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Case report

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Cribriform-Morular Variant of Papillary Carcinoma: Association with Familial Adenomatous Polyposis - Report of Three Cases and Review of Literature

Shylashree Chikkamuniyappa and Jaishree Jagirdar
Department of Pathology, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78229-3900, USA

Abstract

We describe a rare variant of papillary thyroid carcinoma (PTC), the Cribriform-Morular Variant (C-MV). A handful of cases have been described in the literature of this entity. They exhibit the morphologic features of a distinctive papillary neoplasm along with solid, cribriform, and squamoid-morular areas. The cribriform and morular features make this a separate entity which could be mistaken for a high grade aggressive thyroid neoplasm. These lesions are usually associated with familial adenomatosis polyposis (FAP) but rarely may be sporadic. We report three cases that we have encountered.

Key words thyroid neoplasm, papillary thyroid carcinoma, cribriform, squamoid, morular

Author biography

Shylashree Chikkamuniyappa, MD, is a final year Anatomic/Clinical pathology resident at Univ TX Hlth Sci Ctr at San Antonio. She is serving as the Chief resident in the department and serving on various institutional and national committees. She is currently working on several research projects with faculty and presented at national meetings. She will pursue her fellowship in hematopathology for the next 2 years.

Jaishree Jagirdar, MD, is the Professor and Director of Anatomic Pathology at the Uni Tx Hlth Sci Ctr at San Antonio. After completing her residency in AP/CP at Mt. Sinai Medical Center in New York, she stayed on as faculty for 10 years. Following that she worked at New York University for another 11 years. Her area of expertise is in Pulmonary Pathology, both diagnostic and research aspects. She is the Hlth Sci Ctr Pulmonary Pathology Consultant and has published primarily on lung diseases for the last 20 years.

Corresponding address

Shylashree Chikkamuniyappa, MD, Department of Pathology, UTHSCSA Mail Code 7750, 7703 Floyd Curl Drive, San Antonio, Texas 78229-3900. Tel: (210) 567-6731 Fax: (210) 692-1480 Email: chikkamuniya@uthscsa.edu

1. Report of cases

Case 1.

Patient was a 32 year old G1P0 white female who presented with an enlarging painless lump in her neck for the preceding two years. Ultrasound revealed a large, lobulated, right lobe mass. Serum level showed: TSH-0.4 μ IU/ml, T3-1.88ng/ml (N: 0.6-1.81 ng/ml), free T4-1.2 ng/dl (N: 0.8-1.8 ng/dl) and 24 hour radio active iodine uptake-37%. She underwent a total thyroidectomy and is currently on adjuvant radioactive iodine. She also underwent a proctocolectomy for multiple colonic polyps and colonic carcinoma.

Case 2.

Patient was a 14 year old Latin American female with a gradually enlarging right neck mass for 2 years. CT scan showed several bilateral lesions. Fine needle aspiration showed normal follicular cytology. Serum level showed: TSH-1.31 μ IU/ml, T4-0.92ng/ml (N: 0.6-1.81 ng/ml), free T4-2.6 ng/dl (N: 0.8-1.8 ng/dl) and 24 hour radio active iodine uptake-28%. She underwent a total thyroidectomy with subsequent radioactive ablation. There is no family history of colonic polyposis.

Case 3.

Patient was a 34 year old asymptomatic HIV positive female with bilateral neck masses. Fine needle aspiration of the left lobe lesion showed papillary carcinoma. Serum level showed: TSH-1.92 μ IU/ml, free T4-1.1 ng/dl (N: 0.8-1.8 ng/dl) and 24 hour radio active iodine uptake-31%. She underwent a total thyroidectomy with subsequent radioactive ablation. She had a colectomy for multiple colonic polyps.

Gross Pathology

Specimens revealed well-circumscribed, somewhat lobulated tan masses ranging from 1.5-2 cm with multiple satellite nodules. There was no lobe predilection. There was no necrosis or hemorrhage seen. The remainder of the thyroid was lobulated and beefy. Few lymph nodes were also identified.

