-existent. It is characterized by solid whorls of cells forming morules or nests with no keratinization or

Figure 2

(A) CMV-PTC microscopic features: showing the characteristic cribriform pattern of arrangement of the tumour cells. This is composed of back-to-back follicles with anastomosing bars and arches of cancer cells in the absence of intervening fibrovascular stroma (haematoxylin and eosin: $\times 8$). (B) CMV-PTC microscopic appearance: higher magnification showing the morular areas composed of tumour cells with indistinct border and clear nuclei (haematoxylin and eosin: $\times 25$).

intercellular bridges. Some nuclei within this area are clear and biotin rich (Fig. 2B). They can contribute to false immunostaining results.

On electron microscopic examination, the biotin-rich area pushes the nucleoli to the periphery of the nucleus and composed of randomly located fine microfilaments approximately 100nm long (Yamashita *et al.* 1992, Kameyama *et al.* 2004). These clearings are not demarcated by a membrane. The morules do not contain remarkable cytoplasmic organelles.

Apart from the cribriform and morular morphology, aggressive histological features such as spindle cells in trabecular arrangements, tall and columnar cells with oxyphilic cytoplasm and frequent pseudo stratification as well as follicular pattern devoid of colloid could be present. Mitotic figures and necrosis are usually absent.

A case with hyaline globules as seen in adenoid cystic carcinoma was also described (Baloch *et al.* 2011).

In the setting of young patients with papillary thyroid carcinoma, the main clinical differential diagnosis of CMV-PTC is diffuse sclerosing variant of papillary thyroid carcinoma. Diffuse sclerosing variant of papillary carcinoma has prominent squamous areas, which could resemble morules. However, diffuse sclerosing variant had numerous psammoma bodies (Lam & Lo 2006, Pillai *et al.* 2015). In contrast, in CMV-PTC, psammoma bodies are rare or absent. In the literature, psammoma bodies are seldom mentioned in the pathological descriptions. Of the 129 CMV-PTCs, 18 documented that no psammoma body was found. Only 4 cases had a few psammoma bodies present (Soravia *et al.* 1999, Jung *et al.* 2009, Mogoş *et al.* 2012).

Multifocal lesions are common in CMV-PTC. The prevalence of multifocal lesion was more often noted in cases with FAP. In the literature, 118 cases had the data of FAP status as well as presence of multifocal lesions documented. In patients with FAP, 72% (48 of 67) had multifocal cancers, whereas in patients without FAP, 24% (12 of 51) had multifocal cancers ($P=0.0001$). Overall, multiple tumour foci were noted in 51% of the CMV-PTCs.

CMV-PTC is often confined to the thyroid gland. In the literature in which the extent of the CMV-PTC was documented, extra-thyroid or large lesion (T3/4) cancers are noted in slightly more than one quarter (28%; 24 of 87) of the cases. Also, capsular invasion and vascular invasion have been mentioned in a small portion of cases in 15 and 18 cases, respectively.

Immunohistochemical features

In CMV-PTC, the non-morular cancer cells had different staining properties when compared to the morular cancer cells (Dong *et al.* 2009, Jung *et al.* 2009). Both non-morular and morular cells in CMV-PTC are positive for galectin 3 and p53 protein. The proliferative index (Ki-67) is higher in non-morular cancer cells and reported to be 1–5% (Cameselle-Teijeiro & Chan 1999).

The non-morular cancer cells are frequently positive for thyroid transcription factor-1 (TTF-1), vimentin, oestrogen receptor, progesterone receptor, cyclin D1, PTEN, epithelial membrane antigen (EMA) as well as low- and high-molecular-weight cytokeratins such as CK7, CK19 and 34 β E12 (Kwon *et al.* 2015). The staining for thyroglobulin, HBME-1 and CK5/6 are variable and can be either focal or negative.

The morules of CMV-PTC are negative for thyroglobulin, TTF-1, oestrogen receptor, progesterone receptor and many types of cytokeratins. Cytokeratin 19 (CK19) is commonly strongly expressed in papillary thyroid carcinomas. It is also positive in the squamous metaplasia in diffuse sclerosing variant of papillary thyroid carcinoma (Pillai *et al.* 2015). In contrast, CK19 may express only weakly in the morules in CMV-PTC. Cytoplasmic staining of CD10 and nuclear staining of bcl-2 are strongly positive in the morular cells but weak or not positive in the non-morular area (Giannelli *et al.* 2014).

β -Catenin and E-cadherin play a crucial role in cell-to-cell adhesion and maintaining epithelial morphology (Chow *et al.* 2001, Si *et al.* 2001, Chang *et al.* 2002). This cadherin/catenin complex also regulates cell motility and is believed to function as an invasion suppressor system (Rocha *et al.* 2001). β -Catenin is diffusely positive in both cytoplasm and nucleus of both types of cancer cells in CMV-PTC, whereas normal epithelium of thyroid gland shows membranous staining pattern. The strong expression of β -catenin is a hallmark staining in CMV-PTC in both FAP-associated or non-associated cases.

Loss of expression of E-cadherin, a cellular adhesion molecule, contributes to cancer metastases. Accordingly, studies have showed pronounced reduction of E-cadherin protein expression in the cell membrane, which was accompanied by the relocation of the protein staining to the cytoplasm in cancer (Rocha *et al.* 2001). Conventional papillary thyroid carcinoma showed heterogeneous loss of E-cadherin expression. In contrast, in CMV-PTC, E-cadherin was strongly and diffusely membranous positive in morular cells, whereas it was focally positive in non-morular cancer cells. Morular cells may decrease the metastatic or invasiveness of CMV-PTC. They may contribute to the relative lower biological or clinical aggressive of CMV-PTC when compared to other variants of papillary thyroid carcinoma.

Pre-operative investigations

There are two series in the literature focusing on the ultrasonic features of CMV-PTC. Chong and coworkers in 2013 reported that the majority of the thyroid nodules in 5 patients with CMV-PTC were well defined, had oval to round shapes and were hypoechoic and solid without calcification (Chong *et al.* 2013). Also, Fujimoto and coworkers in 2015 from a study of 22 patients with CMV-PTC noted that CMV-PTC had smooth or focal

jagged margin, hypoechoic nodule, lateral shadow, posterior acoustic enhancement, poor marginal and internal vascularity and absence of micro-calcification (Fujimoto *et al.* 2015). These ultrasonic findings of CMV-PTC resembled those of follicular tumour or nodular hyperplasia of thyroid instead of papillary thyroid carcinoma. Therefore, CMV-PTC did not reveal the features of malignancy in ultrasonic examination. These benign ultrasonic features make pre-operative diagnosis of CMV-PTC difficult.

