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Case Report

A Case of Cribriform-Morular Thyroid Carcinoma Presenting Without Thyroid Nodule

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Abstract

Cribriform-morular thyroid carcinoma is a rare type of thyroid cancer. It has a strong association with familial adenomatous polyposis (FAP), a hereditary genetic disorder that predisposes individuals to the development of numerous polyps in the colon and rectum. We describe the case of a young female patient who presented with an enlarging goiter, notably without detectable thyroid nodules or masses on ultrasound, who after total thyroidectomy was found to have cribriform-morular thyroid carcinoma. This diagnosis led to genetic testing and diagnosis of FAP syndrome. We demonstrate that this rare thyroid carcinoma may present with nonsuspicious findings on sonographic evaluation while being a valuable harbinger in the diagnosis of FAP syndrome.

Key Words: thyroid carcinoma, familial adenomatous polyposis, thyroid goiter

Introduction

Cribriform-morular thyroid carcinoma is a rare form of malignancy first recognized in 1994. Originally classified as a variant of papillary thyroid carcinoma, it is now considered a distinct thyroid malignancy of uncertain histogenesis (1). These carcinomas uniformly express TTF1, lack thyroglobulin reactivity, and are known for their distinct cytomorphological features. The features include cribriform architecture, morules without keratinization, papillary architecture, spindle cells, and the absence of colloid (2). This carcinoma is associated with familial adenomatous polyposis (FAP) but can also occur in sporadic form. Germline and somatic disease are associated with alterations in the Wnt/beta-catenin pathway, typically resulting from adenomatous polyposis coli (*APC*) mutations. Previous case series of patients with cribriform-morular thyroid carcinoma have shown observations such as predominance in female sex, larger tumor size in unifocal disease, and evidence of multifocality and earlier disease onset in patients who have FAP syndrome (3).

Although cribriform-morular thyroid carcinoma itself is generally well differentiated with low risk of recurrence and metastasis, its association with FAP begets the need for prompt genetic testing and expeditious colonoscopy. FAP is an autosomal dominant polyposis syndrome characterized by hundreds of adenomatous polyps in the upper and lower gastrointestinal tract, and individuals with FAP have nearly complete penetrance of colorectal carcinoma.

We present a case of a patient with enlarging thyroid goiter, without suspicious features or nodules on thyroid ultrasound, who underwent total thyroidectomy and was diagnosed with cribriform-morular thyroid carcinoma and subsequently found to have FAP syndrome.

Case Presentation

A 20-year-old woman was referred to the endocrinology clinic for thyromegaly and gradual thyroid enlargement over the span of 1 year. She reported dysphagia to solid food over the prior 2 months. She noted fatigue and cold intolerance but had no other symptoms of thyroid dysfunction. She had no known medical problems aside from hypertension and iron deficiency anemia, with regular heavy menstrual cycles and no symptoms of gastrointestinal bleeding. She denied a personal or family history of thyroid disease, thyroid cancer, neck irradiation, or autoimmune disease. Her father died from an unknown cancer before age 50. On physical examination, she had normal vital signs, with markedly enlarged goiter, left side greater than right, without palpable nodules. Physical exam was otherwise unremarkable.

Diagnostic Assessment

The patient was biochemically euthyroid with TSH of 2.46 mIU/L (normal range 0.27-4.20 mIU/L), free T4 of 1.2 ng/dL (15.4 pmol/L) (normal range 0.9-1.7 ng/dL or 12.0-21.9 pmol/L), and total T3 125 ng/dL (1.92 nmol/L) (normal range 80-200 ng/dL or 1.5-3.1 nmol/L). Thyroid peroxidase antibody titer was not elevated. Complete blood count revealed the presence of microcytic anemia with hemoglobin 8.1 g/dL (5.03 mmol/L) (normal range 12.0-16.0 g/dL or 7.4-9.9 mmol/L) and mean corpuscular volume 62.4 fL (normal range 80.0-100.0 fL).

