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Case Report

A Rare Case of Persistent Multifocal Cribriform-Morular Thyroid Carcinoma

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ABSTRACT

Background/Objective: Cribriform-morular thyroid carcinoma (CMTC) was considered a variant of papillary thyroid carcinoma (PTC) but is a separate entity in the 2022 World Health Organization classification. CMTC has an association with familial adenomatous polyposis (FAP). Our objective is to report a case of CMTC who was subsequently diagnosed with FAP, to highlight these associated entities and implications for management.

Case Report: A 15-year-old female with a history of iron-deficiency anemia and alpha-gal syndrome presented with several years of goiter and dysphagia. She also noted unintentional weight loss, abdominal pain, melena and hematochezia, and symptomatic anemia. Physical examination was significant for multiple thyroid nodules. Laboratory results revealed normal thyroid function and iron deficiency. Multiple nodules were visualized on thyroid ultrasound, and fine needle aspiration biopsy was consistent with PTC. Total thyroidectomy was performed with a revised diagnosis of multifocal CMTC, with administration of adjuvant radioactive iodine due to persistent disease. Genetic testing confirmed FAP and she was referred for upper endoscopy, colonoscopy, and an evaluation for colectomy.

Discussion: There are no best practice guidelines for management of CMTC. Management of CMTC is guided by FAP status; sporadic cases can be managed with hemithyroidectomy, while FAP-associated cases are better managed with total thyroidectomy. Recurrence is usually managed with surgical resection. The decision to treat with adjuvant radioactive iodine is often extrapolated from management of classic PTC.

Conclusion: Thyroid carcinoma in the setting of extensive family history of colorectal carcinoma should arouse suspicion for CMTC. Patients with CMTC should receive a referral for colonoscopy and genetic testing for FAP.

Introduction

Cribriform-morular thyroid carcinoma (CMTC) is now a distinct clinical entity from papillary thyroid carcinoma (PTC), based on the 2022 World Health Organization classification. It represents a small fraction of all thyroid carcinomas, with an incidence of roughly 0.16% to 0.30% (when it was considered a variant of PTC) in several large case series from Japan and the United States.[1-4] CMTC occurs almost exclusively in women, with an average age of presentation of 25 years.[1] While it shares many features with classic PTC, notable differences include a lower rate of lymph node metastasis, distant metastasis, cancer recurrence, and mortality as compared to classic PTC.[4]

A unique feature of CMTC is its strong association with familial adenomatous polyposis (FAP), which is caused by germline mutations in the APC gene (Fig. 1).[5,6] FAP is an autosomal dominant condition wherein individuals have hundreds to thousands of

Abbreviations: ATA, Amercian Thyroid Association; CMTC, cribriform-morular thyroid carcinoma; FAP, familial adenomatous polyposis; FNA, fine needle aspiration; PTC, papillary thyroid carcinoma; RAI, radioactive iodine therapy.

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adenomas in the large intestine and rectum, with a nearly 100% lifetime chance of developing colorectal carcinoma.[7] Roughly 53% to 60% of CMTC cases are associated with FAP, and in approximately 40% to 48% of cases, thyroid carcinoma diagnosis precedes the discovery of FAP.[4,5] Patients with FAP are more likely to have a multifocal carcinoma. Among 118 patients whose FAP status was documented, patients with FAP had a 72% chance of a multifocal carcinoma, while non-FAP patients had only a 24% chance of a multifocal carcinoma.[4] Our objective is to report a case of CMTC who was subsequently diagnosed with FAP, to highlight the association between these entities and implications for patient care.

Highlights

- Cribriform-morular thyroid carcinoma (CMTC) is now a distinct entity.
- CMTC has a strong association with familial adenomatous polyposis (FAP).
- Early diagnosis of CMTC and awareness of its association with FAP is imperative.
- CMTC patients should be evaluated for FAP with colonoscopy and a genetics referral.

