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Editorial

Cribriform-morular variant of thyroid carcinoma

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It is very rewarding for endocrine pathologists to see, in the new book of the World Health Organization (WHO) classification of endocrine organs [1], how the molecular characterization of thyroid tumours has confirmed the types and subtypes of tumours previously recognized by less sophisticated techniques. The cribriform-morular variant of papillary thyroid carcinoma (PTC) is a paradigmatic example of this close correlation between the classical morphological aspects and genetic-molecular alterations. In fact, this morphological-molecular correlation in the cribriform-morular variant of PTC is so distinctive that we have recently found that cribriform-morular thyroid carcinoma is a more appropriate denomination [2]. In this brief article, we summarize the main features that have justified this new designation.

After the first descriptions of associations between thyroid tumours and familial adenomatous polyposis (FAP) (for a review, see Cameselle-Teijeiro et al.) [2], it was Harach et al. [3] who first recognized the unusual histological features of thyroid tumours that were commonly multifocal and predominantly occurring in young women in the setting of FAP. Later, Cameselle-Teijeiro and Chan [4] proposed the name of cribriform-morular variant of PTC, for morphologically similar sporadic tumours that usually occur as single nodules in patients with no germline *APC* gene mutation (without FAP). Now, as a consequence, we know that clinicians should be alerted to the possibility of FAP when a case of cribriform-morular thyroid carcinoma is diagnosed [3].

Cribriform-morular thyroid carcinomas are usually well-delimited neoplasms microscopically showing a blending of cribriform, papillary, follicular, solid and trabecular patterns with squamoid morules [2-5] (Fig. 1). Cribriform and follicular structures lack colloid, and solid areas are composed of oval to spindle cells. Papillae are lined by tall or cuboidal cells with occasional nuclear features of conventional PTC and frequent nuclear pseudostratification. Morules with biotin-rich clear nuclei but without keratinization can appear in variable proportions in cribriform, follicular, papillary, solid and/or trabecular areas. This is the only primary thyroid tumour with strong nuclear and cytoplasmic immunoreactivity for β-catenin [2 5]. Tumour cells are negative or focally positive for thyroglobulin, but always positive for thyroid transcription factor 1 (TTF-1) and negative for calcitonin. There is characteristic positivity for alfa and beta-estrogen and progesterone receptors, cytokeratin (CK) 7, CK 19 and negativity for CK 20. Morules are also positive for β-catenin and can easily be distinguished by their positivity for CD10, CA19.9 and CDX2, an intestine-specific homeobox gene transcription factor.

In fine needle aspiration biopsy the cytological samples are hypercellular and usually show nuclear features of conventional papillary thyroid carcinoma, but the presence of cribriform and/or morular structures, as well as the nuclear positivity for β-catenin are highly indicative of cribriform-morular thyroid carcinoma [2 5].

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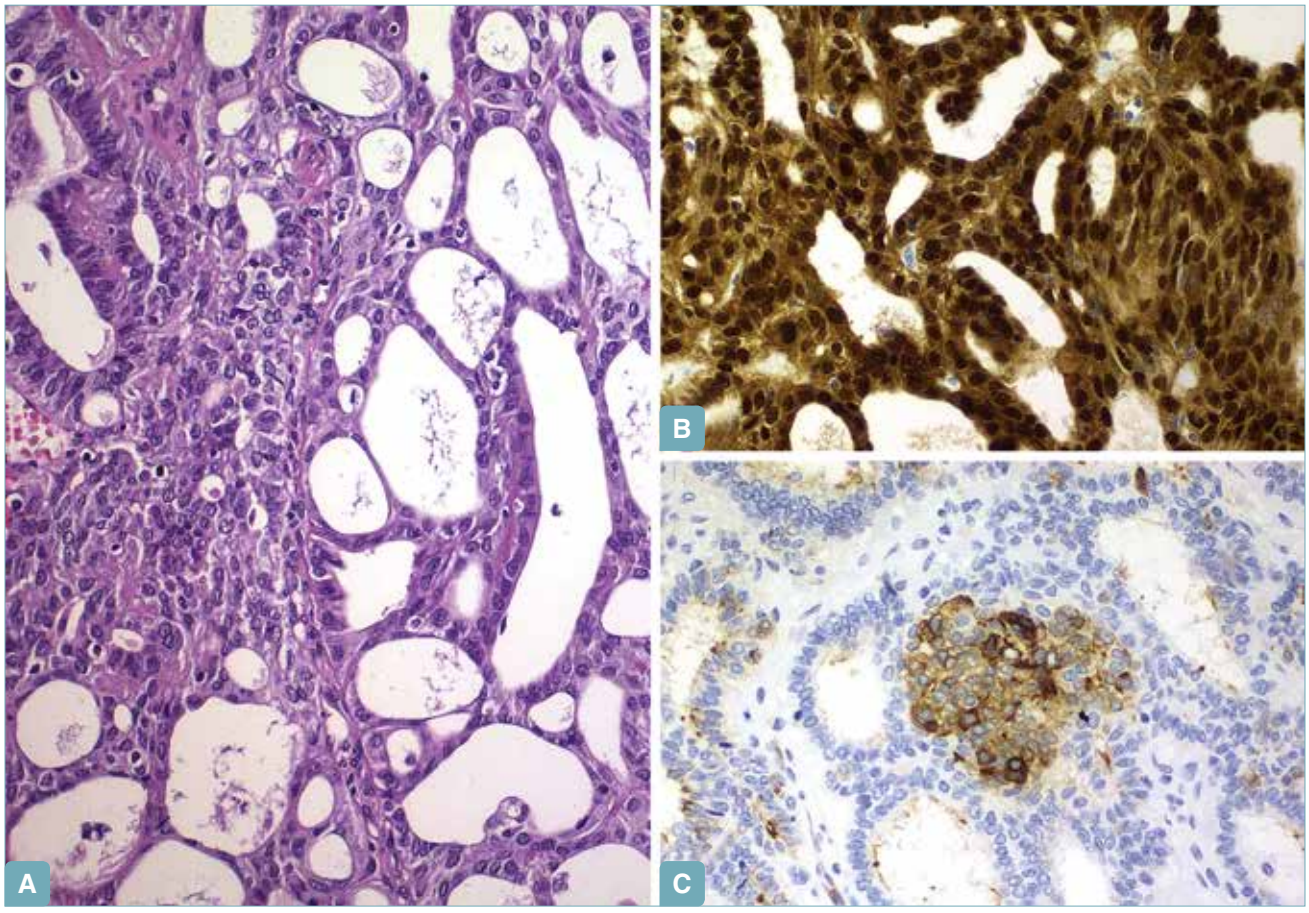