Microscopic Pathology

The typical nuclear features of PTC could be seen. They were complex branching papillary structures lined by cuboidal cells. The nuclei were hyperchromatic, optically clear with longitudinal grooves and showed eosinophilic, intranuclear and cytoplasmic inclusions as in classic PTC (Fig 1). Some lesions showed an intricate blending of several histological patterns (Fig 2). Cribriform areas had back-to-back follicles with anastomozing bars and arches of cells in the absence of intervening fibrovascular stroma and accounted for 30-50% of the lesions (Fig 3). The solid areas, which were approximately 20-30%, consisted of whorls of cells that form squamoid morules or nests that typically do not show any keratinization or intercellular bridges (Fig 4). No colloid or psamomma bodies were found in the tumors. Case 3 also showed foci of tall and columnar cell features.

2. Comment

Cribriform-Morular Variant (C-MV) of PTC is a rare morphologic entity. It was first described by Harach et al. [1] in association with FAP as a distinctive tumor. A total of 44 cases have been documented so far (See Table1). We describe three cases, in two of which the patients have FAP. Case 2 was lost to follow-up.

Two cases were women in their 30's and the third was a 14 year old. The lesions ranged from 1.5 to 2 cm and were associated with several satellite nodules. There was no lymph node metastasis, capsular or vascular invasion. Our cases are similar to that described by Cameselle-Teijeiro et al. [2] who first proposed the term and did a study on nine cases. All the cases were seen in women between ages of 16-30 years (mean: 21.3). The lesions were predominantly solitary and ranged from 1.5-5.6 cm. All except one showed vascular invasion. Two cases also showed lymph node metastasis. In that study, immunohistochemical stains were positive for thyroglobulin, epithelial membrane antigen, cytokeratin, vimentin, estrogen and progesterone receptors, bcl-2 and Rb proteins. Calcitonin and carcinoembryonic antigen were negative. Follow-up showed seven cases with no recurrences.

C-MV of PTC is commonly seen in young females usually less than 30 years of age. The lesions are encapsulated or well-circumscribed. While sporadic forms usually appear as an isolated tumors, the cases associated with FAP are often multifocal due to different somatic mutations added to the germline mutations [3]. They display the characteristic histologic pattern of cribriforming akin that seen in breast cancer with morules. Morules appear squamous with no keratinization or cellular bridges. There are also follicles showing papillary, trabecular and solid patterns.

There have been several cases showing germline mutations in the APC gene which have also been found in the colonic polyps. Hot spots on codons 1061, 1039 and 698 of the APC gene on exon 15 are frequently identified. It has been proposed that β-catenin immunohistochemistry is a feasible screening method to identify occult FAP in young patients with thyroid tumors [4]. Recently Xu B [5] suggested that accumulation of mutant β-catenin contributes to the development of C-MV of PTC. A handful of sporadic cases have also been documented [6]. Table 1 summarizes all the cases in the literature. Molecular studies were performed in all our cases and they did not show the hot spots of the APC gene.

C-MV carries a better prognosis than the other aggressive variants of PTC (tall cell, columnar, diffuse sclerosing and diffuse follicular) and poorly differentiated carcinoma. Tall cell variant lacks morular, cribriform and spindle cell areas. Columnar cell variant presents in older males. The encapsulated form of columnar cell variant is common in females and histologically shows greater overlap with C-MV but does not have the morules and cribriform pattern. Hyalinizing trabecular tumor shows a zellballen pattern in a hyalinized amyloid-like background. Poorly differentiated (insular) carcinoma shows areas mimicking cribriform structures but lacks morules and is associated with a higher proliferation index and necrosis.

This morphologic variant should be borne in mind by pathologists because of its characteristic pattern. The clinician should be alerted to exclude FAP along with appropriate family screening. In 25-30% of cases, this might provide the first indicator of an underlying FAP syndrome.

Conflict of interest:

The authors have declared that no conflict of interest exists.