Clinical Relevance

We describe a 15-year-old patient with multifocal cribriform-morular thyroid carcinoma. She was managed with total thyroidectomy and found to have persistent disease in the thyroid bed requiring adjuvant radioactive iodine ablation.

Case Report

A 15-year-old female with a past medical history of iron-deficiency anemia and alpha-gal syndrome presented with several years of goiter and dysphagia. In the preceding year, she noted 9 kg of unintentional weight loss, abdominal pain, intermittent hematochezia and melena, lightheadedness, and fatigue. She denied menorrhagia and endorsed low intake of animal protein. There was no personal history of radiation exposure or family history of thyroid carcinoma or colorectal carcinoma. Physical examination revealed multiple thyroid nodules but was otherwise unremarkable. She was clinically and biochemically euthyroid. Complete blood count and iron studies were consistent with iron-deficiency anemia: hemoglobin 10.2 g/dL (microcytic), ferritin 7 ng/mL, total iron binding capacity 478 μg/dL, and transferrin saturation 10%.

Thyroid ultrasound revealed a 6.2 × 3.3 × 2.6-cm left-sided solid heterogeneous nodule occupying most of the lobe, 3 additional smaller left-sided nodules (2.3 × 2.0 × 2.2 cm, 2.5 × 1.5 × 2.1 cm, and 0.90 × 0.70 × 0.80 cm), and no cervical lymphadenopathy. Ultrasound-guided fine needle aspiration (FNA) biopsy of the largest nodule revealed Bethesda VI cytopathology, consistent with PTC. The sample was hypercellular and contained numerous papillae, complex arrangements, sheets, and groups of follicular cells with crowded, enlarged round to irregular nuclei. The nuclei had pale chromatin and variable numbers of grooves, intranuclear inclusions, and pinpoint nucleoli.

One month after FNA biopsy, total thyroidectomy was performed with removal of a large white, firm mass replacing the entirety of the left thyroid lobe and causing contralateral tracheal deviation. An isthmus nodule 0.4 cm in size and 2 additional right-sided nodules (0.6 cm and 0.4 cm in size) were discovered during inspection of the surgical specimen. Her postoperative course was uneventful.

The final pathology revealed a multifocal carcinoma with the largest nodule 6 cm in its greatest dimension. There was no evidence of extrathyroidal extension or lymphatic or angioinvasion, and surgical margins were negative. No lymph nodes were submitted. The final pathologic stage was pT3aN0M0. Immunohistochemical stains were positive for β-catenin (nuclear and cytoplasmic staining), estrogen receptor and progesterone receptor diffusely, and thyroglobulin (focal), with variable staining for TTF-1 and PAX8 (Fig. 2). Scattered morular structures were positive for CK5/6 and CD5 and negative for P40 and HBME-1. Molecular analysis was negative for BRAF mutations. The final diagnosis from the surgical

