CLINICAL CURIOSITY: CRIBRIFORM-MORULAR VARIANT OF PAPILLARY THYROID CARCINOMA

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Abstract: There is a growing awareness of the association of papillary thyroid carcinoma (PTC) and familial adenomatous polyposis (FAP). Although the incidence of PTC in FAP is only 1% to 2%, most tend to occur in women. Several authors have described a distinctive histologic variant of papillary thyroid carcinoma, the cribriform-morular variant, which includes intermingled cribriform, follicular, papillary, trabecular, and morular architecture.1,3 Immunohistochemically, these tumors stain positively for thyroglobulin, estrogen, and progesterone receptors.1,4 This variant of papillary carcinoma is extremely unusual and occurs predominantly in patients with FAP.

Methods. A healthy 36-year-old woman was seen with a left thyroid nodule, and a 34-year-old woman with FAP was seen with a right thyroid nodule; both masses were suspicious for papillary thyroid carcinoma. Both patients underwent total thyroidectomy.

Results. Pathologic examination of both specimens revealed papillary thyroid carcinoma, cribriform-morular variant. The first patient subsequently underwent colonoscopy, which was negative for polyposis.

Conclusions. Patients diagnosed with the cribriform-morular variant of papillary thyroid cancer should be screened for the presence of FAP. © 2006 Wiley Periodicals, Inc. Head Neck 28: 471–476, 2006

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There is a growing awareness of the association of papillary thyroid carcinoma (PTC) and familial adenomatous polyposis (FAP). Although the incidence of PTC in FAP is only 1% to 2%, most tend to occur in women.1,2 Several authors have described a distinctive histologic variant of PTC, the cribriform-morular variant, which includes intermingled cribriform, follicular, papillary, trabecular, and morular architecture.1,3 Immunohistochemically, these tumors stain positively for thyroglobulin, estrogen, and progesterone receptors.1,4 This variant of papillary carcinoma is extremely unusual and occurs predominantly in patients with FAP.

However, the cribriform-morular variant may also be encountered in patients with non-FAP. At times, this diagnosis may predate the symptoms of colorectal polyposis. The purpose of this report is to provide an example of each of these clinical situations and to discuss the therapeutic decisions involved.

CASE REPORT

Patient 1. A healthy 36-year-old woman was seen with a left thyroid mass detected by her gynecolo-
gist. Her family history was notable for members with both hyperthyroidism and hypothyroidism; a maternal grandmother had colonic polyps at the age of 70.

On physical examination, she had a 2 x 2 cm, firm, mobile nodule of the left thyroid lobe. No palpable cervical or supraclavicular lymphadenopathy was found. Ultrasound demonstrated a 2.1-cm mass in the left thyroid lobe as well as a 5-mm nodule in the isthmus. A thyroid scan revealed a cold left thyroid nodule. A fine-needle aspiration (FNA) biopsy specimen demonstrated cells suspicious for follicular neoplasia. Thyroid function tests were normal. On review of her disease by our institution, concern was raised for a PTC. The patient underwent a total thyroidectomy. Postoperatively, colonoscopy revealed a normal colon without polyposis.

The final pathology report revealed a 2.05-cm PTC of the left thyroid lobe. The tumor was well differentiated and did not have capsular or vascular invasion, extrathyroidal extension, or multicentricity. Of note, the tumor was a ‘cribriform-morular variant’ of PTC and demonstrated intermingled cribriform, follicular, papillary, trabecular, and morular architecture (Figure 1). The remainder of the thyroid had nodular hyperplasia. Immunohistochemically, the tumor stained positively for thyroglobulin and cytokeratin 7 and was negative for cytokeratin 20, estrogen receptor, and progesterone receptor. No nuclear staining with beta-catenin was found.

**Patient 2.** A 34-year-old woman with a history of FAP was found to have an enlarged thyroid gland on routine physical examination. In 1992, the patient had undergone a proctocolectomy and excision of an abdominal wall desmoid tumor; desmoids occur in up to 10% of FAP patients and are a manifestation of Gardner’s syndrome. The desmoid was also treated with adjuvant radiation. In 1998, the desmoid tumor recurred in the pelvis and was treated with chemotherapy. In 1999, the patient was diagnosed with duodenal tubular adenomas. Her paternal grandmother was the index case of FAP.