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Tables and Figures

Table 1

Cases	Sex/Age (yr)	FAP	Presentation	Main Features	APC Mutation in thyroid	Treatment	Outcome
Harach et al. [1]	F/19	Yes	Right neck mass	16 separate nodules	ND	Total thyroidectomy	A&W at 25 yrs
	F/34	Yes		2 cm	ND		
	F/34	Yes		1 focus	ND		
	F/23	Yes		3 cm	ND		
Cameselle-Teijeiro and Chan [2]	F/30	No	Right neck nodule at 6 months	22 mm	Absent	Hemithroidectomy (R), Subtotal lobectomy (L), Radioactive iodine	A&W at 5 yr
	F/16	No	Left neck nodule for 1 year	15 mm	ND	Total thyroidectomy, Radioactive iodine	A&W at 14 yr
	F/20	No	Left thyroid nodule	12 mm (R), 23 mm (L)	ND	Total thyroidectomy	A&W at 4 yr
	F/19	No	Right neck mass	19mm	ND	Total thyroidectomy	Recent case
Yamashita et al.[7]	F/21	No	Anterior neck mass	40 mm	ND	Surgical resection	A&W at 1-2 yr
	F/23	No	Anterior neck mass	50 mm, LN met +	ND	Surgical resection	A&W at 1-2 yr
	F/20	No	Anterior neck mass	56 mm	ND	Surgical resection	A&W at 1-2 yr
	F/21	No	Anterior neck mass	26 mm	ND	Surgical resection	A&W at 1-2 yr
Mizukami et al.[8]	F/16	No	Left neck nodule	20 mm		Subtotal thyroidectomy and radical neck dissection	A&W at 5 yr
Hizawa et al.[9]	F/20	Yes	Right neck mass	18 mm	Exon 15 at codon 1061	Hemithroidectomy (R), and LN dissection	A&W at 2 yr
Perrier et al.[10] 11/12 cases	F/15-61 yrs	Yes	Bilateral : 5	18 mm (0.2-5 cm) multicentric :8 2 cases with LN met's	All ND	5 Total thyroidectomy 5 near total thyroidectony 2 lobectomy 2 PO Iodine 10 T4 suppression	FU:&mos-30yr, 2 recurred 1 death
Soravia et al.[11]	F/38	Yes	Bilateral mass	Multifocal (3-35 mm) capsular and vascular +	Exon 15 at codon 698	Total thyroidectomy	Recurred and died
	F/24	Yes	Bilateral mass	20-35 mm, capsular invasion	Exon 15 at codon 698	Total thyroidectomy	Recurred
	F/51	Yes	Bilateral mass	6-23 mm	Exon 9 at codon 312	Total thyroidectomy	NP
Fenton et al.[12]	F/20	Yes	Diagnosis made retrospectively	Diagnosis made retrospectively	Exon 15 at codon 1061	Total thyroidectomy	A&W at 14mos
Cameselle-Teijeiro et al. [6]	F/27	Yes	Right neck mass x 14 mos	21 mm with capsular and angioinvasion	Exon 15 at codon 1309 somatic mutation	Total thyroidectomy	A&W at 14mos
Cetta et al.[13]	F/22	Yes	NP	Encapsulated	Exon 15 at codon 1061	NP	NP
	F/20	Yes	NP	8 mm	Exon 15 at codon 1309	NP	NP

	F/36	Yes	NP	11 mm	Exon 15 at codon 1309	NP	NP
Present Cases	F/32	Yes	Anterior neck	Multifocal	In process	Total thyroidectomy	Recent case