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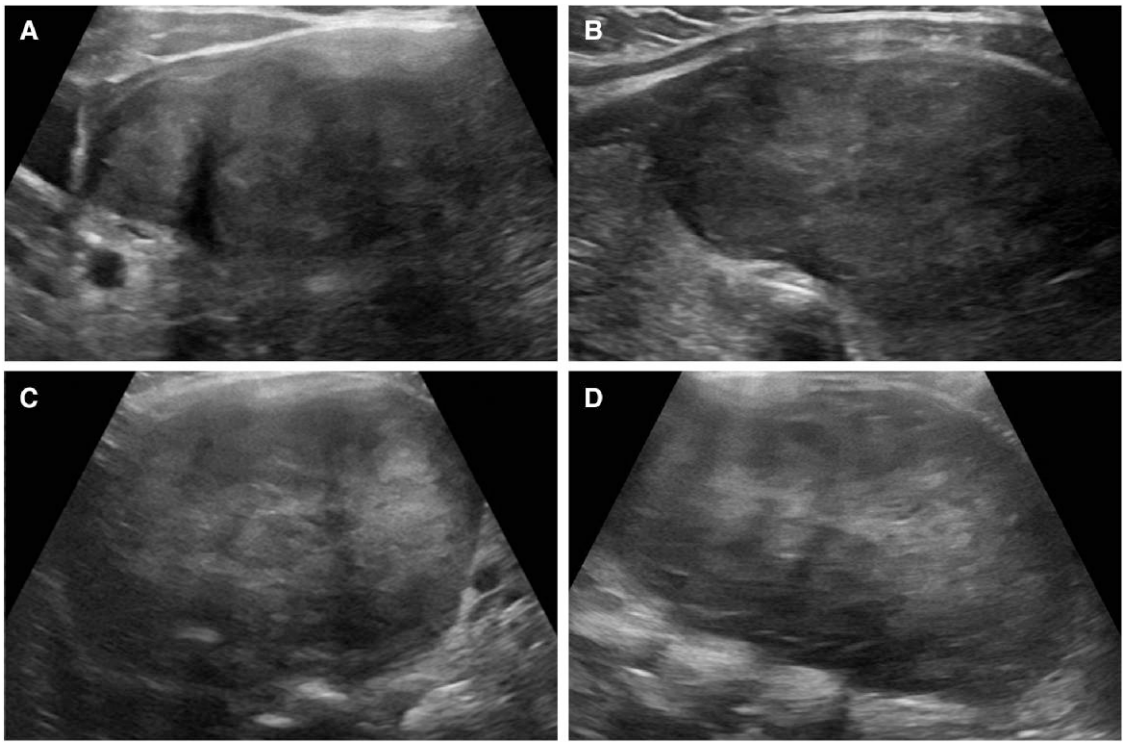

Figure 1. Thyroid ultrasonography showing diffuse goiter with heterogenous echotexture. No discrete nodules were observed on cine images. Rather, the entirety of both thyroid lobes appears to be replaced by a poorly defined mass. The right thyroid lobe measured 3.2 cm deep × 5.9 cm wide × 7.2 cm long (A = transverse, B = sagittal). The left thyroid lobe showed greater enlargement, measuring 4.2 cm deep × 6.0 cm wide × 11.0 cm long (C = transverse, D = sagittal). The isthmus measured 4.6 cm (not shown). No pathologically enlarged lymph nodes or calcifications were seen.

