Case Report
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Cribriform-Morular Variant of a Papillary Carcinoma: A Case Report

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Abstract
Worldwide, thyroid cancers are the most common type of endocrine-related cancers. Papillary carcinoma accounts for the most frequent type of thyroid malignancy. A rare variant of papillary carcinoma of the thyroid is the cribriform-morular variant. We report a case of solitary, cribriform-morular variant of papillary carcinoma in a 55-year-old lady. It is important to identify this variant because of a better prognosis compared to the other aggressive variants and poorly differentiated thyroid cancers. Multifocal cribriform-morular variant of papillary carcinoma may be the first manifestation of familial adenomatous polyposis.

Keywords: Endocrine tumor, Familial adenomatous polyposis, Thyroid

Introduction
Papillary carcinoma of the thyroid is reported as the seventh most common cancer among women. The cribriform-morular variant (C-MV) forms a rare morphologic entity among the different variants of papillary carcinoma. This tumor is distinct in that it may present as the first manifestation of familial adenomatous polyposis. This association has been initially described by Harach et al.1 While the tumors associated with familial adenomatous polyposis (FAP) often appear multifocal because of different germ line and somatic mutations, sporadic forms appear as isolated tumors.2

Case Report
A 55-year-old female presented with swelling in the front of her neck that gradually increased in size over the past eight years. There was no associated pain, hoarseness, or weight loss. Clinical examination showed an enlarged thyroid that measured 6×4cm on the right side and 2×1cm on the left. The swelling moved on deglutition, was non-tender, and non-pulsatile. Thyroid function tests were within normal limits. Ultrasonography showed a large nodule that measured 8×8cm in the isthmus. There was no preoperative fine needle aspiration cytology (FNAC) and the patient underwent a total thyroidectomy.

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The gross specimen received in the histopathology lab showed an enlarged thyroid that weighed 80g. One lobe was enlarged and measured 6×4 cm. The other lobe measured 2×1 cm. There was an enlarged nodule that measured 8×8 cm identified in the isthmus, the cut surface of which revealed a well circumscribed encapsulated lesion with cystic and spongy areas (Figure 1). The remainder of the thyroid had a normal colloid filled appearance.

Histopathology of the well encapsulated neoplasm was remarkable for cells arranged in cribriform (Figure 2a), solid (Figure 2b, c), spindle, morular (Figure 3a, b), and papillary patterns. Luminal spaces were devoid of colloid. Cuboidal or attenuated tumor cells were observed. The nuclei were often chromatin-rich, however nuclear features typical of papillary carcinoma were seen focally. There were single-to-multiple layers of cuboidal epithelial cells with anisonucleosis, overlapping nuclei, optically clear ground glass nuclei, and intranuclear grooves observed in some areas. Focal areas showed psammoma bodies. The remainder of the thyroid tissue was normal with colloid filled follicles. A histopathological diagnosis of C-MV of papillary carcinoma was made. Immunohistochemistry performed showed TTF-1 positivity in the tumor cells (Figure 4). Thyroglobulin was negative within the tumor, but positive in the adjacent normal thyroid. The tumor was negative for calcitonin. β-catenin immunohistochemistry was not performed in this patient.

The patient had an uneventful post-operative period. After screening, we have detected no manifestations of FAP in the patient and close relatives. The patient has been on regular follow-up for the past six months with no complaints.

Discussion
Papillary thyroid carcinoma forms the most common type of thyroid cancer, representing 80% of all thyroid cancer cases. This carcinoma occurs more frequently in women and presents in the 20-55 year age group. It is the predominant thyroid cancer type in children and patients who have had previous radiation to the head and neck.

The term C-MV of papillary thyroid carcinoma (PTC) was coined by Cameselle-Teijeiro and Chanin 1999 and initially used to describe the

![Figure 1. Well encapsulated thyroid tumor with spongy and cystic appearance.](image1)

![Figure 2a. Cribriform areas of tumor with back-to-back follicles that contain anastomosing bars and arches of cells in the absence of intervening fibrovascular stroma. Note the luminal spaces devoid of colloid. (H&E; 100×)](image2)
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sporadic counterpart of FAP-associated thyroid carcinoma. Since these tumors were morphologically indistinguishable from thyroid carcinomas that arise in the FAP, currently the term C-MV has been approved to describe tumors that occur in both conditions.

Mean age at diagnosis of C-MV PTC is 30 years compared with 45 years in sporadic forms of the tumor. The tumors are usually well encapsulated. Sporadic tumors occur as isolated masses, but those associated with FAP are often multifocal. The C-MV exhibits a combination of cribriform, follicular, trabecular, solid, and papillary patterns of growth with morular areas. Cells that line the cribriform and papillary areas show nuclear features of typical papillary carcinoma. Morules appear squamous with no keratinization or cellular bridges.

Familial adenomatous polyposis is an autosomal dominant disorder characterized by numerous adenomatous polyps that develop in the colon and rectum with an intrinsic tendency to progress to adenocarcinoma. It results from a germline mutation on the long arm of chromosome 5 (5q21-22) in the APC gene. In 1949, Crail first reported these malignancies that arose in the brain, rectum, and thyroid. The relationship of FAP and thyroid carcinoma was suggested for the first time by Camiel et al. in 1968.

Studies from
various polyposis registries confirmed the association between FAP and thyroid carcinoma and showed that young women with FAP had 160 times more chance of developing thyroid cancer than healthy subjects. Currently the overall prevalence of thyroid carcinoma in FAP is approximately 12%.

Immunohistochemically, the tumor cells express thyroid transcription factor-1, along with cytoplasmic and nuclear accumulation of β-catenin. Neuron-specific enolase, vimentin, epithelial membrane antigen, high- and low-molecular-weight cytokeratins, and bcl-2 protein are other positive markers. Since the accumulation of mutant β-catenin may contribute to the development of C-MV of PTC, β-catenin immunohistochemistry can be used as a screening method to identify occult FAP in patients with thyroid tumors. Positive neuroendocrine markers predict an aggressive clinical course. Tumor cells are consistently negative for calcitonin and thyroglobulin.

Cytogenetic studies showed a germline heterozygous APC Ex 2-3 duplication mutation in the neoplastic cells along with RET/PTC rearrangement. Hot spots on codons 1061, 1039, and 698 of the APC gene on exon 15 have been frequently identified. A few cases also contained the somatic homozygous silent p.Thr1493Thr gene variant. The molecular pathogenesis of sporadic CMV-PTC is not completely understood. Recent studies conducted on three sporadic cases showed the presence of the PIK3CA mutation, the wild-type KRAS, BRAF, CTNNB1 genes, and intact PTEN expression, which suggested a possible contribution of the PIK3CA mutation in tumor development.

**Conclusion**

This morphologic variant of PTC should be kept in mind by pathologists because of its characteristic pattern. In 25%-30% of cases, this might provide the first indicator of an underlying FAP syndrome. The clinician should be alerted to exclude FAP along with appropriate family screening. Cribriform morular variant carries a better prognosis than the other aggressive variants of PTC (tall cell, columnar, diffuse sclerosing, and diffuse follicular) and poorly differentiated carcinoma, which are the common differential diagnosis based on histopathology.

**Conflict of Interest**

No conflict of interest is declared.

**References**


