Cribriform morular thyroid carcinoma: Clinicopathological and molecular basis for both a preventive and therapeutic approach for a rare tumor (Review)

SOLEDAD CAMESELLE-GARCÍA[1], IHAB ABDULKADER-NALLIB[2,3], MARÍA SÁNCHEZ-ARES[2] and JOSÉ MANUEL CAMESELLE-TEIJEIRO[2,3]

[1]Department of Medical Oncology, University Hospital Complex of Ourense, Galician Healthcare Service (SERGAS), 32005 Ourense, Spain; [2]Department of Pathology, Clinical University Hospital of Santiago de Compostela, Health Research Institute of Santiago de Compostela (IDIS), Galician Healthcare Service (SERGAS), 15706 Santiago de Compostela, Spain; [3]School of Medicine, University of Santiago de Compostela (USC), 15782 Santiago de Compostela, Spain

Received April 11, 2024; Accepted July 1, 2024

DOI: 10.3892/or.2024.8778

Abstract. Cribriform morular thyroid carcinoma (CMTC) has been included within the group of thyroid tumors of uncertain histogenesis in the recent World Health Organization classification of endocrine tumors. Most CMTCs occur in young euthyroid women with multiple (and bilateral) thyroid nodules in cases associated with familial adenomatous polyposis (FAP) or as single nodules in sporadic cases. CMTC generally behaves indolently, while aggressiveness and mortality are associated with high-grade CMTC. This tumor histologically displays a distinctive combination of growth patterns with morular structures. Strong diffuse nuclear and cytoplasmic immunostaining for β-catenin is the hallmark of CMTC. Tumor cells are also positive for thyroid transcription factor-1 and for estrogen and progesterone receptors, but negative for thyroglobulin and calcitonin. It is possible that the CMTC phenotype could result from blockage in the terminal/follicular differentiation of follicular cells (or their precursor cells) secondary to the permanent activation of the Wnt/β-catenin pathway. In CMTC, the activation of the Wnt/β-catenin pathway is the central pathogenetic event, which in FAP-associated cases results from germline mutations of the APC regulator of WNT signaling pathway (*APC*) gene, and in sporadic cases from somatic inactivating mutations in the *APC*, *AXIN1* and *CTNNB1* genes. Estrogens appear to play a tumor-promoting role by stimulating both the PI3K/AKT/mTOR and the RAS/RAF/MAPK signaling pathways. Additional somatic mutations (i.e. RET rearrangements, or KRAS, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α, telomerase reverse transcriptase or tumor protein 53 mutations) may further potentiate the development and progression of CMTC. While hemithyroidectomy would be the treatment of choice for sporadic cases without high-risk data, total thyroidectomy would be indicated in FAP-associated cases. There is insufficient clinical data to propose therapies targeting the Wnt/β-catenin pathway, but multikinase or selective inhibitors could be used in a manner analogous to that of conventional thyroid tumors. It is also unknown whether adjuvant antiestrogenic therapy could be useful in the subgroup of women undergoing surgery with high-risk CMTC, as well as when there is tumor recurrence and/or metastasis.

Correspondence to: Dr José Manuel Cameselle-Teijeiro, Department of Pathology, Hospital Universitario de Santiago de Compostela; Travesía Choupana s/n, 15706 Santiago de Compostela, Spain
E-mail: josemanuel.cameselle@usc.es

Key words: cribriform morular thyroid carcinoma, familial adenomatous polyposis, Wnt/β-catenin signaling pathway, β-catenin, APC, estrogen receptors

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1. Introduction

Cribriform morular thyroid carcinoma (CMTC) is a type of TC associated with familial adenomatous polyposis (FAP), which can also at times occur sporadically (1). This rare tumor was first identified in patients with FAP as a distinctive follicular neoplasm different from conventional follicular TC (FTC)

and papillary TC (PTC), usually presenting with multiple and bilateral tumor foci (2). Later, the sporadic counterpart of this neoplasm was reported as a subtype of PTC (cribriform morular variant) (3). In fact, both the familial and sporadic forms of this tumor were designated as the cribriform-morular variant of PTC in the 4th edition of the classification of thyroid tumors of the World Health Organization (WHO) (4). More recently, the peculiar combination of growth patterns of CMTC has been associated with the permanent activation of the Wnt/β-catenin signaling pathway (5). Consequently, this tumor has been included as a distinct TC in the most recent WHO classification of endocrine and neuroendocrine tumors, within the group of thyroid tumors of uncertain histogenesis (1).

As this new tumor entity remains poorly understood (1,6-9), for the present review, the MEDLINE-PubMed database (https://pubmed.ncbi.nlm.nih.gov) was searched for entries added up to January 2024 with the search terms 'cribriform', 'morular' and 'thyroid' to evaluate the epidemiological, clinicopathological, immunohistochemical and molecular features of CMTC as well as its possible histogenesis. Only papers written in English were reviewed. At the same time, the study aimed to underscore the molecular characteristics of this peculiar neoplasm as a basis for proposing an approach that is both preventive and therapeutic.

2. Epidemiological characteristics

CMTC accounts for 0.16-0.5% of all cases of TC (10,11) and 0.16-0.66% of the cases of PTC (3,12,13). Although a case of CMTC has been reported in a 15-year-old female with hypothyroidism secondary to neck radiotherapy due to Hodgkin's disease (14), no increased prevalence of CMTC was detected in a population exposed to ionizing radiation post-Chernobyl (11). SARS-CoV-2 infection has been reported in one sporadic case of CMTC and lymphocytic thyroiditis (15).

CMTC has been reported in 0.4-2.6% of patients with FAP (16,17), but these percentages increased to 3-12% when ultrasonography (US) was used (17,18), and it was detected in up to 16% of patients with FAP when US in combination with fine needle aspiration cytology (FNAC) was carried out (19). A higher risk and incidence of CMTC in Hispanic patients with FAP have also been reported (20). About 60% of cases of CMTC occur in the setting of FAP and in 40% of these cases, it is the first clinical manifestation of FAP (13,16,18,21-23). Cases of CMTC and a conventional subtype of PTC in different members of the same family sharing the same adenomatous polyposis coli (*APC*) germline mutation have been described (18,24,25). It is possible that cases of conventional PTC in these families are actually cases of incidental PTC not related to the *APC* germline mutation.

3. Clinical findings

Most patients with CMTC are euthyroid young women (female-to-male ratio, ~61:1), and the mean age at diagnosis was determined to be 25 years (range, 8-69 years), both for sporadic and for FAP-associated CMTC (5,12,26). CMTC may be incidentally detected during physical and/or US examination with or without FNAC (19) or present as a painless mass, dysphagia and/or hoarseness (14,27,28). During US screening, most nodules are observed to be well-defined, oval to round, hypoechoic and solid without calcifications (with benign-looking features) (17,18,29,30). While most cases of familial CMTC are multifocal (and bilateral) at diagnosis, most sporadic cases present as single nodules (5,26,31). Because congenital hypertrophy of the retinal pigment epithelium (CHRPE) is reported to occur in up to 80% of individuals with FAP (32,33), and ophthalmoscopic examination can help to clinically confirm hereditary cases of CMTC (34).

In addition to colorectal adenomatous polyps and cancer (33-35), the coexistence of TC with medulloblastoma (36), stomach polyps (37), duodenal polyps (36,38), ampullary neoplasms (25,37), hepatoblastoma (39), adrenal adenoma (25), endometrial cancer (40), osteomas (35), lipomas (35), sebaceous and epidermoid cysts (35), desmoid tumors (25,35,38) as well as bilateral breast fibromatosis in the context of silicone prosthetics (41) have been described in patients with FAP.