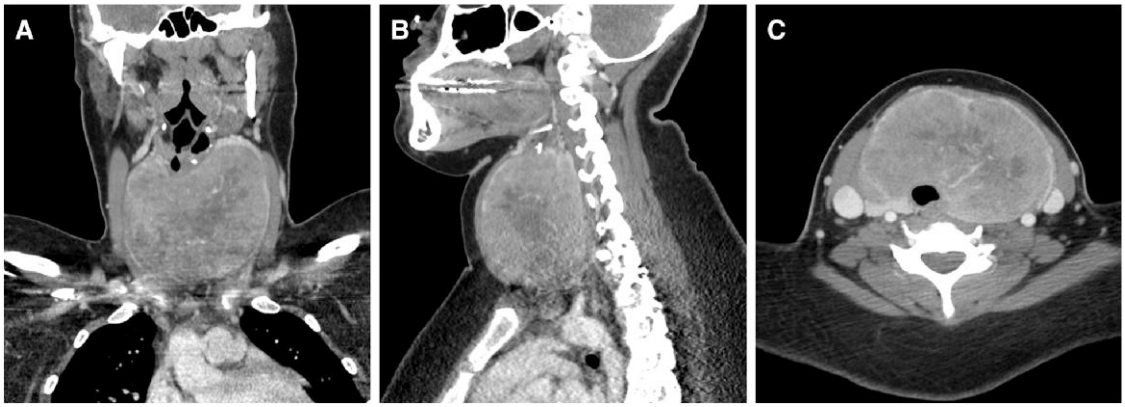

Figure 2. Computed tomography imaging of the neck with intravenous contrast revealed a massive heterogeneously enhancing thyroid goiter. Asymmetric enlargement of the left thyroid lobe is evident in the coronal imaging plane (A). The extent of thyroid enlargement can be further appreciated in the sagittal plane (B). Rightward tracheal deviation due to the asymmetric left thyroid lobe enlargement was observed on transverse imaging (C).

Ultrasound of the thyroid with neck nodal survey showed marked asymmetric enlargement involving the entire thyroid gland. The right thyroid lobe measured 3.2 cm deep by 5.9 cm wide by 7.2 cm long, and the left thyroid lobe measured 4.2 cm deep by 6.0 cm wide by 12.0 cm long (Fig. 1). The gland itself contained no discrete nodules and had heterogenous echotexture. No pathologically enlarged lymph nodes or calcifications were observed. Computed tomography scan of the neck was completed showing massive heterogeneously enhancing goiter, with enlargement of the left thyroid lobe resulting in rightward deviation and mild narrowing of the trachea (Fig. 2).

Treatment

Although no thyroid nodules were identified with ultrasound, the patient had symptoms of compression and elected to explore surgical options including left thyroid lobectomy vs total thyroidectomy with otolaryngology. She underwent uncomplicated total thyroidectomy, and central neck dissection was performed due to the surgeon's assessment of potentially malignant and adherent appearance of the thyroid. Gross thyroid specimen was noted to be firm, vascular, and adherent to adjacent structures. The total weight of the specimen was 427 grams and measured 10.5 by 7.5 by 6.0 cm in size (Fig. 3). Postoperatively, the patient was started on levothyroxine 200 micrograms daily.

Outcome and Follow-up

The pathologic diagnosis was cribriform-morular thyroid carcinoma, with metastases in 1 of 14 lymph nodes (1/14) and no extranodal extension, extrathyroidal extension, or angioinvasion. The microscopic evaluation showed carcinoma arranged in papillary and gland-like arrangement with frequent round nodules of squamoid cells. Intraluminal colloid was absent (Fig. 4A). Immunohistochemical stains indicated positivity for TTF-1 and were focally positive for PAX8 and thyroglobulin and negative for calcitonin and CDX-2. Beta catenin showed diffuse positive nuclear and cytoplasmic staining, with a Ki-67 labeling index of 5% (Fig. 4B).

The pathologic classification was pT3a, pN1a. With her disease classified as intermediate risk for persistence or recurrence, she was provided mild thyroid hormone suppression to target TSH between 0.1 and 0.5 mIU/L (reference range 0.27-4.20 mIU/L). At 6 weeks postoperatively, her TSH was 2.46 mIU/mL and unstimulated thyroglobulin level <0.5 ng/mL (<0.5 µg/L) (normal range 1.3-31.8 ng/mL or µg/L) with negative thyroglobulin antibody. Following withdrawal of thyroid hormone, the patient's TSH reached 173 mIU/L with undetectable thyroglobulin, and I^{123} whole-body scanning revealed neck uptake. The patient subsequently received radioiodine therapy (I^{131}, 104.4 millicuries) and the postablation scan showed questionable uptake in the right lung (Fig. 5). This was believed to be artifact given the undetectable thyroglobulin; however, computed tomography of the chest was ordered and is pending completion.