In the literature, 63% (81 of the 129) of the patients with CMV-PTC had fine-needle aspiration performed before operation. Of these, 95% (77 of 81) of the aspirates showed features either diagnostic or suspicious of thyroid carcinoma.

In 1996, Hizawa and coworkers from Japan first reported that fine-needle aspiration was done before operation of the CMV-PTC. The diagnosis on fine-needle aspiration was consistent with thyroid cancer (Hizawa *et al.* 1996). No detail of the cytological feature was given in the report. In 2010, Koo and coworkers from South Korea described the cytological features of five CMV-PTCs as well as reviewing 10 cases from the previous studies (Koo *et al.* 2011). The authors described that cytological features specific for CMV-PTC included cribriform architecture, epithelial morules and columnar cells. In addition, the β -catenin immunocytochemistry (nuclear and cytoplasmic positivity) could be used to help to diagnose CMV-PTC on cell block (Koo *et al.* 2011). Also in 2010, Hirokawa and coworkers in Japan documented 10 cytological features in 18 CMV-PTCs (Hirokawa *et al.* 2010). In addition to the cribriform architecture, epithelial morules and papillary arrangement of columnar cells, 7 other features were described in the cytological smears including spindle cells, peculiar nuclear clearing (pale-staining area occupying most of the nuclei, usually with condensed chromatin in the periphery of the membrane and positive for biotin), obscure ground-glass nuclei, hyper cellularity, foamy or hemosiderin-laden histiocytes, hyaline materials as well as the absence of colloid in the background. It is worth noting that psammoma body and multi-nucleated giant cells characteristics of papillary thyroid carcinoma were not seen in all the cytological cases in the series. In the case series of Koo and coworkers, one had psammoma body reported in the smear (Koo *et al.* 2011). Thus, in the appropriate settings such as the presence of characteristic cytological features, relative young patients' age, clinical suspicious or confirmation of FAP as well as the presence of material for β -catenin

immunocytochemistry (nuclear and cytoplasmic positivity), the diagnosis of CMV-PTC could be made by fine-needle aspiration biopsy before operation.

Molecular pathogenesis

The works of the Cancer Genome Atlas (TCGA) research network have revolutionized our understanding of molecular pathogenesis of thyroid carcinoma (Cancer Genome Atlas Research Network 2014, Yoo *et al.* 2016). The findings also resulted in a new classification of thyroid tumours that is incorporated in the fourth edition of the WHO classification of endocrine tumours (Lam 2017). In brief, large majority of papillary thyroid carcinomas are driven by mutations in either *BRAF* (specifically *BRAFV600E*) or *RAS*, both of which deregulate the *mitogen-activated protein kinase* (MAPK) signalling pathway. *BRAFV600E*-like tumours have conventional papillary morphology (conventional or tall cell variant of papillary thyroid carcinoma), whereas *RAS*-like tumours have follicular growth pattern and are encapsulated in greater than 80% of cases (Giordano 2016). A portion of the *RAS*-like tumours was now classified as non-invasive follicular thyroid neoplasm with papillary-like features (NIFTP) (Lam 2017). These groups of papillary thyroid carcinoma have distinctive clinical accounted for approximately 75% of papillary thyroid carcinoma. Other than *BRAFV600E*-like tumours and *RAS*-like tumours, the other papillary thyroid carcinomas are labelled as non-*BRAF*-non-*RAS* tumours. They were seen with other genetic alterations such as *EIF1AX* (*eukaryotic translation initiation factor 1A and X-linked*), *PPM1D* (*protein phosphatase and Mg2+/Mn2+-dependent 1D*) and *CHEK2* (*checkpoint kinase 2*) (Cancer Genome Atlas Research Network 2014).

Ninety-eight percent of 402 papillary thyroid carcinomas in TCGA are conventional papillary thyroid carcinoma, follicular variant of papillary thyroid carcinoma and tall cell variant papillary thyroid carcinoma (Cancer Genome Atlas Research Network 2014). Two cases of CMV-PTC were examined in TCGA. They were of pathological stages – T3N1. One is from a 19-year-old female with a *BRAF*-like score whereas the other is from a 28-year-old man with fusion of *RET* and a *RAS*-like score. Thus, the molecular data of CMV-PTC from the TCGA are limited. The molecular pathogenesis of CMV-PTC summarized from the literature in the following sections. CMV-PTC likely belongs to non-*BRAF*-non-*RAS* group of papillary thyroid carcinoma on molecular classification.

MAPK and PI3K/Act pathways and TERT

The *mitogen-activated protein kinase* (MAPK) and *PI3K* (*phosphoinositide 3-kinase*)/*Akt* (*protein kinase B*) pathways are major pathways for pathogenesis of follicular-derived thyroid carcinoma (Rahman *et al.* 2015). Interactions of these two pathways were demonstrated in follicular-derived thyroid carcinoma (Rahman *et al.* 2016). In addition, *TERT* (*telomerase reverse transcriptase*) is also commonly studied in papillary thyroid carcinoma as a prognostic indicator (Vinagre *et al.* 2013, Melo *et al.* 2014).

PI3K/Akt pathway is activated by either the loss of PTEN expression or a *PIK3CA* mutation, resulting in downstream β -catenin activation. In the literature, only Kwon and coworkers in 2015 have reported three CMV-PTCs with *PIK3CA* mutation (Kwon *et al.* 2015). However, the mutation was not detected in a case tested by Oh and coworkers (Oh *et al.* 2016).

MAPK pathway is more commonly studied in cancer and *BRAF*, *RAS* and *RET/PTC* are common activators in the pathway. *K-RAS* mutation has been reported once in an 18-year-old woman with FAP and CMV-PTC by Giannelli and coworkers (Giannelli *et al.* 2014). On the other hand, the other 7 cases tested in the literature were negative for *RAS* mutations (Rossi *et al.* 2012, Nakazawa *et al.* 2013, Kwon *et al.* 2015, Brehar *et al.* 2016, Oh *et al.* 2016). It appears that *RAS* mutation is uncommon in CMV-PTC.