Fig. 1. Cribriform-morular thyroid carcinoma showing a predominant cribriform pattern **(A)**, and strong nuclear and cytoplasmic immunoreactivity for β-catenin **(B)**. The morules are positive for CD10 **(C)**.

In normal follicular cells the APC protein, along with axin, glycogen synthetase kinase 3β (GSK3β) and casein kinase 1α (CK1α), forms a destruction complex that maintains the cytoplasmic concentrations of β-catenin low. The characteristic positivity for β-catenin in familial cases of cribriform-morular thyroid carcinoma results from the permanent activation of the wingless (WTN/β-catenin) signaling pathway secondary to germline *APC* gene mutations. In these cases β-catenin accumulates in the cytoplasm and then is translocated into the nucleus where it produces the constitutive expression of genes such as *MYC*, *CCND1* (cyclin D1), *Axin2* and *DKK1*, involved in cell proliferation and loss of differentiation[2]. Consistent with Knudson's two-hit model, additional *APC* somatic mutations have also been found in about 50% of thyroid carcinomas associated with FAP. Interestingly, the diagnosis of cribriform-morular thyroid carcinoma is previous to the diagnosis of FAP in up to 40% of cases [2 6]. Because most germline *APC* mutations related with thyroid cancer occur in the same genomic area associated with congenital hypertrophy of the retinal pigmented epithelium, fundoscopy is a good clinical approach to confirm the germline *APC* mutation while awaiting genetic studies [5].

In sporadic cribriform-morular thyroid carcinomas, somatic *APC* gene mutations (exon 15 at codon 1309) with a negative dominant effect, or combinations of somatic mutations in phenotypically equivalent genes such as *CTNNB1* and *AXIN1* are involved in the constitutive activation of the WTN/β-catenin pathway. Although *BRAF* gene mutations have not been found in these tumors, it has been proposed that the presence of *RET*/*PTC1* and *RET*/*PTC3* rearrangements, as well as mutations in *PIK3CA* and *K-RAS* genes, could also act as additional upstream effectors in the WTN/β-catenin pathway [2 7]. The striking predominance of this tumour in young women (ratio female-male of 61:1) fits with the strong positivity for alfa and beta-estrogen receptors and progesterone receptors in tumour cells,

and additionally suggests a promoter growth role for sex hormones in the development of this tumour type [2 5]. This neoplasm generally has a good prognosis, but neuroendocrine differentiation [8], poorly differentiated features (including high Ki-67 labeling index) [9] and/or telomerase reverse transcriptase (*TERT*) promoter mutations [10] may help to predict more aggressive clinical behavior in cribriform-morular thyroid carcinomas.

Cribriform-morular thyroid carcinoma is a distinctive neoplasm that seems to emerge from endodermal non-committed follicular cells. In this rare thyroid tumour, the constitutive activation of the WTN/β-catenin pathway justifies its primitive intestinal-like appearance. Its peculiar clinicopathological and molecular features support its consideration as an independent tumour entity.

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Conflict of interest statement

None declared.

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