The patient underwent genetic testing for hereditary cancer gene mutations due to the association of cribriform-morular thyroid carcinoma with FAP. She was found to harbor a monoallelic pathogenic variant in the *APC* gene [c.1982_1983del (p. Cys661Serfs*12)], establishing a diagnosis of FAP. Genetic testing of her paternal relatives was recommended, given her father's history of cancer. She received colonoscopy and was found to have >100 sessile polyps involving the left colon, ranging from 1 to 15 mm. Following polypectomy, the pathology was consistent with tubular adenomas, and the patient was referred to surgery for colectomy. She will receive serial imaging, including computed tomography of the chest, abdomen, and pelvis, and laboratory work to monitor her response to therapy for her thyroid cancer and for her diagnosis of FAP.

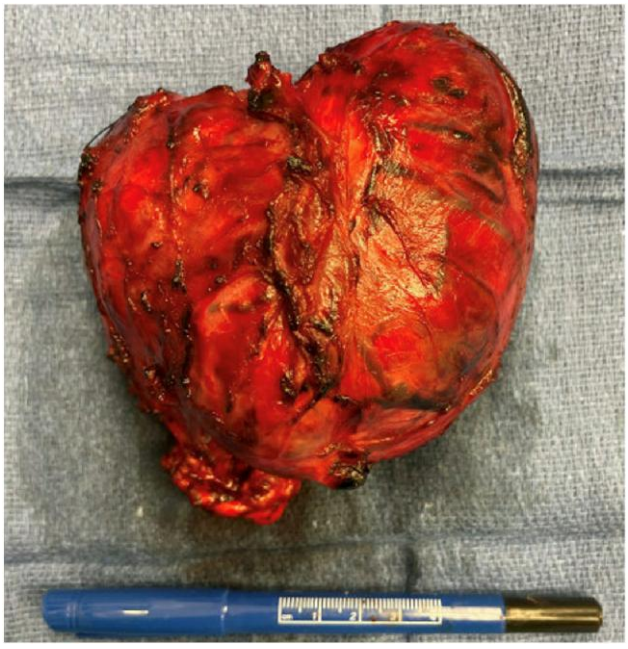

Figure 3. Surgical specimen following total thyroidectomy. The patient's thyroid gland was unusually firm, vascular, and adherent to adjacent structures. The specimen weighed 427 grams and measured 10.5 × 7.5 × 6.0 cm.

Discussion

Cribriform-morular thyroid carcinoma is a rare cancer that can present as an extracolonic manifestation of FAP syndrome. Case reports of cribriform-morular thyroid carcinoma typically have demonstrated evidence of thyroid nodules or a thyroid mass on ultrasound imaging (4-7). A retrospective review of ultrasonographic and clinical characteristics of 5 patients with cribriform-morular variant thyroid carcinoma showed that all had either palpable discrete lesions or nodules on ultrasound. Importantly, none of the nodules had particularly suspicious or malignant features on sonographic evaluation (8).

In this case, the patient presented with an enlarging goiter as well as iron deficiency anemia. Her anemia was attributed to her menstrual cycles, without work-up for occult