BRAF mutation was noted in approximately 45% of papillary thyroid carcinoma (Pakneshan *et al.* 2013). It was often noted in conventional papillary thyroid carcinoma of advanced pathological stages as well as those associated with lymphocytic thyroiditis (Smith *et al.* 2011). Multi-national studies have demonstrated that *BRAF* mutation in papillary thyroid carcinoma is associated with increased mortality and cancer recurrent rate (Xing *et al.* 2013, 2015). In the literature, *BRAF* mutation was tested in 18 cases of CMV-PTC (Rossi *et al.* 2012, Nakazawa *et al.* 2013, Giannelli *et al.* 2014, Kwon *et al.* 2015, Brehar *et al.* 2016, Oh *et al.* 2016), and the results showed that these cancers were negative for *BRAF* mutation. The absence of *BRAF* mutation in CMV-PTC may explain the relative indolent nature of this type of papillary thyroid carcinoma.

Rearrangement of the *RET* oncogene (also known as *RET/PTC* rearrangement) is an important genetic alteration that has been reported in earlier years. It is an early molecular event identified in papillary thyroid carcinomas (Lam *et al.* 1998). *RET/PTC* rearrangement is more commonly found in thyroid carcinomas in children and young adults as well as in papillary thyroid carcinomas

associated with radiation exposure (Klugbauer *et al.* 1995, Nikiforov 2002). In CMV-PTC, 4 of the 6 cases (67%) tested in 4 different studies showed *RET/PTC* rearrangement (Soravia *et al.* 1999, Rossi *et al.* 2012, Giannelli *et al.* 2014, Brehar *et al.* 2016). Thus, *RET/PTC* rearrangement appears to be involved in the pathogenesis of a portion of papillary thyroid carcinomas in young patients. These papillary thyroid carcinomas include diffuse sclerosing variant of papillary thyroid carcinoma and CMV-PTC (Pillai *et al.* 2015).

Telomerase activation has been detected in papillary thyroid carcinoma (Lo *et al.* 1999). *TERT* (telomerase reverse transcriptase) is a catalytic subunit of telomerase that maintains telomere repeats in DNA strands. *TERT* promoter mutations have been observed in thyroid carcinomas with aggressive biological behaviours. It is associated with tumour size, advanced stage, extra-thyroidal invasion, lymph node metastases, distant metastases, *BRAF* mutation positivity, cancer recurrence and poor prognosis of patients with papillary thyroid carcinoma (Vinagre *et al.* 2013, Melo *et al.* 2014). Oh and coworkers in 2016 have reported the mutation in a 45-year-old woman with CMV-PTC (Oh *et al.* 2016). The case also had aggressive clinical course with lymph nodes and bone metastases.

Wnt signalling pathway

Wnt signalling pathway is important in carcinogenesis, tissue regeneration and embryonic development (Reguart *et al.* 2005). *APC* and β -catenin are the key members of the pathway. The mutations of either of these genes will elevate levels of β -catenin in the nucleus and cytoplasm. Nuclear and cytoplasmic β -catenin protein expression is a feature of CMV-PTC.

In patients with FAP, germline mutations of *APC* occurring before codon 1220 have a strong correlation with the development of thyroid cancer (Cetta *et al.* 2000). In CMV-PTC, germline mutations, somatic mutations and loss of heterozygosity of *APC* are frequently observed. In the literature, 18 of 28 (64%) of CMV-PTC tested positive for aberrations in *APC* gene. Both somatic and germline mutations of *APC* were reported in CMV-PTC (Iwama *et al.* 1999, Uchino *et al.* 2006).

The accumulation of β -catenin could be caused by mutation of the β -catenin gene, *CTNNB1*. The mutation was first reported by Xu and coworkers in 5 CMV-PTCs (Xu *et al.* 2003). Mutation of *CTNNB1* was also reported in one of the CMV-PTCs by Jung and coworkers

(Jung *et al.* 2009). In the literature, 32% (6 of the 19) of CMV-PTC was positive for mutation of *CTNNB1* (Xu *et al.* 2003, Uchino *et al.* 2006, Cameselle-Teijeiro *et al.* 2009, Dong *et al.* 2009, Jung *et al.* 2009, Nakazawa *et al.* 2013, Kwon *et al.* 2015). The mutation could occur in CMV-PTC not associated with FAP, indicating that the mutation could play a role in non-FAP-associated CMV-PTC. As β -catenin accumulation is critical in the epithelial budding, branching and follicular formation in embryogenesis, Dalal and coworkers proposed that the cribriform pattern of CMV-PTC resembles the epithelial budding in embryos and the morules look like the hair formation noted in embryogenesis (Dalal *et al.* 2006).

In cases where *APC* and *CTNNB1* are not found, aberrant upstream events in Wnt signalling may be related to aberrant nuclear localization of β -catenin noted in immunohistochemistry as well as the carcinogenesis of CMV-PTC.

Metastases

In contrast to conventional papillary thyroid carcinomas or diffuse sclerosing variant of papillary thyroid carcinoma, CMV-PTC had low prevalence of lymph node metastases (Table 2). In large series, lymph node metastases were noted in 43% of patients with conventional papillary thyroid carcinoma and in 80% of patients with diffusing sclerosing variant of papillary thyroid carcinoma (Lam *et al.* 2005, Pillai *et al.* 2015). In CMV-PTC, 12% (14 of 120) of patients had lymph nodes metastases at the time of surgery.

Distant metastases were uncommon in patients having CMV-PTC. In the literature, only 4 patients with CMV-PTC had distant metastases, accounting for 3% of the reported CMV-PTC in the literature. The first case was documented by Fenton and coworkers in 2001. The authors reported a CMV-PTC with cancer recurrence and bone metastases in a 50-year-old woman 30 years after the resection of primary thyroid cancer (Fenton *et al.* 2001). Also, Cameselle-Teijeiro and coworkers presented a 42-year-old man with known FAP having a CMV-PTC associated with neuroendocrine carcinoma component. The patient died with lung and brain metastases (Cameselle-Teijeiro *et al.* 2009). In addition, Nakazawa and coworkers reported a 35-year-old woman having CMV-PTC with a component of poorly differentiated thyroid carcinoma having bone and lung metastases (Nakazawa *et al.* 2013). Furthermore, in 2016, Oh and coworkers presented a 45-year-old woman with CMV-PTC

showing TERT (telomerase reverse transcriptase) promoter mutation and having bone metastases (Oh *et al.* 2016). Overall, CMV-PTCs with distant metastases were seen in patients of age older than mean age of the patients with CMV-PTC. It is worth noting that three of these four patients with distant metastases had either unusual histological or molecular features.