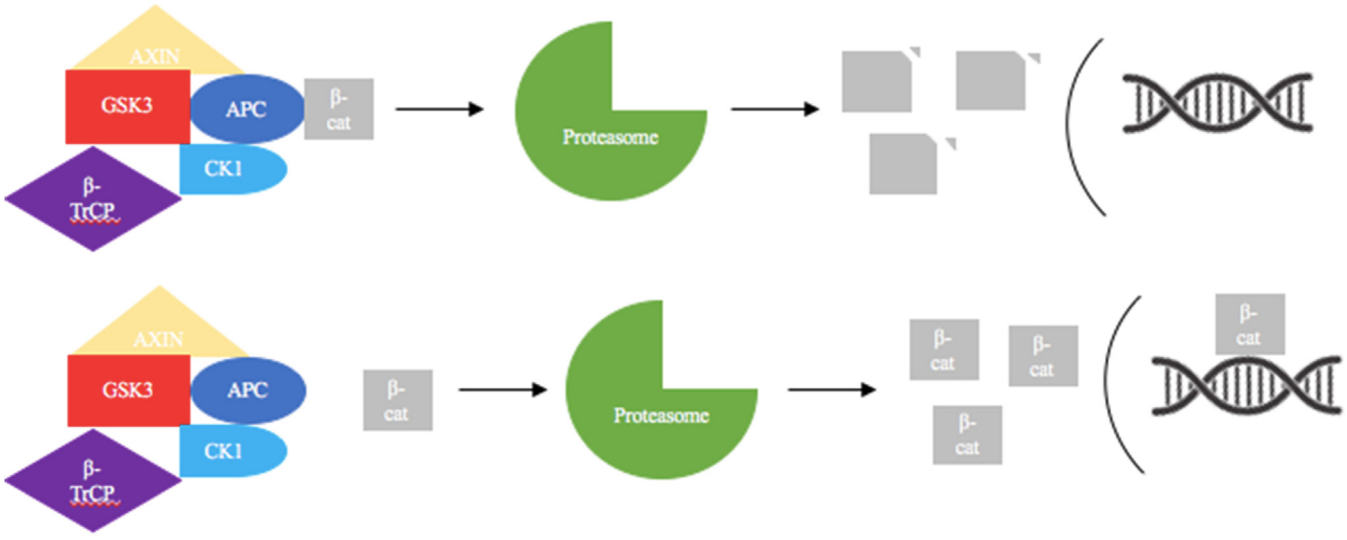

Fig. 1. Top: In normal circumstances, APC functions as a tumor suppressor protein in the Wnt/β-catenin signaling pathway. APC protein forms a destruction complex with several other proteins (AXIN, CK1, GSK3, and β-TrCP), which phosphorylates β-catenin and targets it for ubiquitination. β-Catenin is then degraded by proteasomes.
Bottom: Familial adenomatous polyposis results from germline mutations in the APC gene, located on 5q21-22. Mutations of APC lead to truncation of the protein and loss of its β-catenin binding site. β-Catenin is not targeted for proteasomal degradation and instead accumulates in the cytoplasm with subsequent translocation to the nucleus. This results in constitutive activation of several target genes involved in cell proliferation and differentiation.[5,6]

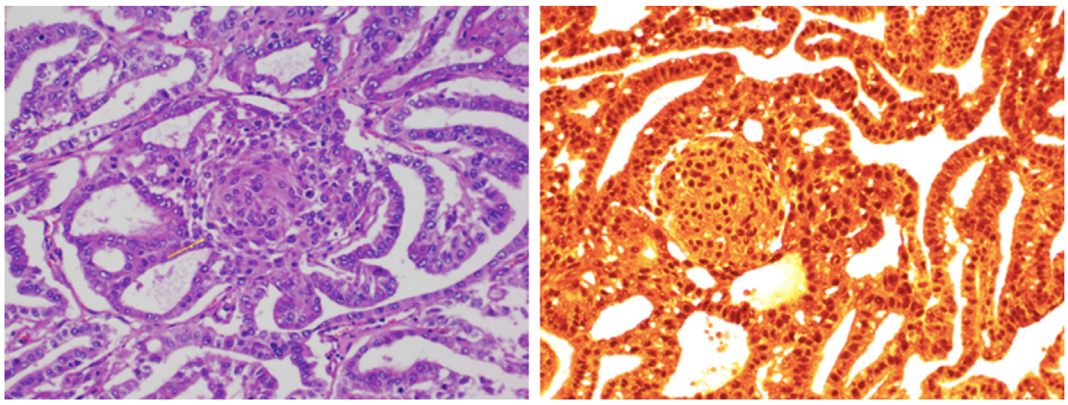

Fig. 2. Left: CMTC showing cribriform, morular (arrow), papillary, and follicular patterns.
Right: β-Catenin immunohistochemical stain showing nuclear and cytoplasmic staining. *CMTC* = cribriform-morular thyroid carcinoma.

specimen was revised to CMTC, rather than PTC as initially diagnosed on FNA.