Physical examination revealed a 2-cm, smooth dominant nodule of the right thyroid lobe and vague nodularity of the left thyroid lobe. Examination of the larynx revealed normal mobile vocal cords. Ultrasound demonstrated three nodules in the right lobe and two smaller nodules in the left

![FIGURE 1. The variegated histologic appearance of the cribriform-morular variant. This sporadic case (patient 1) displays cribriform (upper left), papillary (upper right), and hyalinized areas (lower left). Interspersed islands of squamoid and spindle cells (mainly spindle cells in this case) known as morules were also seen (delineated by the arrows; lower right). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]]
lobe. The most suspicious nodule was located in the middle of the right thyroid lobe, had coarse, punctuate calcifications, and measured 1.6 cm in diameter. FNA cytology under ultrasonographic guidance strongly suggested PTC. The patient underwent a total thyroidectomy and had an uneventful postoperative recovery.

The final pathology revealed a 2.3-cm PTC located in the right thyroid lobe. The tumor was described as containing the ‘cribriform-morular variant’ of PTC (Figure 2). Although the tumor was well encapsulated and had no extrathyroidal extension, there was evidence of focal capsule invasion. No vascular invasion was identified. Of interest, the papillary carcinoma was multifocal with three additional foci of the ‘cribriform-morular variant’ ranging from 0.17 to 0.8 cm, located in both thyroid lobes. The tumor was positive for thyroglobulin and cytokeratin 7 and was negative for cytokeratin 20. The tumor also showed diffuse aberrant nuclear staining for beta-catenin, whereas the adjacent normal thyroid showed a membranous staining pattern (Figure 3). In addition, there was strong and diffuse nuclear positivity for both estrogen and progesterone receptors.

**DISCUSSION**

In 1968, the relationship between FAP and thyroid carcinoma was first suggested. Although the incidence of PTC in patients with FAP is rare at 1% to 2%, the relative risk for thyroid carcinoma in patients with FAP younger than 35 years of age is estimated at 160 times that of the general population.

The cribriform-morular variant of papillary cancer of the thyroid is often associated with FAP, as was seen in our second patient. Clinically, this entity has a female predominance, is multifocal, and tends to occur in patients under the age of 30. Histologically, this variant has been described as having distinct features, including an intricate blending of cribriform, trabecular, solid, follicular, morular, and papillary architecture. The uncharacteristic cribriform growth pattern can mislead the pathologist into diagnos-
ing more aggressive variants of thyroid carcinomas, such as poorly differentiated thyroid carcinoma. The cribriform-morular variant often shows pseudostratified nuclei, leading to an erroneous diagnosis of columnar cell carcinoma, a potentially aggressive variant of PTC. The reverse is also true, in the sense that hyalinized areas, a frequent occurrence in the cribriform-morular variant, can point toward a diagnosis of hyalinizing trabecular tumor, a neoplasm with excellent prognosis (even better than the cribriform-morular variant) if strictly defined.

The diagnosis of thyroid cancer can predate the symptoms of colorectal polyposis by 4 to 12 years in up to 30% of patients in some series. In one study of seven patients with the cribriform-morular variant of PTC, two patients were found to have polyposis; both tested positively for germ-line adenomatous polyposis coli (APC) gene mutation, and both underwent subsequent colectomy. Because of the potential of detecting FAP early in patients diagnosed with the cribriform-morular variant, we strongly encouraged our first patient to undergo screening colonoscopy. Fortunately, colonoscopy ruled out the presence of colonic polyposis. If screening can detect FAP, it is possible to reduce the development of an individual’s risk of colorectal cancer.

Immunohistochemically, these tumors stain positively for estrogen and progesterone receptors that may correlate with the female predominance in the cribriform-morular variant. The tumors also stain well for thyroglobulin, cytokeratins AE1/AE3 and cytokeratin 7, and have also been shown to stain positively for cytokeratin 34betaE12, neuron-specific enolase, vimentin, bcl-2, and retinoblastoma protein. The tumor in our patient with FAP stained for thyroglobulin and cytokeratin 7 and was negative for cytokeratin 20, indicating its lineage from the thyroid follicular epithelium.