Prognosis

In the literature, 8.5% ($n=11$ of 129) of patients with CMV-PTC showed recurrence of cancer (Table 2). For reference, the recurrence rate of diffuse sclerosing variant of papillary thyroid carcinoma was 14% (Pillai *et al.* 2015). In multi-national study, the recurrence rate in conventional papillary thyroid carcinoma was 16.1% (Xing *et al.* 2015). The recurrence rate in aggressive variant of papillary thyroid carcinoma, tall cell variant, was 27.3% whereas that of follicular variant of papillary thyroid carcinoma was 9.1%. Thus, the overall recurrence rate of CMV-PTC was low and similar to that of follicular variant of papillary thyroid carcinoma.

Three deaths were reported from the patients with CMV-PTC. Perrier and coworkers in 1998 recorded a 29-year-old female patient with CMV-PTC who had cancer recurrence at 6 months and died at 85 months after the operation (Perrier *et al.* 1998). In this study having 11 cases of CMV-PTC, the 5-year and 20-year survivals of the patients with CMV-PTC were 90% and 77%, respectively. Also, Fenton and coworkers in 2001 reported a 20-year-old woman with recurrence having distant metastases died 30 years after the resection of primary thyroid cancer (Fenton *et al.* 2001). In addition, Cameselle-Teijeiro and coworkers in 2009 presented a case in a 42-year-old man with known FAP having a neuroendocrine carcinoma component and died with lung and brain metastases 17 months after diagnosis (Cameselle-Teijeiro *et al.* 2009). Thus, patients with CMV-PTC have low mortality rate. On the other hand, cancer-related death could occur after a long lag time after the primary operation.

Disease-related mortality is uncommon and was noted in 2% ($n=3/129$) of the patients with CMV-PTC (Table 2). In multi-national study, disease-related mortality in conventional papillary thyroid carcinoma was found to be 2.5% (Xing *et al.* 2015). On the other hand, the disease-related mortality in aggressive variant of papillary thyroid carcinoma, tall cell variant, was 6.7% whereas that of follicular variant of papillary thyroid carcinoma was 0.6%. Also, the disease-related mortality in diffuse

sclerosing variant of papillary thyroid carcinoma was 3% (Pillai *et al.* 2015). Thus, the prognosis of the CMV-PTC is similar to that of conventional thyroid carcinoma.

Clinical management

As the prognosis of CMV-PTC is similar to conventional papillary thyroid carcinoma, standard approach for the management of conventional papillary thyroid carcinoma based on the clinical and pathological risk factors should be appropriate (Pacini & Castagna 2012, Raue & Frank-Raue 2016). Total thyroidectomy is sufficient for the treatment of most cancers. Lymph node dissection could be performed when necessary. The patients may have radioiodine therapy to detect and destroy any metastases and residual disease in thyroid. External beam radiotherapy may be used as adjuvant therapy in patients having locally invasive disease and in the older patients. In addition, CMV-PTC could be related to FAP and occur before the other manifestations of other diseases associated with FAP. Therefore, the management of the patients with CMV-PTC should also focus on the detection of other pathologies related to FAP as well as awareness of genetic implications of FAP in other family members.

Conclusion

CMV-PTC is characterized by unique clinical features (younger age at presentation, almost exclusively in women as well as the association with FAP). It has specific microscopic features (predominate cribriform and morular pattern of carcinoma cells with biotin-rich nuclei, multifocality and lack of psammoma bodies) as well as immunohistochemical pattern (positive to beta-catenin). In addition, CMV-PTC has distinctive molecular pathogenesis through the *Wnt* signalling pathway. These characteristics of CMV-PTC cast doubts on labelling the cancer as a variant of papillary thyroid carcinoma. Nevertheless, CMV-PTC had nuclear characteristic of papillary thyroid carcinoma and *Wnt* signalling pathway alternations are noted in some conventional papillary thyroid carcinomas. Thus, CMV-PTC is grouped as an uncommon and a very unique variant of papillary thyroid carcinoma.

Patients with CMV-PTC have low incidence of lymph node metastases and cancer recurrence. Despite this, late recurrence could occur, and long-term follow up is required for this group of patients. In the settings of FAP,

family screening and detection for other manifestations are important in the management of the patients. It is important to recognize this unique variant of papillary thyroid carcinoma as it occurs in specific clinical context and has unique pathological, immunohistochemical and molecular features.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