Postoperatively, she was started on levothyroxine 125 μg daily, with laboratory results as follows: TSH 0.011 mcIU/mL, serum thyroglobulin 0.1 ng/mL, and thyroglobulin antibody <1.0 IU/mL. Three months following thyroidectomy, she underwent an I-123 scan, which showed residual activity in the left inferior thyroid bed and a right-sided focus of activity superior to the thyroid cartilage, representing a lymph node or a thyroid bed remnant. She underwent radioactive iodine (RAI) therapy with 124.5 mCi. A post-ablation scan revealed thyroid remnants in the thyroid bed; she is awaiting further management and surveillance. Her levothyroxine is dosed for a goal TSH of 0.5 to 2.0 mcIU/mL.

The patient was referred to genetic counseling for screening for FAP. Genetic testing was positive for a germline mutation in the APC gene, confirming a diagnosis of FAP. She began supplementation with oral iron and was referred to gastroenterology for colonoscopy and upper endoscopy, as well as colorectal surgery for a colectomy.

Discussion

Owing to the rarity of CMTC, there are no best practice guidelines for management. Surgical management of CMTC is often informed by FAP status,[8,9] and the decision to treat with adjuvant RAI appears to follow the management of classic PTC.[8-10] In 1 case series from Japan, 11 of 12 FAP-associated cases underwent total thyroidectomy, and 9 of 19 sporadic cases underwent total thyroidectomy, with the remainder of sporadic cases receiving hemithyroidectomy. All patients were node negative, and only 2 patients (both with FAP-associated CMTC) had recurrence in the thyroid bed, which was treated with a second surgery (86 and 90 months following the first) with no further recurrence. None of the patients required RAI ablation.[8] A second case series of 12 FAP-associated patients diagnosed with PTC with “atypical” histology (likely before CMTC was a well-described entity) noted that only 5 patients received total thyroidectomy and that there was a recurrence in 2 patients in a mean-follow-up period of 142 months. The first patient required several local resections, while the second patient required laryngectomy, radical neck dissection, and external radiation therapy. Five patients underwent adjuvant RAI treatment, presumably for metastatic disease or a large primary tumor size.[9] In another example, 3 cases of CMTC were treated with total thyroidectomy with adjuvant RAI, because 2 had extensive multifocal disease.[10]

While disease recurrence is not uncommon, it is often managed successfully with surgical resection. However, based on the literature, a minority of cases present with persistent disease, and there is a paucity of data in the literature to guide management. Due to the extensive size of her largest tumor (>4 cm), our patient is classified in the American Thyroid Association (ATA) low to intermediate-risk category for classic PTC. Given this risk status, multifocal disease, and persistence in the thyroid bed, it was determined that the patient would benefit from adjuvant RAI treatment. Although controversial, adjuvant RAI is a recommended management option for intermediate-risk patients as per the 2015 ATA guidelines for classic PTC. There is a small absolute risk difference in survival (1%) noted in patients with pT3 node-negative PTC in which the primary tumor is >4 cm.[11] This benefit was felt to outweigh the relatively minimal risk associated with RAI therapy.

In conclusion, CMTC is a distinct clinical entity with a strong association with FAP. FAP-associated cases are more likely to have multifocal disease, and results from several case series indicate that total thyroidectomy results in better outcomes in FAP-associated cases. In lieu of best practice guidelines for this rare entity, the decision to treat with adjuvant RAI can be extrapolated from the management of classic PTC. A diagnosis of thyroid carcinoma in a patient with an extensive family history of colonic malignancy or known FAP should trigger evaluation for CMTC. Alternatively, a diagnosis of CMTC in a patient with no known history of FAP should result in a referral for colonoscopy and genetic testing, given the near guarantee of colonic malignancy by age 40 years in these patients.

Disclosure

The authors have no multiplicity of interest to disclose.

Acknowledgment

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