Fig 1

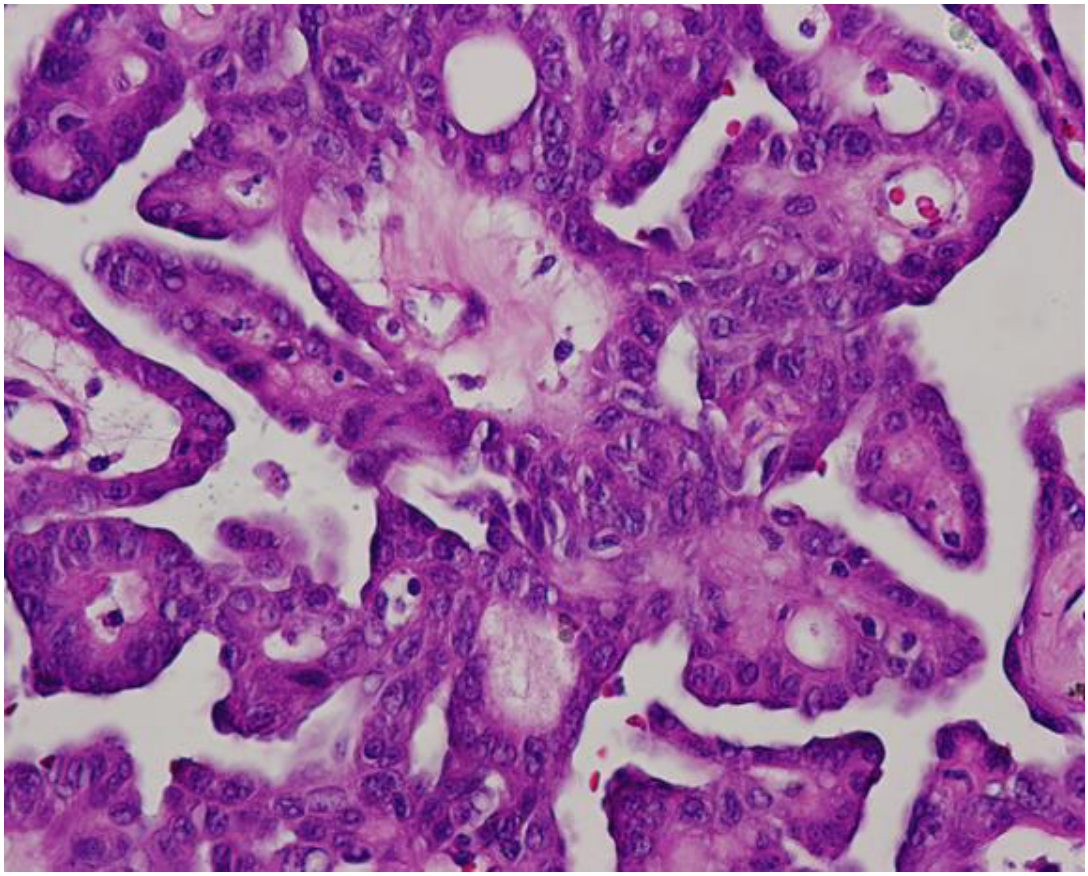

Fig 2