- Abdullah Suhaimi SN, Nazri N, Nani Harlina ML, Md Isa N & Muhammad R 2015 Familial adenomatous polyposis-associated papillary thyroid cancer. *Malaysian Journal of Medical Sciences* **22** 69–72. (available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4683851/>)
- Alikhan M, Koshy A, Hyjek E, Stenson K, Cohen RN & Yeo KT 2015 Discrepant serum and urine β -hCG results due to production of β -hCG by a cribriform-morular variant of thyroid papillary carcinoma. *Clinica Chimica Acta* **438** 181–185. (doi:10.1016/j.cca.2014.08.026)
- Baloch ZW, Segal JP & Livolsi VA 2011 Unique growth pattern in papillary carcinoma of the thyroid gland mimicking adenoid cystic carcinoma. *Endocrine Pathology* **22** 200–205. (doi:10.1007/s12022-011-9174-7)
- Boonyaaarunnate T, Olson MT, Bishop JA, Yang GC & Ali SZ 2013 Cribriform morular variant of papillary thyroid carcinoma: clinical and cytomorphological features on fine-needle aspiration. *Acta Cytologica* **57** 127–133. (doi:10.1159/000345879)
- Brehar AC, Terzea DC, Ioachim DL, Procopiuc C, Brehar FM, Bulgăr AC, Ghemigian MV & Dumitrache C 2016 Cribriform-morular variant of papillary thyroid carcinoma at pediatric age – case report and review of the literature. *Romanian Journal of Morphology and Embryology* **57** 531–537. (available at: <http://www.rjme.ro/RJME/resources/files/570216531537.pdf>)
- Bülow C & Bülow S 1997 Is screening for thyroid carcinoma indicated in familial adenomatous polyposis? The Leeds Castle Polyposis Group. *International Journal of Colorectal Disease* **12** 240–242. (doi:10.1007/s003840050097)
- Cameselle-Teijeiro J & Chan JK 1999 Cribriform-morular variant of papillary carcinoma: a distinctive variant representing the sporadic counterpart of familial adenomatous polyposis-associated thyroid carcinoma? *Modern Pathology* **12** 400–411.
- Cameselle-Teijeiro J, Ruiz-Ponte C, Loidi L, Suarez-Peñaranda J, Baltar J & Sobrinho-Simoes M 2001 Somatic but not germline mutation of the APC gene in a case of cribriform-morular variant of papillary thyroid carcinoma. *American Journal of Clinical Pathology* **115** 486–493. (doi:10.1309/T9CC-JNMD-1WGP-YPAF)
- Cameselle-Teijeiro J, Menasce LP, Yap BK, Colaco RJ, Castro P, Celestino R, Ruiz Ponte C, Soares P & Sobrinho-Simões M 2009 Cribriform-morular variant of papillary thyroid carcinoma: molecular characterization of a case with neuroendocrine differentiation and aggressive behavior. *American Journal of Clinical Pathology* **131** 134–142. (doi:10.1309/AJCP7ULSOVSISBEB)
- Camiel MR, Mulé JE, Alexander LL & Benninghoff DL 1968 Association of thyroid carcinoma with Gardner's syndrome in siblings. *New England Journal of Medicine* **278** 1056–1058. (doi:10.1056/NEJM196805092781908)
- Cancer Genome Atlas Research Network 2014 Integrated genomic characterization of papillary thyroid carcinoma. *Cell* **59** 676–690. (doi:10.1016/j.cell.2014.09.050)
- Casellas-Cabrera N, Díaz-Algorri Y, Carlo-Chévere VJ, González-Pons M, Rodríguez-Mañón N, Pérez-Mayoral J, Bertrán-Rodríguez C, Soto-Salgado M, Giardiello FM, Rodríguez-Quilichini S, et al. 2016 Risk of thyroid cancer among Caribbean Hispanic patients with familial adenomatous polyposis. *Familial Cancer* **15** 267–274. (doi:10.1007/s10689-015-9862-4)
- Cetta F, Montalto G, Gori M, Curia MC, Cama A & Olschwang S 2000 Germline mutations of the APC gene in patients with familial adenomatous polyposis-associated thyroid carcinoma: results from a European cooperative study. *Journal of Clinical Endocrinology and Metabolism* **85** 286–292. (doi:10.1210/jc.85.1.286)
- Chan JK & Loo KT 1990 Cribriform variant of papillary thyroid carcinoma. *Archives of Pathology and Laboratory Medicine* **114** 622–624.
- Chang HW, Chow V, Lam KY, Wei WI & Yuen A 2002 Loss of E-cadherin expression resulting from promoter hypermethylation in oral tongue carcinoma and its prognostic significance. *Cancer* **94** 386–392. (doi:10.1002/cncr.10211)
- Chikkamuniyappa S & Jagirdar J 2004 Cribriform-morular variant of papillary carcinoma: association with familial adenomatous polyposis – report of three cases and review of literature. *International Journal of Medical Science* **1** 43–49. (doi:10.7150/ijms.1.43)
- Chong J, Koshiishi N, Kurihara K, Kubono S, Kawai T & Fukayama M 2000 Aspiration and imprint cytopathology of thyroid carcinoma associated with familial adenomatous polyposis. *Diagnostic Cytopathology* **23** 101–115. (doi:10.1002/1097-0339(200008)23:2<101::AID-DC7>3.0.CO;2-0)
- Chong Y, Shin JH, Oh YL, Han BK & Ko EY 2013 Cribriform-morular variant of papillary thyroid carcinoma: ultrasonographic and clinical characteristics. *Thyroid* **23** 45–49. (doi:10.1089/thy.2011.0534)
- Chow V, Yuen APW, Lam KY, Tsao GSW, Ho WK & Wei WI 2001 A comparative study of the clinicopathological significance of E-cadherin and catenins (α , β , γ) expression in the surgical management of oral tongue carcinoma. *Journal of Cancer Research and Clinical Oncology* **127** 59–63. (doi:10.1007/s004320000177)
- Chuah KL, Hwang JS, Ng SB, Tan PH, Poh WT & Au VS 2005 Cytologic features of cribriform-morular variant of papillary carcinoma of the thyroid: a case report. *Acta Cytologica* **49** 75–80. (doi:10.1159/000326100)
- Crail HW 1949 Multiple primary malignancies arising in the rectum, brain, and thyroid; report of a case. *United States Naval Medical Bulletin* **49** 123–128.
- Crippa S, Saletti P, Barizzi J & Mazzucchelli L 2012 The clinical management in familial adenomatous polyposis deserves continuous monitoring for thyroid carcinoma. *BMJ Case Reports* **2012** bcr2012007046. (doi:10.1136/bcr-2012-007046)
- Dalal KM, Moraitis D, Iwamoto C, Shaha AR, Patel SG & Ghossein RA 2006 Clinical curiosity: cribriform-morular variant of papillary thyroid carcinoma. *Head and Neck* **28** 471–476. (doi:10.1002/hed.20383)
- Devic C & Busy J 1912 Un cas de polypose adenomateuse generalisee a tout l'intestin. *Archives Francaises Des Maladies De L'Appareil Digestif* **6** 278–289.