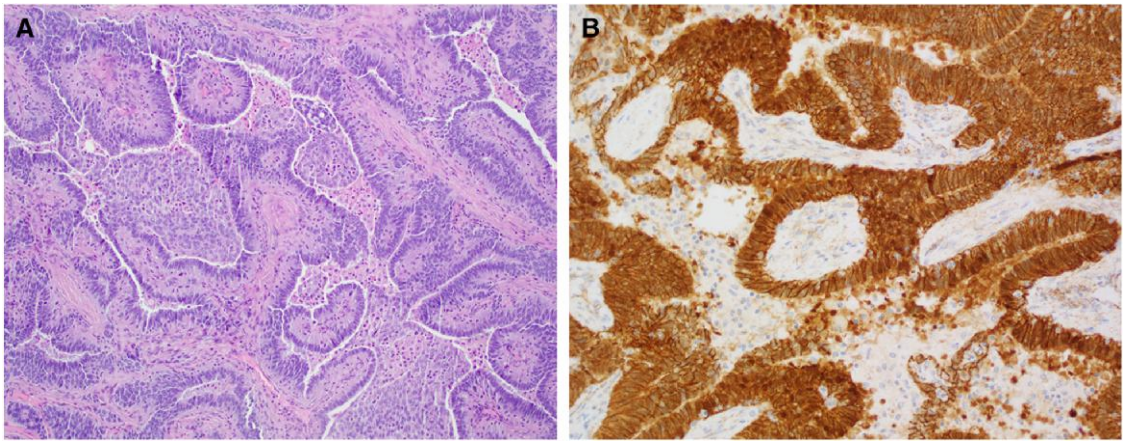

Figure 4. Sections of the tumor specimen stained with hematoxylin and eosin showed a carcinoma arranged in papillary and gland-like arrangements with frequent round nodules of squamoid cells, morphologic features that respectively constitute cribriform architecture and focal morulae (A). Beta-catenin immunohistochemistry showed diffuse nuclear and cytoplasmic positivity (B).

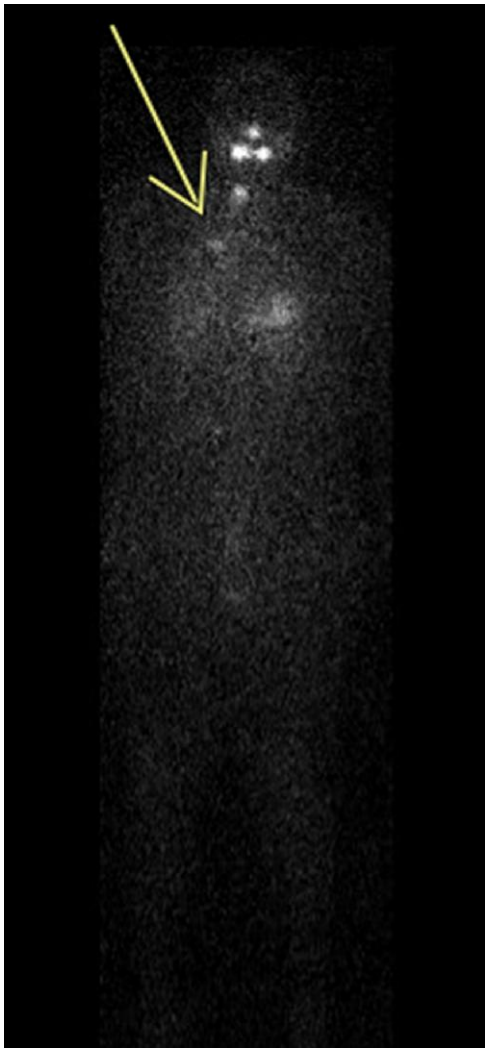

Figure 5. One week after radioiodine ablation with I-131, planar whole-body scan imaging showed focal tracer uptake in the right thyroid bed consistent with thyroid remnant or lymph node metastasis. Focal tracer uptake was also noted overlying the right upper chest, concerning for possible right lung or right upper mediastinal lymph node metastasis (arrow). Physiologic distribution of tracer was seen in the salivary glands and bowel.

gastrointestinal bleeding. Thyroid ultrasound did not indicate features such as discrete nodules, masses, or abnormal lymph nodes. Consequently, there was no immediate indication for thyroid biopsy or thyroidectomy based on the radiographic findings. She underwent thyroidectomy for compressive symptoms, and prior to surgery, the suspicion for malignancy was low. The histologic diagnosis provided by the thyroid pathology proved to be crucial for our patient, since cribriform-morular thyroid carcinoma was her initial manifestation of FAP. As a result, she was able to receive genetic testing that identified the causative germline mutation and undergo prompt colonoscopy that discovered >100 precancerous colonic lesions, and genetic testing was extended to at-risk family members. Similar to other patients with cribriform-morular thyroid carcinoma described in the literature, our patient was a young female who presented with thyroid enlargement, was diagnosed with thyroid cancer, and was later found to have *APC* gene mutation. Previous studies of cribriform-morular thyroid carcinoma in association with FAP have shown that the thyroid malignancy is identified before the FAP diagnosis in up to 40% of patients (9). This finding highlights the importance of performing genetic testing in all patients diagnosed with cribriform-morular thyroid carcinoma. Patients with FAP are at much higher than average risk of thyroid cancer, and current guidelines support screening with thyroid ultrasound at the time of diagnosis and then annually, although this is backed by low quality of evidence. Other clinical manifestations of FAP include abdominal symptoms, diarrhea, and hematochezia or blood in the stool. Although our patient did not have these, she had a microcytic anemia with iron deficiency indicating potential occult gastrointestinal bleeding.