4. Pathological features

CMTC is encapsulated or well demarcated and often partially lobulated by sclerotic septa (2,3). Histologically, the tumor exhibits 'an intricate blending of cribriform, follicular, papillary, trabecular and solid patterns of growth, with morular (squamoid) areas' (3) (Fig. 1). In different cases of CMTC and even within the same tumor, the percentage of these different growth patterns is variable. The cribriform pattern is composed of tumor cells without interposed stroma that merge with tubulo-glandular follicles (devoid of colloid), as well as with papillae. The papillae are lined by cuboidal or tall cells, often mimicking the tall-cell or columnar-cell subtypes of PTC (3,8). There is also continuity with areas of the trabecular pattern, reminiscent of the hyalinizing trabecular tumor and areas of solid patterns with spindle-like cells (1,3,5). Psammoma bodies are rare. Nuclei are round to oval, clear and can show irregular contours, grooves and pseudoinclusions. Morular structures are nests of nonkeratinized cells having biotin-rich nuclei with characteristic chromatin clearance (1,3,5). Ultrastructurally, these clear morular nuclei have numerous aligned quasiparallel filaments (10,42,43).

There are usually <5 mitotic figures per 2 mm^2. Vascular and capsular invasion have been reported in 30 and 40% of tumors, respectively (2,3,5,44-47). Isolated cases with marked stromal hyalinization and calcification (48), adamantinous-like pattern (44), adenoid cystic carcinoma-like areas (49) or focal squamous differentiation (9) have been reported.

According to the criteria of the new edition of the WHO classification of thyroid tumors (1,6), rare cases of 'high-grade CMTC' with necrosis and/or high proliferative activity have also been reported (7,9,46,50-52).

5. Immunohistochemical profile

Strong diffuse nuclear and cytoplasmic immunostaining for β-catenin is the hallmark of CMTC (1,5,7) (Fig. 1). The immunohistochemical profile of CMTC is summarized in Table I. Tumor cells are always immunoreactive for thyroid transcription factor-1 (TTF1)/NK2 homeobox 1 (NKX2-1)

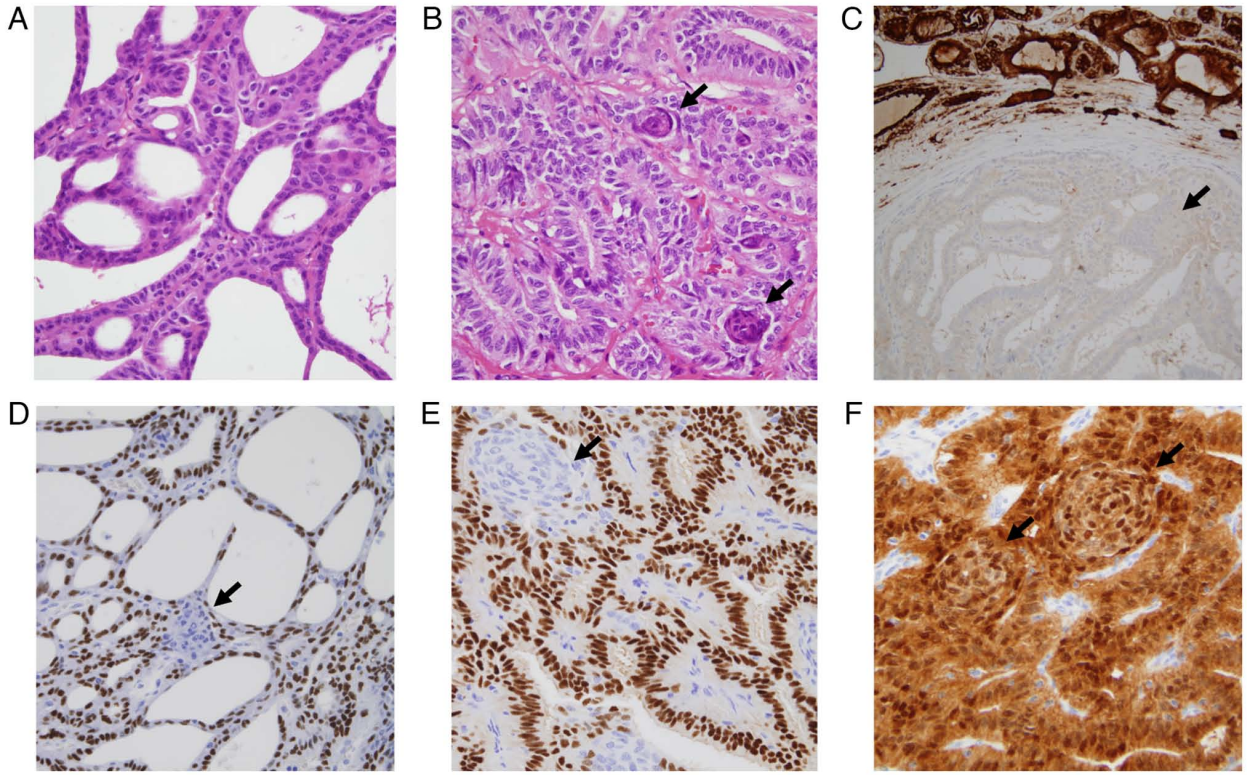


Figure 1. Microscopic features of morular cribriform thyroid carcinoma. (A) Characteristic cribriform and follicular tumor growth pattern without colloid. (B) Tumor area with predominance of trabecular and follicular patterns (without colloid) and presence of morular structures (arrows). (C) Well-defined tumor area showing predominance of the cribriform pattern, a morular (squamoid) structure (arrow), papillae, lack of colloid and thyroglobulin negativity. (D) Cribriform and papillary tumor area with nuclear positivity for TTF1/NKX2-1 except in the morular structure (arrow). (E) Diffuse nuclear positivity for estrogen receptors in the areas of the tumor with a trabecular growth pattern and negativity in the morular component (arrow). (F) Tumor area with predominance of the trabecular, follicular growth pattern and morular structures (arrows) showing diffuse nuclear and cytoplasmic positivity for β-catenin (original magnification: A, C and D, x200x; B, E and F, x400. Stains: A and B, hematoxylin-eosin; C, thyroglobulin; D, TTF1/NKX2-1; E, estrogen receptors; and F, β-catenin). TTF1/NKX2-1, NK2 homeobox 1.

(clones 8G3G7/1 and SPT24) and keratin (KRT) (7), as well as negative for thyroglobulin (Tg), calcitonin and KRT20 (1,5,53). Variable staining for paired box-8 (PAX8) (clones MRQ-50 and SP348) has been detected (5,7,8). Strong positivity for estrogen receptor (ER) (Fig. 1) and progesterone receptor (PR) is highly characteristic, but focal reactivity for androgen receptors has also been detected (1,5,7,11,53). The Ki-67 proliferative index is usually <5% (1,5).

Morular structures also show aberrant nuclear and cytoplasmic positivity for β-catenin (Fig. 1) and can be easily identified in the tumor by their characteristic positivity for caudal type homeobox 2 (CDX2), CA19.9, CD10, CD5 and KRT5 (3,5,7,56,57).