- Dong Y, Zhou X, Yin H, Wang J, Zhou H & Lu G 2009 Cribriform-morular variant of papillary thyroid carcinoma: report of three cases and review of the literature. *Pathology* **41** 509–512. (doi:10.1080/00313020903041101)
- Donnellan KA, Bigler SA & Wein RO 2009 Papillary thyroid carcinoma and familial adenomatous polyposis of the colon. *American Journal of Otolaryngology* **30** 58–60. (doi:10.1016/j.amjoto.2008.01.001)
- Fenton PA, Clarke SE, Owen W, Hibbert J & Hodgson SV 2001 Cribriform variant papillary thyroid cancer: a characteristic of familial adenomatous polyposis. *Thyroid* **11** 193–197. (doi:10.1089/105072501300042965)
- Fujimoto T, Hirokawa M, Ota H, Yabuta T, Fukushima M, Kobayashi K, Amino N & Miyauchi A 2015 Characteristic sonographic features of cribriform papillary thyroid carcinoma for differentiation from other thyroid nodules. *Journal of Medical Ultrasound* **42** 83–87. (doi:10.1007/s10396-014-0555-7)
- Gadish T, Tulchinsky H, Deutsch AA & Rabau M 2005 Pinealoblastoma in a patient with familial adenomatous polyposis: variant of Turcot syndrome type 2? Report of a case and review of the literature. *Diseases of Colon and Rectum* **48** 2343–2346. (doi:10.1007/s10350-005-0201-y)
- Gardner EJ 1951 A genetic and clinical study of intestinal polyposis, a predisposing factor for carcinoma of the colon and rectum. *American Journal of Human Genetics* **3** 167–176. (available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1716321/>)
- Giannelli SM, McPhaul L, Nakamoto J & Gianoukakis AG 2014 Familial adenomatous polyposis-associated, cribriform morular variant of papillary thyroid carcinoma harboring a K-RAS mutation: case presentation and review of molecular mechanisms. *Thyroid* **24** 1184–1189. (doi:10.1089/thy.2013.0589)
- Giordano TJ 2016 Follicular cell thyroid neoplasia: insights from genomics and the Cancer Genome Atlas research network. *Current Opinion in Oncology* **28** 1–4. (doi:10.1097/CCO.0000000000000248)
- Gómez García EB & Knoers NV 2009 Gardner's syndrome (familial adenomatous polyposis): a cilia-related disorder. *Lancet Oncology* **10** 727–735. (doi:10.1016/S1470-2045(09)70167-6)
- Gronnier C, Donatini G, Leteurtre E, Do Cao C & Carnaille B 2012 Cribriform-morular variant of papillary thyroid carcinoma: characteristic histologic feature of adenomatous polyposis: a case report. *Annales D'endocrinologie* **73** 213–215. (doi:10.1016/j.ando.2012.01.003)
- Harach HR, Williams GT & Williams ED 1994 Familial adenomatous polyposis associated thyroid carcinoma: a distinct type of follicular cell neoplasm. *Histopathology* **25** 549–561. (doi:10.1111/j.1365-2559.1994.tb01374.x)
- Hirokawa M, Maekawa M, Kuma S & Miyauchi A 2010 Cribriform-morular variant of papillary thyroid carcinoma – cytological and immunocytochemical findings of 18 cases. *Diagnostic Cytopathology* **38** 890–896. (doi:10.1002/dc.21309)
- Hizawa K, Iida M, Yao T, Aoyagi K, Oohata Y, Mibu R, Yamasaki K, Hirata T & Fujishima M 1996 Association between thyroid cancer of cribriform variant and familial adenomatous polyposis. *Journal of Clinical Pathology* **49** 611–613. (doi:10.1136/jcp.49.7.611)
- Ito Y, Miyauchi A, Ishikawa H, Hirokawa M, Kudo T, Tomoda C & Miya A 2011 Our experience of treatment of cribriform morular variant of papillary thyroid carcinoma; difference in clinicopathological features of FAP-associated and sporadic patients. *Endocrine Journal* **58** 685–689. (doi:10.1507/endocrj.EJ11-0022)
- Iwama T, Konishi M, Iijima T, Yoshinaga K, Tominaga T, Koike M & Miyaki M 1999 Somatic mutation of the APC gene in thyroid carcinoma associated with familial adenomatous polyposis. *Japanese Journal of Cancer Research* **90** 372–376. (doi:10.1111/j.1349-7006.1999.tb00757.x)
- Jung CK, Choi YJ, Lee KY, Bae JS, Kim HJ, Yoon SK, Son YI, Chung JH & Oh YL 2009 The cytological, clinical, and pathological features of the cribriform-morular variant of papillary thyroid carcinoma and mutation analysis of CTNNB1 and BRAF genes. *Thyroid* **19** 905–913. (doi:10.1089/thy.2008.0332)
- Kameyama K & Takami H 2001 FAP associated thyroid carcinoma in mother and her daughter. *Familial Cancer* **1** 83–86. (doi:10.1023/A:1013848307459)
- Kameyama K, Mukai M, Takami H & Ito K 2004 Cribriform-morular variant of papillary thyroid carcinoma: ultrastructural study and somatic/germline mutation analysis of the APC gene. *Ultrastructural Pathology* **28** 97–102. (doi:10.1080/01913120490431435)
- Klugbauer S, Lengfelder E, Demidchik EP & Rabes HM 1995 High prevalence of RET rearrangement in thyroid tumors of children from Belarus after the Chernobyl reactor accident. *Oncogene* **11** 2459–2467.
- Koo JS, Jung W & Hong SW 2011 Cytologic characteristics and β -catenin immunocytochemistry on smear slide of cribriform-morular variant of papillary thyroid carcinoma. *Acta Cytologica* **55** 13–18. (doi:10.1159/000320856)
- Kuma S, Hirokawa M, Xu B, Miyauchi A, Kukudo K & Sano T 2004 Cribriform-morular variant of papillary thyroid carcinoma. Report of a case showing morules with peculiar nuclear clearing. *Acta Cytologica* **48** 431–436. (doi:10.1159/000326399)
- Kwon MJ, Rho YS, Jeong JC, Shin HS, Lee JS, Cho SJ & Nam ES 2015 Cribriform-morular variant of papillary thyroid carcinoma: a study of 3 cases featuring the PIK3CA mutation. *Human Pathology* **46** 1180–1188. (doi:10.1016/j.humpath.2015.04.010)
- Lam AK 2017 Pathology of endocrine tumors update: WHO new classification 2017 – other thyroid tumors. *AJSP: Reviews and Reports* [in press].
- Lam AK & Lo CY 2006 Diffuse sclerosing variant of papillary carcinoma of the thyroid: a 35-year comparative study at a single institution. *Annals of Surgical Oncology* **13** 176–181. (doi:10.1245/ASO.2006.03.062)
- Lam KY, Montone KT, Nolan KA & LiVolsi VA 1998 Ret oncogene activation in papillary thyroid carcinoma: Prevalence and implication on the histological parameters. *Human Pathology* **29** 565–568. (doi:10.1016/S0046-8177(98)80004-X)
- Lam AK, Lo CY & Lam KS 2005 Papillary carcinoma of thyroid: a 30-year clinicopathological review of the histological variants. *Endocrine Pathology* **16** 323–330. (doi:10.1385/EP:16:4:323)
- Lam AK, Carmichael R, Gertraud Buettner P, Gopalan V, Ho YH & Siu S 2011 Clinicopathological significance of synchronous carcinoma in colorectal cancer. *American Journal of Surgery* **202** 39–44. (doi:10.1016/j.amjsurg.2010.05.012)
- Lam AK, Chan SS & Leung M 2014 Synchronous colorectal cancer: clinical, pathological and molecular implications. *World Journal of Gastroenterology* **20** 6815–6820. (doi:10.3748/wjg.v20.i22.6815)
- Leoz ML, Carballal S, Moreira L, Ocaña T & Balaguer F 2015 The genetic basis of familial adenomatous polyposis and its implications for clinical practice and risk management. *Application of Clinical Genetics* **8** 95–107. (doi:10.2147/TACG.S51484)
- Levy RA, Hui VW, Sood R, Fish S, Markowitz AJ, Wong RJ & Guillem JG 2014 Cribriform-morular variant of papillary thyroid carcinoma: an indication to screen for occult FAP. *Familial Cancer* **13** 547–551. (doi:10.1007/s10689-014-9732-5)
- Liyanapathirana N, Seneviratne SA & Samarasekera DN 2015 A distinct variant of papillary thyroid carcinoma indicating familial adenomatous polyposis (FAP): a case report and brief review. *BMC Research Notes* **8** 795. (doi:10.1186/s13104-015-1736-1)
- Lo CY, Lam KY, Chan KT & Luk JM 1999 Telomerase activity in thyroid malignancy. *Thyroid* **9** 1215–1220. (doi:10.1089/thy.1999.9.1215)
- Melo M, da Rocha AG, Vinagre J, Batista R, Peixoto J, Tavares C, Celestino R, Almeida A, Salgado C, Eloy C, et al. 2014 TERT

- promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas. *Journal of Clinical Endocrinology and Metabolism* **99** E754–E765. (doi:10.1210/jc.2013-3734)
- Mizukami Y, Nonomura A, Michigishi T, Noguchi M & Ishizaki T 1996 Encapsulated follicular thyroid carcinoma exhibiting glandular and spindle cell components: a case report. *Pathology Research Practice* **192** 67–71. (doi:10.1016/S0344-0338(96)80134-8)
- Mogoş V, Mogoş S, Sfarti C, Băcăuanu R, Huşanu O, Cotea E, Ciobanu D, Tudorache C & Tărcoveanu E 2012 Familial syndromic papillary thyroid carcinoma report of two cases. *Revista Medico-Chirurgicala A Societăţii de Medici si Naturalisti din Iasi* **116** 1048–1054.
- Nakazawa T, Celestino R, Machado JC, Cameselle-Teijeiro JM, Vinagre J, Eloy C, Benserai F, Lameche S, Soares P & Sobrinho-Simões M 2013 Cribriform-morular variant of papillary thyroid carcinoma displaying poorly differentiated features. *International Journal of Surgical Pathology* **21** 379–389. (doi:10.1177/1066896912473355)
- Ng SB, Sittampalam K, Goh YH & Eu KW 2003 Cribriform-morular variant of papillary carcinoma: the sporadic counterpart of familial adenomatous polyposis-associated thyroid carcinoma: a case report with clinical and molecular genetic correlation. *Pathology* **35** 42–46. (doi:10.1080/00313020307507)
- Nikiforov YE 2002 RET/PTC rearrangement in thyroid tumors. *Endocrine Pathology* **13** 3–16. (doi:10.1385/EP:13:1:03)
- Oh EJ, Lee S, Bae JS, Kim Y, Jeon S & Jung CK 2016 TERT promoter mutation in an aggressive cribriform morular variant of papillary thyroid carcinoma. *Endocrine Pathology* **28** 49–53. (doi:10.1007/s12022-016-9454-3)
- Pacini F & Castagna MG 2012 Approach to and treatment of differentiated thyroid carcinoma. *Medical Clinics North America* **96** 369–383. (doi:10.1016/j.mcna.2012.01.002)
- Pakneshan S, Salajegheh A, Smith RA & Lam AK 2013 Clinicopathological relevance of BRAF mutations in human cancer. *Pathology* **45** 346–356. (doi:10.1097/PAT.0b013e328328360b61d)
- Perea Del Pozo E, Ramirez Plaza C, Padillo Ruiz J & Martos Martínez JM 2015 Cribriform variant of papillary thyroid cancer and familial adenomatous polyposis. *International Journal of Surgery Case Reports* **16** 192–194. (doi:10.1016/j.ijscr.2015.08.013)
- Perrier ND, van Heerden JA, Goellner JR, Williams ED, Gharib H, Marchesa P, Church JM, Fazio VW & Larson DR 1998 Thyroid cancer in patients with familial adenomatous polyposis. *World Journal of Surgery* **22** 738–742. (doi:10.1007/s002689900462)
- Pillai S, Gopalan V, Smith RA & Lam AK 2015 Diffuse sclerosing variant of papillary thyroid carcinoma-an update of its clinicopathological features and molecular biology. *Critical Reviews in Oncology Hematology* **94** 64–73. (doi:10.1016/j.critrevonc.2014.12.001)
- Rahman MA, Salajegheh A, Smith RA & Lam AK 2015 Multiple proliferation-survival signalling pathways are simultaneously active in BRAF V600E mutated thyroid carcinomas. *Experimental and Molecular Pathology* **90** 492–497. (doi:10.1016/j.yexmp.2015.09.006)
- Rahman MA, Salajegheh A, Smith RA & Lam AK 2016 Inhibition of BRAF kinase suppresses cellular proliferation, but not enough for complete growth arrest in BRAF V600E mutated papillary and undifferentiated thyroid carcinomas. *Endocrine* **54** 129–138. (doi:10.1007/s12020-016-0985-7)
- Raue F & Frank-Raue K 2016 Thyroid cancer: risk-stratified management and individualized therapy. *Clinical Cancer Research* **22** 5012–5021. (doi:10.1158/1078-0432.CCR-16-0484)
- Reguart N, He B, Taron M, You L, Jablons DM & Rosell R 2005 The role of Wnt signaling in cancer and stem cells. *Future Oncology* **1** 787–797. (doi:10.2217/14796694.1.6.787)
- Rocha AS, Soares P, Seruca R, Máximo V, Matias-Guiu X, Cameselle-Teijeiro J & Sobrinho-Simões M 2001 Abnormalities of the E-cadherin/catenin adhesion complex in classical papillary thyroid carcinoma and in its diffuse sclerosing variant. *Journal of Pathology* **194** 358–366. (doi:10.1002/path.905)
- Rohaizak M, Jasmi AY, Ismail MA, Munchar MJ & Meah FA 2003 Thyroid carcinoma in patients with familial adenomatous polyposis. *Asian Journal of Surgery* **26** 183–185. (doi:10.1016/S1015-9584(09)60381-X)
- Rosen EJ, Newlands SD & Rampy BA 2003 Pathology quiz case: cribriform-morular variant of papillary thyroid carcinoma. *Archives of Otolaryngology - Head and Neck Surgery* **129** 679–681. (doi:10.1001/archotol.129.6.679)
- Rossi ED, Revelli L, Martini M, Taddei A, Pintus C, Panunzi C & Fadda G 2012 Cribriform-morular variant of papillary thyroid carcinoma in an 8-year-old girl: a case report with immunohistochemical and molecular testing. *International Journal of Surgical Pathology* **20** 629–632. (doi:10.1177/1066896912441830)
- Schaeffer DF, Yoshida EM, Owen DA & Berean KW 2011 Familial adenomatous polyposis-rendering a diagnosis based on recognition of an unusual primary thyroid neoplasm. *Case Report in Medicine* **2011** article ID 767610. (doi:10.1155/2011/767610)
- Si HX, Tsao SW, Lam KY, Srivastava G, Liu Y, Wong YC, Shen ZY & Cheung ALM 2001 E-cadherin expression is commonly downregulated by CpG island hypermethylation in esophageal carcinoma cells. *Cancer Letters* **173** 71–78. (doi:10.1016/S0304-3835(01)00646-2)
- Skomorowski M, Taxier M & Wise W Jr 2012 Turcot syndrome type 2: medulloblastoma with multiple colorectal adenomas. *Clinical Gastroenterology and Hepatology* **10** A24. (doi:10.1016/j.cgh.2012.06.013)
- Smith RA, Salajegheh A, Weinstein S, Nassiri M & Lam AK 2011 Correlation between BRAF mutation and the clinicopathological parameters in papillary thyroid carcinoma with particular reference to follicular variant. *Human Pathology* **42** 500–506. (doi:10.1016/j.humpath.2009.09.023)
- Soravia C, Sugg SL, Berk T, Mitri A, Cheng H, Gallinger S, Cohen Z, Asa SL & Bapat BV 1999 Familial adenomatous polyposis-associated thyroid cancer: a clinical, pathological, and molecular genetics study. *American Journal of Pathology* **154** 127–135. (doi:10.1016/S0002-9440(10)65259-5)
- Subramaniam MM, Putti TC, Anuar D, Chong PY, Shah N, Salto-Tellez M & Soong R 2007 Clonal characterization of sporadic cribriform-morular variant of papillary thyroid carcinoma by laser microdissection-based APC mutation analysis. *American Journal of Clinical Pathology* **128** 994–1001. (doi:10.1309/YXR3PKK4TV3DJCS6)
- Tomoda C, Miyauchi A, Uruno T, Takamura Y, Ito Y, Miya A, Kobayashi K, Matsuzuka F, Kuma S, Kuma K, et al. 2004 Cribriform-morular variant of papillary thyroid carcinoma: clue to early detection of familial adenomatous polyposis-associated colon cancer. *World Journal of Surgery* **28** 886–889. (doi:10.1007/s00268-004-7475-4)
- Uchino S, Noguchi S, Yamashita H, Yamashita H, Watanabe S, Ogawa T, Tsuno A, Murakami A & Miyauchi A 2006 Mutational analysis of the APC gene in cribriform-morula variant of papillary thyroid carcinoma. *World Journal of Surgery* **30** 775–779. (doi:10.1007/s00268-005-0368-3)
- Vinagre J, Almeida A, Pópulo H, Batista R, Lyra J, Pinto V, Coelho R, Celestino R, Prazeres H, Lima L, et al. 2013 Frequency of TERT promoter mutations in human cancers. *Nature Communications* **4** 2185. (doi:10.1038/ncomms3185)
- Waller A, Findeis S & Lee MJ 2016 Familial adenomatous polyposis. *Journal of Pediatric Genetics* **5** 78–83. (doi:10.1055/s-0036-1579760)
- Xing M, Alzahrani AS, Carson KA, Viola D, Elisei R, Bendlova B, Yip L, Mian C, Vianello F, Tuttle RM, et al. 2013 Association between BRAF V600 mutation and mortality in patients with papillary thyroid cancer. *JAMA* **309** 1493–1501. (doi:10.1001/jama.2013.3190)

