CRIBRIFORM-MORULAR VARIANT OF PAPILLARY THYROID CARCINOMA - A RARE CASE REPORT

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ABSTRACT
A rare histologic subtype of papillary thyroid carcinoma (PTC) is cribriform-morular variant (CMV) showing a combination of growth patterns including cribriform, morular and spindle cell areas. It can be rarely sporadic but are mostly associated with familial adenomatous polyposis (FAP). Multicentric CMV of PTC should alert clinician to search for FAP and thus can result in early detection of its associated colonic cancer. Sporadic forms are said to have good prognosis as compared to those associated with FAP. But its rarity and difficulty to differentiate from other aggressive thyroid tumors often leads to misdiagnosis and mismanagement. We report a rare case of sporadic CMV-PTC in a 45 year old female in the absence of FAP.

INTRODUCTION
Papillary thyroid carcinoma (PTC) represents 70-80% of all thyroid malignancies and 1% of all malignancies. The Cribriform-Morular Variant (CMV) of Papillary Thyroid Carcinoma (PTC) is a rare histologic subtype having prevalence of 0.16% among all PTCs [1, 4]. As CMV of PTC shows multiple growth patterns and is rare, so it is easily confused with highly aggressive PTC variants. We report a rare case of sporadic CMV-PTC in a 45 year old female.

CASE HISTORY
A 45 year old lady came with chief complaint of midline neck swelling since four years, which was nodular, painless, slowly increasing in size and moving with deglutition. Family history was negative for FAP, goiter, or any other endocrine disorders. Colonoscopy was normal. FNAC diagnosis was Papillary Thyroid Carcinoma. Total thyroidectomy was done and specimen was sent for histopathological examination.

Gross specimen consisted of two masses. 1) Right thyroid lobe which was a single, soft to firm, encapsulated, solid grey brown mass measuring 9.5 x 7 x 4 cm. On cut section, it was grey white with area of hemorrhage in center measuring 2 x 1.5 cm. 2) Separately sent left lobe and isthmus of thyroid gland measured 5 x 2 x 0.2 cm and was tan brown on cut section.

Microscopic sections studied from right thyroid lobe mass revealed a well encapsulated malignant tumor showing focal capsular invasion with tumor cells arranged in cribriform, papillary, solid and morular pattern. Complex branching papillary structures were seen lined by cuboidal cells whose nuclei were optically clear with longitudinal grooves and showed eosinophilic, intranuclear and cytoplasmic inclusions. Several interspersed morular (squamoid) areas were seen. Cribriform areas had back to back follicles with anastomosing bars and arches of cells in...
the absence of fibro vascular stroma. Compressed thyroid follicles devoid of colloid were also seen surrounding the capsule. Areas of hemorrhage and necrosis were also noted.

Sections from separately sent isthmus and left lobe of thyroid were unremarkable. Based on these features, histopathological diagnosis of Sporadic, Cribriform-Morular Variant of Papillary Thyroid Carcinoma (CMV of PTC) was made. Immunohistochemically it showed positivity for thyroglobulin, epithelial membrane antigen (EMA) and Bcl2. Follow-up for one year after surgery showed no recurrence of disease.

**Fig 1.** H&E, 10X, showing complex branching papillary projections in papillary thyroid carcinoma.

**Fig 2.** H&E, 10X, showing cribriform areas having back to back follicles with anastomosing bars and arches of cells in the absence of fibro vascular stroma

**Fig 3.** H&E, 4X, showing various histological patterns of Papillary Thyroid Carcinoma

**DISCUSSION**

PTC is a common malignant neoplasm with an excellent clinical behavior, but there are histological variants which can modify the course of this neoplasm. The CMV of PTC is the term initially coined for a sporadic type of PTC morphologically indistinguishable from most of the thyroid carcinomas that arise in the setting of FAP [2]. Now it is said that CMV of PTC, a rarer variant can occur sporadically (usually solitary tumors) or in association with FAP (usually multifocal with extensive metastasis and aggressive behavior). This Thyroid tumor is seen in female of younger age group (usually <30 years) than usual (classic) PTC [3, 4].