6. Follicular lineage

CMTC has been initially considered a distinct type of follicular cell neoplasm associated with FAP (2). According to its nuclear characteristics and the immunohistochemical data (particularly the KRT profile), this tumor was later considered a variant of PTC (3,4). Of note, *RET* rearrangements, a molecular alteration typical of PTC, have also been described in certain cases of CMTC (44,40,58). Despite the features shared by PTC and CMTC, our group postulated that the latter deserves to be considered its own tumor category, CMTC, based on its 'peculiar primitive endodermal (intestinal-like) type phenotype and permanent activation of the wingless (Wnt/β-catenin) signaling pathway' (5). Different researchers have proposed that CMTC arises due to germline or somatic *APC* mutations or because of somatic mutations in functionally equivalent genes related to the Wnt/β-catenin signaling pathway (5,58-60).

The immunohistochemical profile (KRT pattern, positivity for TTF1, variable staining for PAX8 and negativity for calcitonin and CEA), fits with a primary non-neuroendocrine epithelial neoplasm of the thyroid gland. A conclusive follicular cell derivation has not been demonstrated, however, due to negativity for Tg (both at the protein and mRNA levels), thyroperoxidase and solute carrier family 5 member 5 (NIS) (8).

A putative thymic/ultimobranchial pouch-related differentiation has also been proposed due to the lack of Tg in the tumor cells, the occasional negativity for PAX8 and the phenotype of the morular component, positivity for KRT5 and CD5 and negativity for p63, p40, TTF1 and PAX8 (7). Others (8), however, considered that the negativity for p40 and p63 described by Boyraz *et al* (7) in the same series contradicts their own hypothesis due to the recognized positivity for p40 and p63 in both thymic tissue and intrathyroidal remains of the ultimobranchial body (solid cell nests) (61). A relation to the ultimobranchial body has also been proposed in a unique case of CMTC based on positivity for p40 in the poorly differentiated component (9); in this case, however, the

Table I. Immunohistochemical profile of morular cribriform thyroid carcinoma.

Marker	Main tumor cells	Morular structures	(Refs.)
β-catenin	+	+	(1,5,7,8,56)
TTF1/NKX2-1	+	-	(1,5,7-9,56)
PAX8	-/+[a]	-	(1,5,7,8)
Thyroglobulin	-	-	(1,5,8,56)
Thyroperoxidase	-	-	(8)
Calcitonin	-	-	(1,5)
CEA	-	-	(5,8)
Chromogranin	-[b]	-	(5,44)
Synaptophysin	-[b]	-	(5,44)
β-estrogen receptors	+	-	(1,5,8,11)
Progesterone receptors	+	-	(1,5,8,11)
Androgen receptors	+/-	-	(5)
KRT5	-	+	(1,7)
KRT7	+	+/-	(5,8)
KRT19	+	-	(5)
KRT20	-	-	(1,5,8)
KRT5/6	+	+	(1,8)
KRT (clone AE1/AE3)	+	+	(5)
KRT (clone 34βE12)	+	+	(1,5)
KRT (clone CAM5.2)	+	+	(5)
EMA	+	NS	(1,3,5)
Vimentin	+	-	(5)
CA 19.9	-	+	(5)
CA 125	-	-	(5)
CDX2	-	+	(1,5,8,56,57)
CD5	-	+	(1,7-9)
CD10	-/+	+	(1,5,7-9)
CD117 (c-KIT)	-/+	-	(5,8)
E-cadherin	+	-/+	(1,5)
HBME1	+/-	-	(5,7)
Galectin-3	+	-/+	(5,8)
APC	+	NS	(51)
LEF-1	+	NS	(54)
BCL-2	+	+	(5,44)
p27	+	NS	(5,44)
Rb	+	NS	(3,5)
β-hCG	+	NS	(5,55)
NIS	-	-	(8)
EGFR	-	-	(5,7,8,44)
p53	+/-[c]	NS	(7,8)
p63	-	-	(5,7,8)
p40	-[d]	-	(7-9)
Calretinin	-	-	(5)
WT1	-	-	(1,5,44)
SATB2	-	-	(8)

[a]Negativity and positivity have been described with both monoclonal and polyclonal antibodies; [b]an isolated case has been described with tumor areas positive for chromogranin and synaptophysin (44); [c]diffuse nuclear positivity has been reported to be associated with high tumor grade; [d]an isolated case with strong nuclear positivity in poorly differentiated areas has been described (9). TTF1/NKX2-1, NK2 homeobox 1; PAX8, paired box 8; CEA, carcinoembryonic antigen; KRT, keratin; EMA, epithelial membrane antigen; CA, carbohydrate antigen; CD, cluster of differentiation; HBME1, Hector Battifora mesothelial cell-1; APC, adenomatous polyposis coli; LEF-1, lymphoid-enhancing factor-1; Rb, retinoblastoma; β-hCG, human chorionic gonadotropin beta; NIS, sodium-iodide symporter; EGFR; epidermal growth factor receptor; WT1, Wilms tumor protein; SATB2, SATB homeobox 2; NS, not specified.

negativity for p40 in the differentiated component of the tumor (including the morulae) as well as the total negativity for CD5 argue against both the ultimobranchial and the thymic derivations, respectively. Another case, however, supports an origin from follicular cells (or their endodermal precursors) based on the cytopathological similarities of this tumor with classic PTC (8).

Morular structures (positive for CD10 and CDX2) have been the subject of different interpretations (62-64). Of note, they are characteristically present in a series of tumors such as fetal adenocarcinoma of the lung (65), pancreatoblastoma (66), mesonephric-like adenocarcinoma of the ovary (67), colorectal polyps (68) and others (69), all of which share the permanent activation of the Wnt/β-catenin pathway. It is recognized that the activation of Wnt/β-catenin signaling, through transcription factor CDX2, activates small intestine gene expression at low levels and colonic gene expression at higher levels (70). These mechanisms of embryonic intestinal induction would explain both the blockage in the terminal/follicular differentiation of follicular cells (or their precursor cells) in CMTC, as well as its phenotype. CMTC would be another example of TC with endodermal/intestinal-like (non-committed) differentiation (71). In fact, the immunophenotype of CMTC cells fits into the progenitor stem cell phase in its continuum toward thyroid follicular cells, according to a recent study (72).

In summary, the molecular alterations linked to the constitutive activation of the Wnt/β-catenin pathway are consistent with the development and phenotype of the CMTC from follicular cells (5). Additional points supporting an origin of CMTC from follicular cells (or their precursor cells) are as follows (8): a) The cytoarchitectural and immunohistochemical similarities with other neoplasms of follicular lineage, particularly with PTC; and b) the multicentricity of CMTC associated with patients with FAP (usually with molecularly different tumors), which is easier to explain when they are derived from different follicular cells (or precursor thyroid cells) than from multiple intrathyroid thymic or branchial remnants. Of note, a light increase in Tg levels along with a slight iodine uptake in pulmonary metastases of CMTC after treatment with ^{131}I has been described (73). Furthermore, a rapid increase in serum Tg levels parallel to histologically confirmed lung metastases has also been reported in another case of CMTC after treatment with ^{131}I and a selective inhibitor of receptor tyrosine kinases (lenvatinib) (74). It is still necessary to carry out functional studies on Wnt/β-catenin pathway inactivation in primary CMTC cell cultures to confirm (or discard) this hypothesis (8).

7. Pathogenesis

FAP is an autosomal dominant genetic disorder caused by germline mutations in the *APC* gene (34). The constitutive activation of the Wnt/β-catenin signaling pathway has a central role in the pathogenesis of CMTC, mainly through inactivating mutations in the *APC*, *CTNNB1* and *AXIN1* genes (5) (Fig. 2). Additional molecular alterations may have a synergistic effect on this pathway, while sex hormones appear to play a promoting role in CMTC development, which is elaborated on further below.