- Xing M, Alzahrani AS, Carson KA, Shong YK, Kim TY, Viola D, Elisei R, Bendlová B, Yip L, Mian C, *et al.* 2015 Association between BRAF V600E mutation and recurrence of papillary thyroid cancer. *Journal of Clinical Oncology* **33** 42–50. (doi:10.1200/JCO.2014.56.8253)
- Xu B, Yoshimoto K, Miyauchi A, Kuma S, Mizusawa N, Hirokawa M & Sano T 2003 Cribiform-morular variant of papillary thyroid carcinoma: a pathological and molecular genetic study with evidence of frequent somatic mutations in exon 3 of the beta-catenin gene. *Journal of Pathology* **199** 58–67. (doi:10.1002/path.1225)
- Yamashita T, Hosoda Y, Kameyama K, Aiba M, Ito K & Fujimoto Y 1992 Peculiar nuclear clearing composed of microfilaments in

papillary carcinoma of the thyroid. *Cancer* **70** 2923–2928. (doi:10.1002/1097-0142(19921215)70:12<2923::AID-CNCR2820701232>3.0.CO;2-G)

- Yeoh EC, Lim LC, Ng SB, Tan KY & Rajasoorya C 2014 Cribiform morular variant of papillary thyroid carcinoma in a patient with an incidental neck lump: a case report and review of the literature. *Endocrine Pathology* **25** 302–306. (doi:10.1007/s12022-013-9274-7)
- Yoo SK, Lee S, Kim SJ, Jee HG, Kim BA, Cho H, Song YS, Cho SW, Won JK, Shin JY, *et al.* 2016 Comprehensive analysis of the transcriptional and mutational landscape of follicular and papillary thyroid cancers. *PLoS Genetics* **12** e1006239. (doi:10.1371/journal.pgen.1006239)

Received in final form 7 February 2017

Accepted 13 February 2017