It is reported to be due to germline mutations in the adenomatous polyposis coli (APC) gene located in the 5q21 region resulting in an inherited disorder named FAP [3, 6]. FAP, an autosomal dominant disorder have intrinsic tendency to progress to colon adenocarcinoma. FAP associated thyroid carcinoma is now a distinct tumor type because of its histologic differences from follicular and papillary carcinomas [5, 6]. On Fine needle aspiration cytology, this variant is diagnosed by the presence of numerous follicular cells with unusually abundant eosinophilic cytoplasm [3]. Histopathologically, CMV of PTC shows encapsulation or circumscription, mixed solid, papillary, cribriform and morular pattern with the presence of follicles usually devoid of colloid and morular metaplasia with peculiar nuclear clearing [5]. These morules resembles squamous metaplasia, but they usually lacks intercellular bridges and keratinization and shows typical nuclear clearing due to deposition of lightly eosinophilic, homogenous, biotin containing inclusions [4]. The cribriform and morular features could be mistaken for a high grade aggressive thyroid neoplasm [6].

Histologically, Morules are associated with aberrant nuclear and cytoplasmic localization of beta catenin and not an early form of squamous metaplasia [4]. It is said that these unusual histopathological characteristics in a thyroid tumor, especially if multicentric, should alert the clinician to ask in detail for family history to rule out the possibility of FAP and associated colonic cancer [1]. However in our case, colonoscopy was normal. Immunohistochemically, the tumor cells show positivity for vimentin, thyroglobulin,
epithelial membrane antigen, neuron-specific enolase, CD15, estrogen and progesterone receptors, and bcl-2 protein. Unlike squamous metaplastic cells, morules show negativity for epithelial membrane antigen, vimentin, high-molecular-weight cytotkeratins, and estrogen and progesterone receptors [3]. S100 protein positive dendritic cells are seen in squamous metaplastic cells and not in morules [4].

It is reported that CD 10 immunostaining is also a useful marker for detecting morules in the “biotin –rich, optically clear nuclei” family of tumors occurring in different organs, all sharing APC/beta catenin pathway alterations [5].

CMV-PTC behavior is similar to that of conventional PTC including frequent occurrence of cervical metastases [4]. Prognosis of PTC is linked with many clinical variables such as age, tumor size, and histological parameters like lymph node metastasis, extra capsular extension and histological variants.

Differential diagnosis of CMV of PTC includes tall cell variant of PTC, Columnar cell carcinoma and poorly differentiated carcinoma of thyroid. Tall cell variant of PTC is a highly papilliferous tumor comprising of columnar cells having height at least three times of their width and has basally located nuclei. Columnar cell carcinoma shows much overlap with CMV of PTC, both showing solid areas, pseudostratified columnar cells and elongated empty follicles looking like tubular glands. However, Columnar cell carcinoma have prominent nuclear hyperchromasia and may contain subnuclear and supranuclear cytoplasmic vacuoles. Poorly differentiated carcinoma of thyroid has a solid – trabecular – insular pattern, high mitotic index with no conventional features of PTC and are CD 10 negative [5].

In addition to CMV of PTC, morules with peculiar nuclear clearings and lacking immunoreactivity for estrogen and progesterone receptors have also been reported in pulmonary endodermal tumors, pancreaticoblastomas, and colonic tubular adenoma. Peculiar nuclear clearing without morule formation is seen in endometrial tissue after medroxyprogesterone acetate injection, endometrium during pregnancy and in ovarian endometrioid carcinoma. These were thought to be associated closely with the effects of female sex hormones [3].

**CONCLUSION**

The Sporadic CMV-PTC is the rare clinical entity having good prognosis as compared to those associated with FAP. It is necessary to differentiate this variant from other aggressive thyroid neoplasm. Early diagnosis of FAP associated CMV of PTC can help in early detection of its associated colonic cancer. Clinical, pathological and IHC studies helps in diagnosis of such a rare tumor.

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None

**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.

**REFERENCES**