CMTC and FAP. More than 85% of germline *APC* mutations in patients with CMTC have been detected in exon 15 (codons 463 to 1,387), in the same genomic location usually associated with CHRPE (39). This area also includes a hotspot (codon 1,061) for CMTC and hepatoblastoma (25,35,37,39), but mutations in codons 140, 159, 161, 213, 278, 302, 313, 325, 332, 418, 471, 499, 554, 578, 582, 593, 625, 654, 698, 704, 737, 769, 778, 804, 834, 848, 935, 937, 938, 964, 976, 977, 979, 993, 1,062, 1,068, 1,073, 1,105, 1,110, 1,157, 1,275, 1,307, 1,309, 1,394, 1,465 and 2,092 have also been described (33,56,75,76). When comparing the prevalence of *APC* mutations in patients with FAP and TC in relation to the prevalence of such mutations in unselected individuals with FAP, a higher risk of CMTC exists in the population harboring *APC* mutations proximal to the 5' end (proximal to codon 528) as well as in the established high-risk group with mutation at codon 1,061 (75). It is noteworthy that part of the β-catenin binding sites and the axin binding sites are outside the mutation cluster region (codons 1,286 to 1,513) of the *APC* gene (7).

When Wnt/β-catenin signaling is not activated, the APC protein, together with the scaffolding protein Axin, serine/threonine kinases CK1 and glycogen synthase kinase (GSK)3β and β-catenin, form a 'destruction complex' that phosphorylates β-catenin, thus promoting its ubiquitination and proteosomal degradation (Fig. 2). *APC* mutations lead to a truncated APC protein unable to bind to the destruction complex, which prevents β-catenin phosphorylation and leads to its accumulation in the cytoplasm (77) (Fig. 2). Therefore, the accumulated β-catenin translocates to the nucleus where it binds to T-cell factor (TCF)/lymphoid enhancer factor family DNA-binding proteins triggering the constitutive expression of Wnt target genes (*MYC, cyclin D1, AXIN2* and *Dickkopf 1*) involved in proliferation, invasion and loss of differentiation, as well as in oncogenesis (77). The Wnt/β-catenin pathway plays a key role in the maintenance of the intestinal stem cell niche (78) and it is well known that activation of this signaling pathway by *APC* mutation is sufficient to induce intestinal epithelial hyperproliferation and polyposis (78), matching both the phenotype and the risk of CMTC in patients with FAP.

As the function-inactivating germline mutation of the *APC* gene can be partially compensated for by the other allele, an additional somatic mutation of the *APC* gene or another phenotypically equivalent gene (second hit), is required for tumor development (25,52). In fact, in patients with FAP, CMTC is frequently multifocal and shows different somatic *APC* mutations in each tumor (79). A missense *AXIN1* somatic mutation in exon 7 was detected by our group in a case of CMTC associated with FAP (80). In other cases of familial CMTCs, second-hit somatic mutations in the lysine methyltransferase 2D (*KMT2D*) and *KMT2C* genes have been reported (25). Of note, both *KMT2D* and *KMT2C* have been shown to be transcriptional regulators of the ER gene (81).

Sporadic CMTC. In cases of CMTC without *APC* germline mutation, the coexistence of two different oncogenic somatic variants of the *APC* gene has been detected (8,82). In a sporadic case of CTCM with a single somatic *APC* mutation at codon 1,309, the dominant negative effect of this mutation agrees with the two-hit Knudson hypothesis (59).

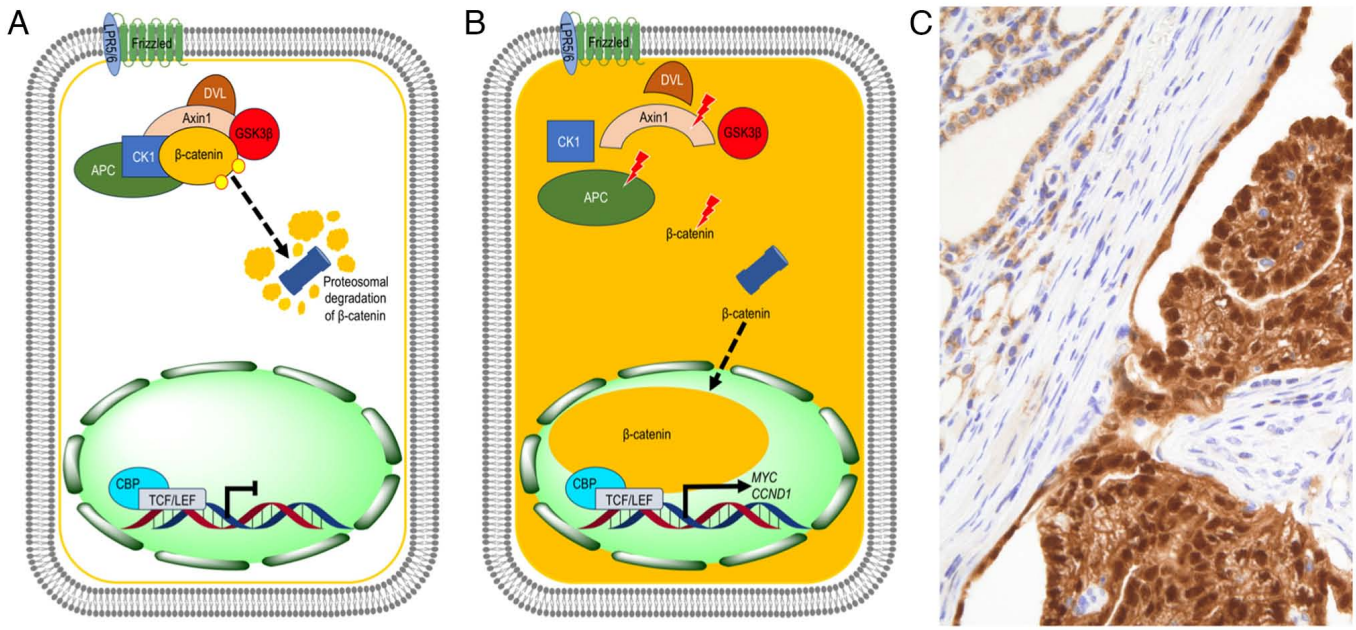


Figure 2. Schematic representation of the WNT signaling pathway in CMTC. (A) In normal thyroid cells, the canonical (β-catenin-dependent) WNT signaling is in the 'off' state because the *APC* protein, together with the scaffolding protein Axin, serine/threonine kinases CK1 and GSK3β, and β-catenin, form a 'destruction complex' that phosphorylates β-catenin, thus promoting its ubiquitination and proteasomal degradation. (B) In CMTC cells, different somatic mutations in *APC*, *CTNNB1* and/or *AXIN1* genes alter the destruction complex, impairing β-catenin phosphorylation and degradation in the proteasome. β-catenin accumulates in the cytoplasm and subsequently translocates to the nucleus, where it binds to the TCF/LEF family to activate the transcription of target genes involved in proliferation and loss of differentiation, such as *MYC* and *CCND1*. (C) Localization of β-catenin in CMTC. Tumor cells (right) show characteristic nuclear and cytoplasmic positivity for β-catenin, while non-tumor cells (left) show membrane positivity with discrete cytoplasmic immunostaining (original magnification, x400). CMTC, cribriform morular thyroid carcinoma; TCF/LEF, T-cell factor/lymphoid enhancer factor; CCND1, cyclin D1; APC, APC regulator of WNT signaling pathway; CK1, casein kinase 1; GSK3β, glycogen synthase kinase 3β; DVL, disheveled; CBP, cyclic adenosine monophosphate responsive element binding protein 1 binding protein; LRP5/6, low-density lipoprotein receptor-related protein 5/6.