Our case adds to the existing literature on this rare form of thyroid cancer but also shows that cribriform-morular thyroid carcinoma can present radiographically as a diffuse goiter, without the presence of discrete masses or nodules. Other types of thyroid cancer that can present diffusely include the diffuse sclerosing variant of papillary thyroid carcinoma and thyroid lymphoma. In young patients who present with thyromegaly, a thorough family cancer history is imperative. Radiographic findings must be interpreted in the context of the full clinical picture. Surgical consultation should be considered for patients with enlarging goiter and compressive symptoms. Although not done in this case, thyroid biopsy should be considered prior to surgery, even in the absence of evidence of malignancy, to aid in establishing the cause of the thyroid enlargement and to exclude the presence of tumor.

Learning Points

- Cribriform-morular thyroid carcinoma can present radiographically without nodules or masses, with malignancy encompassing the entire thyroid.
- Thyromegaly may be the first indicator of FAP syndrome.
- Fine needle aspiration thyroid biopsy may be warranted before a thyroidectomy if the etiology of the thyroid enlargement remains questionable.

Contributors

All authors made individual contributions to authorship. E.H. and L.N. were involved in the diagnosis and management of this patient. A.R. and E.H. drafted and submitted the manuscript. L.L. was responsible for the patient's surgeries. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Baloch ZW, Asa SL, Barletta JA, *et al.* Overview of the 2022 WHO classification of thyroid neoplasms. *Endocr Pathol*. 2022;33(1): 27-63.
2. Hirokawa M, Maekawa M, Kuma S, Miyauchi A. Cribriform-morular variant of papillary thyroid carcinoma–cytological and immunocytochemical findings of 18 cases. *Diagn Cytopathol*. 2010;38(12):890-896.
3. Boyraz B, Sadow PM, Asa SL, Dias-Santagata D, Nosé V, Mete O. Cribriform-Morular thyroid carcinoma is a distinct thyroid malignancy of uncertain cytogenesis. *Endocr Pathol*. 2021;32(3):327-335.
4. Corean J, Furtado LV, Kadri S, Segal JP, Emerson LL. Cribriform-Morular variant of papillary thyroid carcinoma with poorly differentiated features: a case report with immunohistochemical and molecular genetic analysis. *Int J Surg Pathol*. 2019;27(3):294-304.
5. Brehar AC, Terzea DC, Ioachim DL, *et al.* Cribriform-morular variant of papillary thyroid carcinoma at pediatric age—case report and review of the literature. *Rom J Morphol Embryol*. 2016;57(2): 531-537.
6. Yeoh EC, Lim LC, Ng SB, Tan KY, Rajasoorya C. Cribriform morular variant of papillary thyroid carcinoma in a patient with an incidental neck lump: a case report and review of the literature. *Endocr Pathol*. 2014;25(3):302-306.
7. Dettmer MS, Hürlimann S, Scheuble L, Vassella E, Perren A, Wicke C. Cribriform morular thyroid carcinoma—ultimobranchial pouch-related? Deep molecular insights of a unique case. *Endocr Pathol*. 2023;34(3):342-348.
8. Chong Y, Shin JH, Oh YL, Han BK, Ko EY. Cribriform-morular variant of papillary thyroid carcinoma: ultrasonographic and clinical characteristics. *Thyroid*. 2013;23(1):45-49.
9. Cameselle-Teijeiro JM, Peteiro-González D, Caneiro-Gómez J, *et al.* Cribriform-morular variant of thyroid carcinoma: a neoplasm with distinctive phenotype associated with the activation of the WNT/β-catenin pathway. *Mod Pathol*. 2018; 31(8):1168-1179.