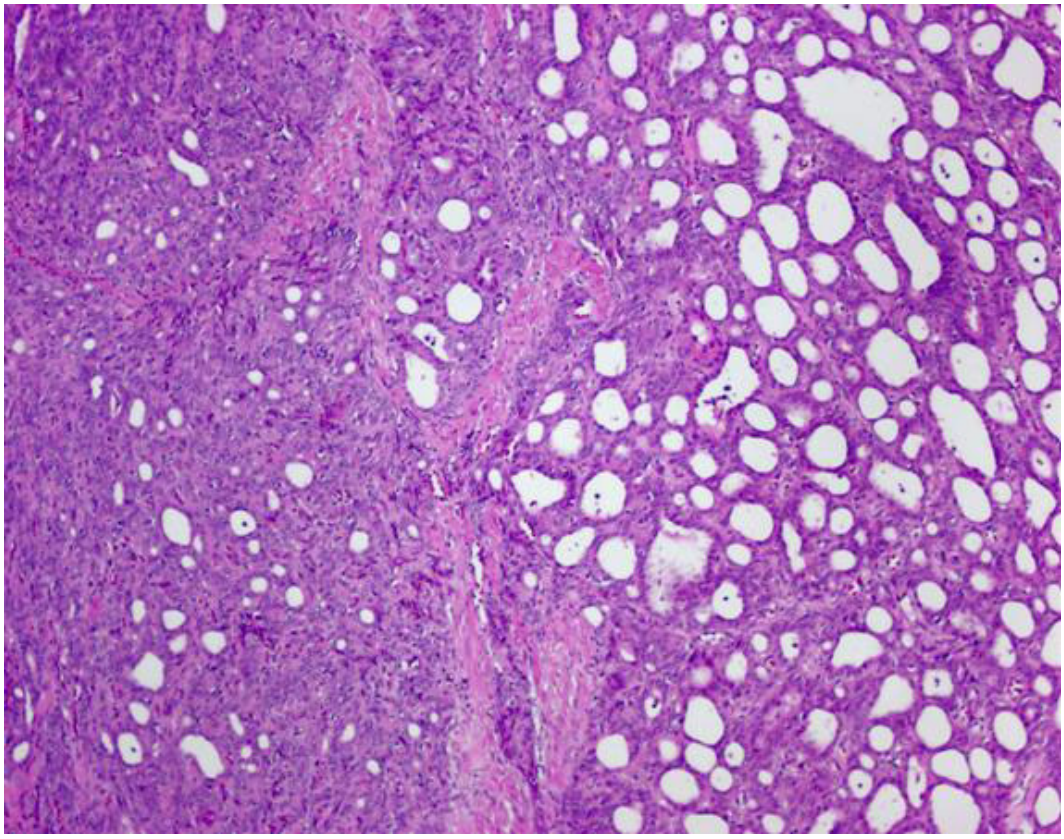

Fig 3

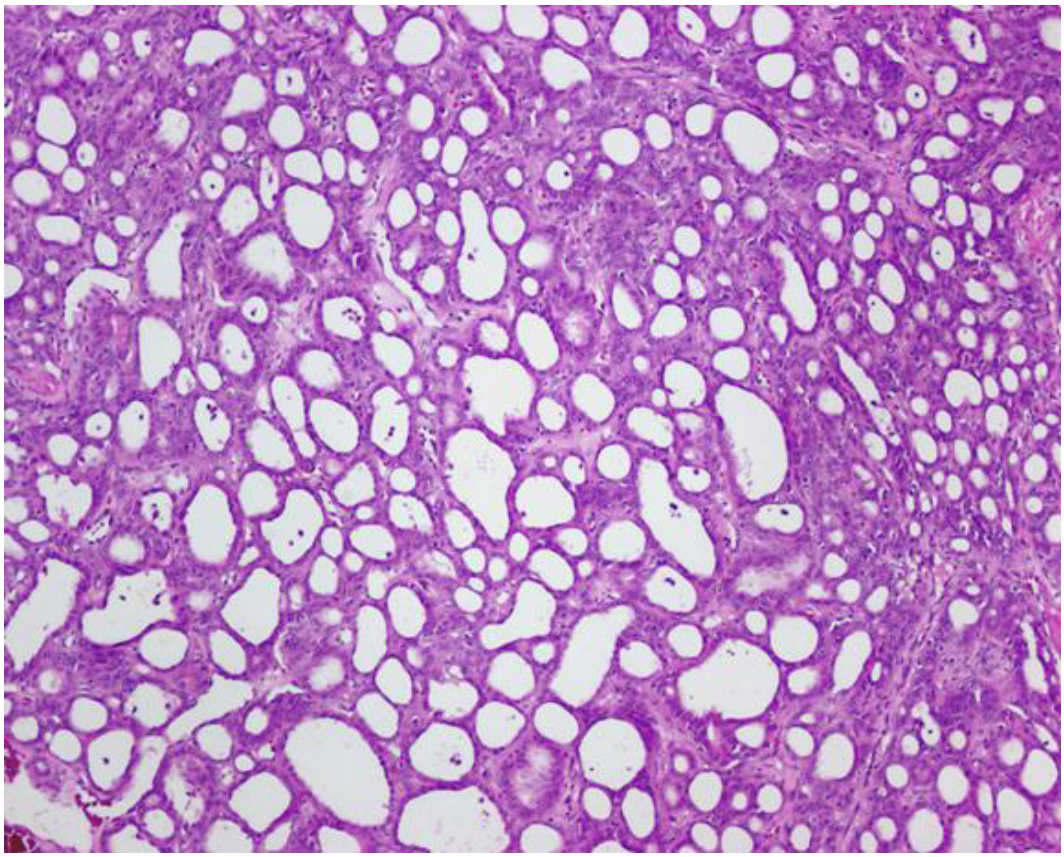

Fig 4