The existence of sporadic cases of CMTC with missense somatic mutations of exon 3 of the β-catenin gene (*CTNNB1*) lacking mutations in *APC* or loss of heterozygosity near the *APC* gene (83), have confirmed the key role of the constitutive activation of the Wnt/β-catenin pathway in the development of CMTC. In these cases, mutations in exon 3 of *CTNNB1* were located at codons 29, 22, 39, 44, 49, 54 and 56. In a way similar to that described for the *APC* gene, the multicentric CMTCs showed different somatic mutations of *CTNNB1* (83), additionally supporting an independent origin of each of the foci of these multifocal tumors.

In another sporadic case of CMTC, a missense *AXIN1* somatic mutation, has been identified in exon 1 (80).

Additional molecular alterations in FAP-associated CMTC. In addition to germline *APC* mutations, certain cases of familial CMTC showed molecular alterations typically described in follicular-derived TC. In fact, *coiled-coil domain containing 6::RET* and *nuclear receptor coactivator 4::RET* rearrangements have been reported in two CMTC cases (III-1 and III-11) from a family (kindred #1) with FAP-associated CMTC (40), and *RET* translocations have also been described in other series (44,58). A somatic *K-RAS* mutation (p.Gln61Lys) was detected in FAP-associated CMTC (84). An activating *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α* (*PIK3CA*) mutation and copy number gains of *BRCA2*, *fibroblast growth factor* (*FGF23*), *FGFR1* and *PIK3CB* have been detected exclusively in the high-grade component of a FAP-associated CMTC, with tumor protein (*TP*)*53* mutation in the well-differentiated component and concurrent *APC* and telomerase reverse transcriptase (*TERT*) promoter mutations in both tumor components (9).

Additional molecular alterations in sporadic CMTC. Somatic *KRAS* mutation was reported in one case of sporadic CMTC (80). The same mutation in exon 9, codon 545 of the *PIK3CA* gene (p.Glu545Ala) was detected in 3 cases of sporadic CMTC (85). *TERT* promoter mutation was described in sporadic CMTC (47). As has been confirmed in conventional follicular cell differentiated TC (86), as well as in cases with FAP, sporadic CMTC cases with *TERT* promoter mutations have been associated with aggressive behavior (47). Alterations of *TP53* do not appear to be an early event in CMTC tumorigenesis (8,40).

Sex hormones as a growth promoter of CMTC. ERs may have a role in follicular-lineage TC through genomic (ER-α and ER-β isoforms) and non-genomic pathways, stimulating both the PI3K/AKT/mTOR and the RAS/RAF/MAPK signaling pathways, resulting in increased reactive oxygen species production and cell cycle progression/proliferation through the modulation of cyclin D1, as well as angiogenesis and migration (87). Since genetic alterations in the PI3K/AKT/mTOR pathway mainly promote the transformation of TC with follicular growth pattern (FTC and follicular subtype of PTC) and alterations in the MAPK pathway are associated with PTC with a papillary growth pattern (88), the activation of both pathways by estrogens is consistent with the mixed (papillary

Table II. Main clinicopathological features of patients with cribriform morular thyroid carcinoma and distant metastasis.

Author(s), year	Sex/age, years	FAP	Relevant tumor findings	Distant metastasis	Follow-up, months	Outcome	(Refs.)
Okamoto *et al*, 1995	F/29	NS	TS: 50 mm	Bone and lungs	45.6	Died with widespread metastases	(10)
Okamoto *et al*, 1995	F/36	NS	TS: 17 mm	Lungs	92.4	Alive with metastases	(10)
Perrier *et al*, 1998	F/36	Yes	Two local recurrences at 6 and 84 months after the initial surgery	Extensive mediastinal adenopathy	85	Treatment after TT with ^{131}I and T_4 suppression. Died of cardiac tamponade due to tumor infiltration.	(16)
Fenton *et al*, 2001	F/20	Yes	Recurrence in the right supraclavicular fossa[a] 29 years after TT	Extensive metastasis in the cervical spine (C2-C4, T1 and T2), 360 months after TT	360	Initial TT followed by ^{131}I. After radiotherapy sessions on the metastases, the patient developed basal pneumonia and died.	(36)
Cameselle-Teijeiro *et al*, 2009	M/42	Yes	Angioinvasive neoplasm with positivity for chromogranin and synaptophysin in 40% of tumor cells. 7 MF/10 HPF. Ki-67 index: 60%. *APC* p.Thr1493Thr *RET* rearrangements	Bilateral lung metastases at diagnosis	23	After diagnosis, radiolabeled somatostatin analogue therapy (dotatoc-^{90}Yttrium, 5 GBq) was attempted with partial response to treatment. Developed multiple brain metastases treated with palliative whole-brain radiotherapy. The patient continued to deteriorate and died.	(44)
Nakazawa *et al*, 2013	F/35	No	TS: 90 mm. Poorly differentiated features (50%). Necrosis and prominent venous invasion. 4 MF/10 HPF. Ki-67 index: 15-20%. *APC* p.Cys520Tyr_fsX534	Multiple osteolytic metastases (pelvis and left femur), bilateral lung metastases[a] and hilar lympha-denopathy[a] at diagnosis	9	TT followed by external radiotherapy (23 Gy) and therapy with ^{131}I. Alive with multiple bone and pulmonary metastases.	(46)
Alikhan *et al*, 2015	F/25	Yes	Tumor infiltration of surgical margins. Positivity for β-hCG in tumor cells. Tumor recurrence and cervical lymph node metastasis 12 months after TT.	Left pleural effusion and pleural metastases 36 months after TT	49	TT followed by 30 mCi ^{131}I. An additional dose of 100 mCi ^{131}I 12 months later. Palliative surgical debulking of the tumor in the neck was performed 48 months after TT.	(55)

Table II. Continued.

Author(s), year	Sex/age, years	FAP	Relevant tumor findings	Distant metastasis	Follow-up, months	Outcome	(Refs.)
Oh *et al*, 2017	F/45	No	TS: 27 mm. Lymphatic and venous tumor invasion with perithyroid soft tissue infiltration. Metastasis in 5 central compartment lymph nodes. *TERT*p (C228T)	Bone metastasis (right humerus, left seventh rib, C7, L2 and L5 vertebrae, and left iliac bone 16 months after diagnosis	48	TT with central lymphadenectomy followed by 150 mCi ^{131}I. Partial resection of left 7th rib and curettage of the right distal humerus and palliative radiotherapy (3,000 cGy) for bone metastases. Second ablation with 200 mCi ^{131}I. Patient is alive multiple metastases and continues to be with followed up.	(47)
Tsuji *et al*, 2018	F/28	No	TS: 91 mm. 6 MF/10 HPF. Ki-67 index: 40·2% (primary tumor) and 22.1% (lung metastases)	Multiple bilateral metastases 36 months after TT	36	TT with cervical lymph node dissection followed by thyrotropin suppression, radioactive iodine ablation and sorafenib therapies.	(51)
Akaishi *et al*, 2018	F/37	NS	TS: 95 mm. Presence of lymphatic and venous tumor invasion	Lung metastases	84	Treated with 3 sessions of high doses of ^{131}I. Alive with lung metastases.	(93)
Ito *et al*, 2019	F/24	Yes	TS: 87 mm. Ki-67 index: 50% (primary tumor) and 70% (lung metastases). No lymph node metastases.	Multiple bilateral metastases 42 months after TT	70	TT with prophylactic central node dissection and right modified radical neck dissection followed by 100 mCi ^{131}I 45 months after surgery. Subsequently, treatment with lenvatinib for 24 months with partial and sustained response of lung metastases during follow-up[b].	(74)
Laforga *et al*, 2020	F/45	NS	TS: 55 mm.	Multiple bilateral metastases 84 months after TT	84	TT followed by 99.5 mCi ^{131}I. Sixty months later, ultrasound findings and slightly increased Tg levels led to a right neck dissection that identified metastasis in 2 lymph nodes. Then, repeated treatment with ^{131}I (147.5 mC1) resulted in slight iodine uptake in pulmonary metastases (histologically confirmed).	(73)