In PTC associated with FAP, genetic alterations include germline APC mutations, somatic mutations, or loss of heterozygosity of the APC gene. In addition to loss of function of the APC gene, genetic alterations in FAP-associated thyroid cancer involve gain of function of the ret proto-oncogene. In fact, two small series have shown a 80% to 100% frequency of ret/PTC rearrangement and activation of the ret/PTC1 and ret/PTC3 isoforms in these patients.

As seen in our first patient, the cribriform-morular variant may be encountered in patients with non-FAP. First described in 1999, the sporadic cribriform-morular variant of PTC tends to be well circumscribed and solitary and also occurs in women younger than 30. Immunohistochemically, these tumors stain positively for thyroglobulin, as with our first patient, and for cytokeratins, vimentin, estrogen, and progesterone receptors, bcl-2, and retinoblastoma protein. In one study of seven patients diagnosed with the cribriform-morular variant, four patients had no evidence of polyposis or APC gene mutation. However, a somatic APC mutation was found in a
patient without a germline APC mutation. \(^{17}\) These patients with the sporadic cribriform-morular variant have an excellent prognosis, with one report describing no recurrence of tumor up to 13 years after diagnosis. \(^{16}\)

Mutant beta-catenin contributes to the development of the cribriform-morular variant of PTC in both FAP and sporadic forms. \(^{11}\) APC forms a macromolecular complex with beta-catenin and is involved in the Wnt transduction signaling pathway, sequestering beta-catenin and targeting it for degradation. \(^{18,19}\) Mutations in the APC gene lead to a truncated APC protein that lacks the ability to degrade beta-catenin, leading to increased cytoplasmic beta-catenin levels. \(^{20}\) Cytoplasmic and nuclear immunolocalization of beta-catenin in FAP-associated cribriform-morular variant of PTC suggests an abnormality in the Wnt transduction signaling pathway. \(^{21}\) Xu et al \(^{11}\) demonstrated somatic mutations in the beta-catenin gene CTNNB1 in patients with either FAP-associated or sporadic cribriform-morular variant of PTC. Cytoplasmic and nuclear immunolocalization of beta-catenin was noted in both sets of patients, suggesting that the aberrant nuclear accumulation of mutant beta-catenin can occur independently from APC mutations and may contribute to the genesis of these tumors. \(^{11}\) Beta-catenin also seems to be responsible for the peculiar morphology (i.e., cribriform growth and morules) seen in these tumors. Indeed, beta-catenin accumulation has also been found in ex-trathyroidal neoplasms displaying morules and intricate glandular growth patterns, such as fetal lung adenocarcinoma and endometrioid-type adenocarcinoma of the endometrium. \(^{22}\)

Also, supporting a role in the morphogenesis of the cribriform-morular variant is the fact that beta-catenin nuclear/cytoplasmic accumulation is critical in the epithelial budding, branching, and hair follicle formation in embryogenesis. The cribriform pattern may, therefore, recapitulate the epithelial budding seen in embryos, and the morules may recapitulate the hair formation seen in embryogenesis. \(^{22}\)

In our patient with FAP, we found aberrant accumulation of beta-catenin in the tumor nuclei, in agreement with previous reports. However, the tumor in our sporadic case did not show beta-catenin nuclear or cytoplasmic staining, and there was no estrogen or progesterone immunoreactivity. These findings suggest alternative pathways (other than beta-catenin) may be responsible for the formation of these neoplasms.

Because of their multicentricity and bilaterality, total thyroidectomy is the treatment of choice for the cribriform-morular variant of PTC. \(^{1}\) Although the tumor in our patient with non-FAP did not reveal multicentricity, the tumor of the patient with FAP did demonstrate multicentricity, supporting the argument for total thyroidectomy in these patients. These tumors may metastasize to regional lymph nodes. Long-term prognosis is excellent for patients with FAP-associated cribriform-morular variant, with 5-year and 20-year survival rates of 90% and 77%, respectively. \(^{1}\)

**CONCLUSIONS**

The cribriform-morular variant of papillary thyroid cancer may be associated with familial adenomatous polyposis. Patients with FAP in whom there is a concern for PTC should undergo total thyroidectomy. Although rare, when the cribriform-morular variant is diagnosed, patients should undergo screening colonoscopy to rule out the presence of colonic polyposis. The prognosis of this variant of PTC is similar to that of the classical type. This distinct histologic finding should alert physicians to screen such patients and their family members for FAP, thereby facilitating early diagnosis of FAP.

**REFERENCES**