[a]The octeotride-^{111}Indium scan showed intense uptake. [b]At the same time, lenvatinib was also associated with a reduction in the number and size of colon polyps, as well as an increase in Tg levels. FAP, familial adenomatous polyposis; F, female; M, male; NS, not specified; TS, tumor size; TT, total thyroidectomy; ^{131}I, iodine-131; T_4, levothyroxine; MF, mitotic figures; HPF, high-power field; β-hCG, human chorionic gonadotropin; Tg, thyroglobulin.

and follicular) growth pattern of CMTC. Circulating estrogen levels would produce activation of PI3K/AKT/mTOR and the RAS/RAF/MAPK pathways, which, acting synergistically with the Wnt/β-catenin pathway, would explain the notable predominance of CMTC in women, even among patients with FAP (5).

Recent studies using human colonic epithelial cells demonstrated that activation of ERα but not ERβ increased the protein levels of cyclin D1, proliferating cell nuclear antigen and β-catenin, indicating increased proliferation and migration (89). Consequently, an analogous activation mechanism may be hypothesized to be present in CMTC cells, given their 'intestinal/non-committed' phenotype and their richness in ERα, producing and thus further increasing the levels of β-catenin. Since ERβ is overexpressed in PTC stem cells (90), estrogens could also participate in the maintenance of the non-committed status of CMTC cells through the effect on ERβ.

Estrogen-related receptor γ (ERRγ) acts as a tumor suppressor in gastrointestinal cancers through inhibition of the Wnt/β-catenin pathway (91). In preclinical models, it was recently shown that an inverse agonist of ERRγ, GSK5182, enhances the function of NIS protein via the modulation of ERRγ and MAPK signaling, thereby leading to increased responsiveness to radioiodine (RAI) in previously RAI-refractory PTC cells (92). This suggests that estrogens could also participate in the lack of expression of follicular differentiation markers in CMTC cells.

8. Prognostic markers

CMTC generally behaves more indolently than PTC (26,93), with ~12% of cases having lymph node metastases at diagnosis (3,16,18,27,36,45-47,55,58,93,94) and 5% have distant metastases (mainly to the lung, bone and brain) (10,36,44,46, 47,51,55,73,74,93) (Table II). To our knowledge, mortality due to CMTC has been reported in only 4 patients (10,16,36,44).

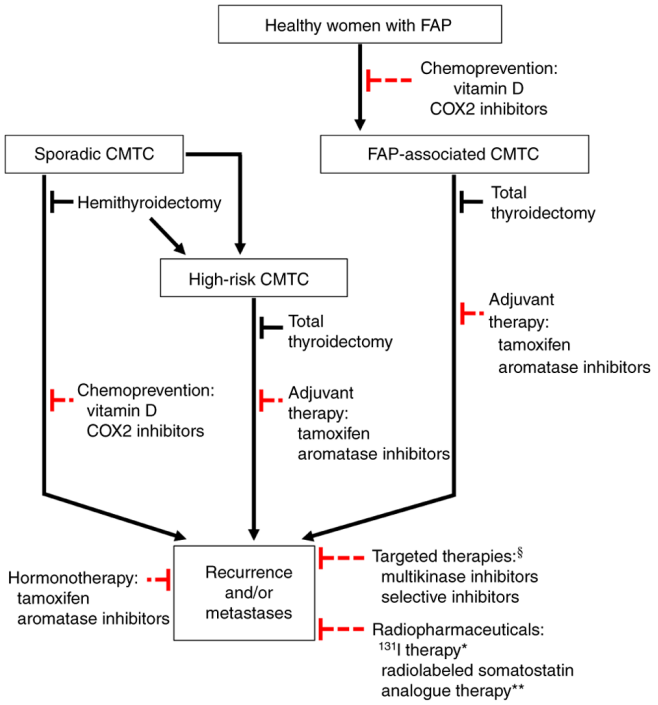
Although cases of encapsulated CMTC with both a high Ki-67 percentage and apoptotic cell count have a favorable prognosis (95), tumors with necrosis and/or a high proliferative index (high-grade CMTC) usually behave aggressively (1,44,46,51). In agreement with the immunohistochemical negativity of CMTC cells for Tg, radioactive iodine whole-body scans show no iodine-avid lesions (47,74), and the serum Tg levels without anti-Tg antibodies are not reliable for following up CMTC patients (47,55,73,96). Curiously, in a case with lung metastases, Tg levels were low for tumor volume, but the associated Tg doubling time was short (74). Uptake of octreotide-^{111}Indium by the CMTC cells has been described in two cases (36,44).

9. Therapeutic and preventive approaches

This review confirms that the permanent activation of the Wnt/β-catenin signaling pathway constitutes the key pathogenetic event for the development of CMTC. High expression of sex hormone receptors (mainly ERα) in tumor cells would act synergistically in young women promoting tumor development through the PI3K/AKT/mTOR and the RAS/RAF/MAPK signaling pathways. Different somatic mutational events (e.g., *RET* rearrangements, or *KRAS*, *PIK3CA*, *TERT* or *TP53* mutations) may further potentiate the development and/or progression of CMTC. These molecular events constitute the basis for the establishment of targeted therapies but given their current state of development, it is reasonable to propose surgical treatment as an initial approach. This treatment should follow the same surgical approach as that currently recommended for PTC (97), with the specifications described below. The role of radioactive isotopes, hormone therapy and the so-called precision medicine treatments are also discussed.

At the same time, all patients with CMTC should be informed and investigated in relation to the FAP syndrome (97), including genetic counseling with screening for colonic tumors and other extracolonic manifestations of the disease in FAP-positive cases.

Surgical treatment. Hemithyroidectomy would be sufficient in cases of sporadic CMTC without high-risk data (Fig. 3). Total thyroidectomy would be indicated in high-risk cases (high-grade



§A synergistic effect could be obtained combining targeted therapies and ^{131}I due to redifferentiation of tumor cells.
*If evidence of elevation of serum levels of thyroglobulin and/or iodine uptake in tumor.
**If evidence of somatostatin receptors in tumor cells and/or positivity in the screening with somatostatin analogues.

Figure 3. Proposal of algorithm for possible treatment and prevention of CMTC. Hemithyroidectomy should be the treatment of choice in cases of sporadic CMTC without high-risk data; however, due to multicentricity, total thyroidectomy should be indicated in FAP-associated cases. Although clinical evidence is still scarce, it may be hypothesized that for FAP-associated CMTC and high-risk CMTC, adjuvant therapy with tamoxifen or aromatase inhibitors could be beneficial. In all cases with recurrence and/or metastases, it may be suggested that hormonotherapy (tamoxifen or aromatase inhibitors), targeted therapies (multikinase or selective inhibitors) and/or radiotherapy (^{131}I treatment or radiolabeled somatostatin analogues) are used. Vitamin D or COX2 inhibitors could hypothetically play a chemopreventive role in healthy women with FAP, as well as in sporadic cases after hemithyroidectomy. A dotted red line was used to indicate the therapeutic proposals where clinical evidence is limited. CMTC, cribriform morular thyroid carcinoma; FAP, familial adenomatous polyposis; COX, cyclooxygenase.

tumors, widely invasive tumors, those with extensive lymphatic or venous vascular invasion and/or with extrathyroidal extension), as well as in all cases of CMTC associated with FAP due to their association with multicentricity and bilaterality. Prophylactic and therapeutic central neck dissection should be performed with the same criteria as those currently used for the treatment of differentiated TC (DTC) of a follicular lineage (97).

Radiopharmaceutical therapy. RAI with ^{131}I has occasionally been used in CMTC (see Table II). However, the use of this isotope in CMTC is controversial, given its uncertain histogenesis and the consistent immunohistochemical negativity of tumor cells for Tg. A few isolated cases with elevation of serum Tg levels (73,74), as well as with slight iodine uptake in pulmonary metastases, have been described (73). Recent data suggest that multikinase inhibitors (MKIs) have the potential for re-establishing ^{131}I uptake in selected patients with RAI refractory metastatic DTC (mDTC) of follicular lineage (98,99). These drugs may also enhance ^{131}I uptake in these mDTCs on a diagnostic and/or post-therapy radioiodine scan, as well as increase the likelihood of a better therapeutic effect for the administered ^{131}I activity (99). Therefore, a divergence between increasing Tg and structural response may be a reliable biomarker of redifferentiation in certain TCs of follicular lineage refractory to radioactive iodine (100). Whether the increase in Tg associated with lenvatinib treatment in a patient with metastatic CMTC (74) represents an example of redifferentiation deserves further investigation. If these findings could be demonstrated in more patients with CMTC, both the follicular lineage of the CMTC and an opportunity for additional ^{131}I therapy would be confirmed.

A partial response to radiolabeled somatostatin analogue therapy (^{90}Yttrium-dotatoc) was reported in a patient with an aggressive CMTC who showed neuroendocrine differentiation in 40% of the tumor cells (44) (Table II). Intense uptake of ^{111}Indium-labelled octreotide was detected in lung and lymph node metastases from another patient with chromogranin- and synaptophysin-negative CMTC (46). The expression of somatostatin receptors in cell cultures and tumor tissue of non-medullary thyroid cancers has been described (101), but limited information is available about these receptors and their possible clinical utility in CMTC (44).

Hormone therapy

Levothyroxine and thyroid stimulating hormone (TSH). There is no rational basis for TSH suppression in patients with CMTC until their follicular lineage has been demonstrated and/or the existence of TSH receptors in their tumor cells has been confirmed. Replacement treatment with levothyroxine, however, should be indicated in patients with CMTC after total thyroidectomy to prevent hypothyroidism; in addition, TSH suppression could be considered given the existence of isolated cases with elevated Tg and/or uptake of ^{131}I in metastases (73,74,93) (Table II).

Antiestrogens. The use of drugs with antiestrogenic activity widely used in hormone-dependent breast cancer, such as tamoxifen and aromatase inhibitors (102), could imply therapeutic repositioning in patients undergoing surgery with high-risk CMTC, as well as when there is tumor recurrence and/or metastasis (Fig. 4); however, there are currently insufficient clinical data in this regard.

The efficacy of preventive therapy with selective ER modulators or aromatase inhibitors in women with germline *APC* gene mutation (FAP) may be questionable, however. The preventive benefits in these patients do not seem clear, since they would mainly be young women who need long periods of treatment with drugs that have serious adverse effects (102-104).

Targeted therapy

Targeting the Wnt/β-catenin pathway. Blocking the constitutive activation of the Wnt/β-catenin pathway constitutes the theoretical cornerstone of targeted treatment of CMTC (Fig. 4). These therapies should be aimed at restoring the β-catenin destruction complex and/or neutralizing the TCF/β-catenin transcription complex, since the initial component of this signaling cascade, i.e., the Wnt ligand/receptor interface, usually does not participate in the development of CMTC (see above). An antineoplastic effect of tankyrase inhibitors has been demonstrated through the degradation of β-catenin by stabilizing axin 2 (105), and CK1 agonists such as SSTC3 have been shown to inhibit the growth of colorectal cancer in mice (106). Inhibitors targeting β-catenin-TFC transcription complex such as LF3 and ICG-001 (107) as well as CREB binding protein inhibitors have shown antineoplastic efficacy with minimal off-target effects (108), but most of these data still come from preclinical models. Small-molecule compounds targeting the Wnt/β-catenin cascade have been used to inhibit cancer stem cells (109). Unfortunately, phase I/II studies using some of these molecules, such as WNT9748 (a first-in-class Porcupine inhibitor) in colorectal cancer have not shown improved antitumor efficacy (110), and data from another study with niclosamide, an anti-helminthic agent inhibitor of the Wnt/β-catenin pathway in colorectal cancer (111) were not published. Therefore, insufficient data exist to support the therapeutic efficacy and safety of therapies targeting the Wnt/β-catenin pathway in CMTC.

Cyclooxygenase (COX)1 and COX2 inhibitors may inhibit the Wnt/β-catenin pathway in cancer cells; they could therefore be used for adjuvant therapy or chemoprevention of CMTC in a manner analogous to that used in Lynch syndrome and FAP (112), but clinical data are still lacking.

Unfortunately, despite these preclinical data, randomized clinical trials have not demonstrated a clear impact of vitamin D supplementation on colorectal cancer incidence, progression or mortality (113). Vitamin D receptor increases the levels of E-cadherin in the plasma membrane and decreases the levels of β-catenin in the nucleus in differentiated TC (114). Therefore, it is possible that vitamin D could play a chemopreventive role in women with FAP.

Other precision therapy. Although the evidence is scarce, a sustained response to treatment with lenvatinib was observed in a patient with lung metastases of CMTC during follow-up of the patient (74) (Table II). The clinical response to this MKI is consistent with the signaling of the PI3K/AKT/mTOR and the RAS/RAF/MAPK pathways induced by estrogens in CMTC. Lenvatinib, sorafenib, cabozantinib and other MKIs have shown antiangiogenic activity and could be used as treatments for CMTC with progression after surgery in a manner analogous to that of differentiated TC (114) (Fig. 4). Furthermore, selective *RET* inhibitors (i.e. selpercatinib and pralsetinib) may be used in cases of CMTC with *RET* rearrangements (115).

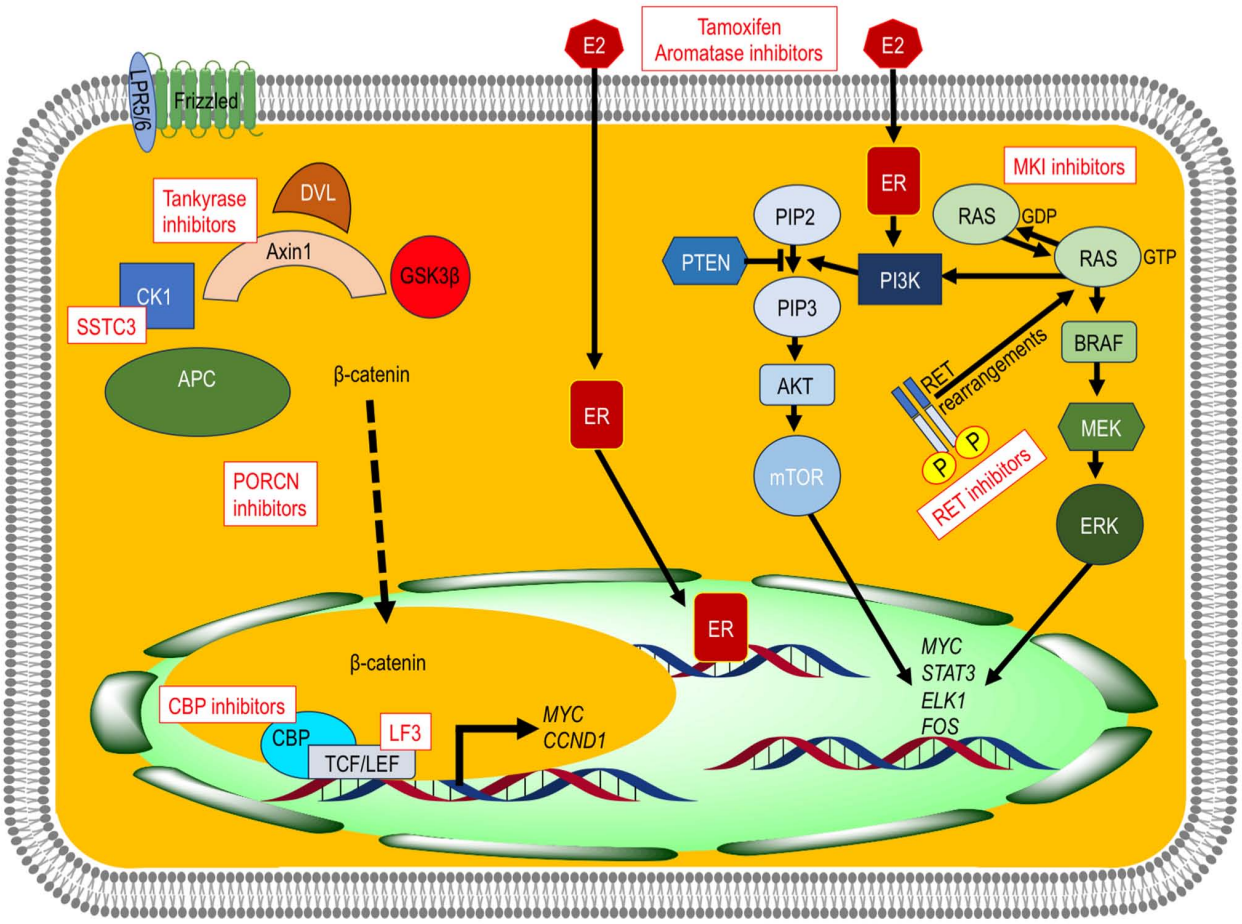


Figure 4. Schematic illustration of the rationale for possible targeted therapies in CMTC. Blocking the constitutive activation of the Wnt/β-catenin signaling pathway could play an essential role in the treatment of CMTC through the degradation of β-catenin by stabilizing Axin2 (tankyrase inhibitors), CK1 agonists (SSTC3), inhibitors targeting β-catenin-TFC transcription complex (LF3), CBP inhibitors, as well as porcupine inhibitors, but data on clinical efficacy and safety are still insufficient. E2 via ER would have a tumor-promoting role through the PI3K/AKT/mTOR and the RAS/RAF/MAPK signaling pathways, which would justify treatment with both antiestrogens (tamoxifen and aromatase inhibitors) and MKI inhibitors. The detection of additional somatic events (e.g. *RET* rearrangements) could be subsidiary to treatment with specific inhibitors. CMTC, morular cribriform thyroid carcinoma; E2, estrogens; ER, estrogen receptors; MKI, multikinase; TCF/LEF, T-cell factor/lymphoid enhancer factor; CTNNB1, β-catenin 1; CCND1, cyclin D1; APC, APC regulator of WNT signaling pathway; CK1, casein kinase 1; GSK3β, glycogen synthase kinase 3β; DVL, disheveled; CBP, cyclic adenosine monophosphate responsive element binding protein 1 binding protein; LRP5/6, low-density lipoprotein receptor-related protein 5/6; PI3K, phosphatidylinositol 3-kinase, AKT, serine/threonine kinase; mTOR, mechanistic target of rapamycin kinase; RAS, small GTPase; RAF, Raf-1 proto-oncogene, serine/threonine kinase; MAPK, mitogen-activated protein kinase.

Thus, although the clinical evidence is still insufficient, the detection of somatic mutations through next-generation sequencing could represent a precision therapeutic alternative in CMTC.

10. Limitations

In this review, hypotheses are proposed in an attempt to understand the nature of CMTC and establish a therapeutic approach. As most of the information comes from isolated cases or small series, the level of evidence is limited. Therefore, additional validations and appropriate clinical trials are still necessary.

11. Conclusions

CMTC is the TC associated with FAP. This rare tumor usually occurs in young women with multiple lesions or as a single nodule in sporadic cases. Constitutive activation of the WNT/β-catenin signaling pathway plays a key role in the distinctive growth pattern of CMTC and its immunohistochemical profile. Strong nuclear and cytoplasmic positivity for β-catenin is the hallmark of CMTC. Tumor cells are also positive for ER and PR and for TTF1/NKX2-1, but negative for Tg and calcitonin. Although the histogenesis of CMTC is controversial, the presence of a follicular or follicular precursor cell lineage may be postulated, whose block in differentiation would be secondary to WNT/β-catenin signaling. In FAP cases, total thyroidectomy is the treatment of choice due to the frequent multifocality and bilaterality of CMTC. Despite the central role of the Wnt/β-catenin signaling pathway in the pathogenesis of this tumor, more studies seem necessary to be able to translate the targeting of this signaling pathway into clinical practice. Although there is still little clinical evidence, in cases of CMTC recurrence and metastasis, targeted treatments with MKIs or more selective inhibitors could be useful. And although sufficient clinical data are also lacking, adjuvant antiestrogenic therapy could also be useful in women undergoing surgery with high-risk CMTC as well as when there is tumor recurrence and/or metastasis. The chemopreventive

role of vitamin D and COX inhibitors in women with FAP requires additional investigation.

Acknowledgements

Not applicable.

Funding

This work was supported by the Instituto de Salud Carlos III (ISCIII), Spain (grant nos. PI19/01316 and PI23/00722), co-funded by the European Union (EU).

Availability of data and materials

Not applicable.

Authors' contributions

All authors contributed to the conception of the review and interpretation of the data. SCG: Review of the literature, writing-original draft and editing. IAN and MSA: critical review and editing. JMCT: Review of the literature, writing-original draft and editing, and funding acquisition. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The images in Figs. 1 and 2C were obtained from cases in the TIROCHUS collection. TIROCHUS is a registered collection of human tissues at the ISCIII national biobank (no. c.0003960 to JMCT) of the Department of Pathology of the Hospital Clínico Universitario (Santiago de Compostela, Spain). Informed consent was obtained from each patient with a specific signed document updated to the current legislation.

Competing interests

The authors declare that they have no competing interests.

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