**Case Report**

**Cribriform morular variant of papillary thyroid carcinoma: Cytomorphology, differential diagnosis and diagnostic implications in patients with adenomatous polyposis coli**

**ABSTRACT**
Cribriform-morular variant of papillary thyroid carcinoma (CMV-PTC), which has a better prognosis, is seen mostly in the setting of familial adenomatous polyposis (FAP). The cytomorphology of CMV-PTC is diverse; hence, it could be mistaken for other thyroid neoplasms with bad prognostic outcome. This case is of a 24-year-old female diagnosed with polyposis coli found to have thyroid nodules at screening ultrasonography. Aspirated thyroid smears were hypercellular with epithelial cells arranged in monolayer sheets, papillae with discohesion, and spindling of cells at the edges, cribriform clusters, and cell morules. Individual cell morphology ranged from polygonal, tall columnar to spindle cells. Nuclei were round-to-oval with coarse chromatin, indistinct nucleoli, and mitotic figures. Nuclear inclusions and grooves were rare and colloid was sparse. Cytomorphology was suspicious, however, was not classical of CMV-PTC documented so far. Subsequent histology confirmed a CMV-PTC.

**Key words:** Cribriform-morular variant (CMV); cytomorphology; papillary thyroid carcinoma (PTC)

**Introduction**
Cribriform-morular variant of papillary thyroid carcinoma (CMV-PTC) is a distinct PTC with a better prognosis. The affected patients have shown both germline and somatic mutations of adenomatous polyposis coli (APC) genes.[1] Unlike

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classic PTC, BRAF mutation does not contribute significantly to the development of CMV-PTC.\(^2\)

We report a case of CMV-PTC in a patient with APC, comparing with its documented cytomorphology and discuss its useful cytomorphological features in discriminating from other thyroid neoplasms.

## Case Report

A 24-year-old female presented with altered bowel habits and bleeding per rectum was diagnosed with APC. There was no history of familial adenomatous polyposis (FAP). At the same visit, she was diagnosed to have a multinodular goiter on imaging. The nodules on both lobes were aspirated for cytology.

Hypercellular smears showed cells arranged in monolayer sheets, discohesive papillae, cribriform clusters, cell morules with scattered single cells in a clean background [Figure 1]. Cell morules were three-dimensional with sharp rounded borders. Cribriform clusters showed slit-like and oval-to-round empty spaces surrounded by broad anastomosing bars of cells. The papillae had well-formed branching fibrovascular cores [Figure 2a], however, lacked sharp anatomical borders or nuclear palisading, unlike those seen in conventional PTC. The cells of papillae showed discohesion and spindling at the borders instead. The cellular composition varied with columnar cells at the edges of cell clusters, spindle cells attached to fibrovascular cores of papillae, and polygonal cells with small indistinct nucleoli in monolayer sheets. Nuclei were enlarged and mildly pleomorphic with identifiable mitotic figures. Clearing of occasional nuclei, rare nuclear inclusions, and grooves were present. Colloid was sparse and psammoma bodies were absent.

These cytomorphological features were unusual for conventional PTC. They were suspicious; however, were not the classic features of CMV-PTC documented in the literature. Therefore, it was placed in Bethesda thyroid cytology diagnostic category 5, suspecting a PTC variant. Total thyroidectomy and cervical lymph node dissection was done. The thyroid contained multiple, circumscribed whitish nodules, distributed in both lobes and isthmus. Some nodules contained hemorrhagic and cystic areas. Histology confirmed a multifocal CMV-PTC [Figure 2b]. Tumor metastasis was present in cervical lymph nodes.

## Discussion

Cytomorphological features of CMV-PTC are reported in a few recent case series.\(^3,5\) Immunocytochemical staining with beta-catenin and biotin as well have shown a value in cytological diagnosis.\(^6\) A series of 18 cases describe varying cellular arrangements with papillary pattern, which had been the predominant pattern in three-fourths of described cases.\(^4\) These papillae comprised cohesive cells with nuclear palisading around fibrovascular cores. In contrast, papillae were rare in this case and those present showed cell discohesion with spindling at the edges instead of palisading. Tall cells and spindle cells described as individual cells in the case series were present at the edges of flat monolayer sheets and papillary structures respectively in this case. The peculiar form of nuclear clearing, foamy/hemosiderin-laden histiocytes and background hyaline material additionally described in the case series were absent in this case. Lack of colloid has been a constant feature both in the case series and this case.

Fascicular and solid patterns are described as additional architectural patterns in another series of five CMV-PTC cases.\(^4\) Classical PTC nuclear features have been a constant feature in this case series. Even though some degree of nuclear clearing and occasional nuclear inclusions were present, classical PTC nuclear features were absent in this case and the nuclei in general appeared to be of a higher grade than those seen in conventional PTC.

The most salient features described in a series of another eight cases was the hypercellularity and papillary architectures in which the papillae have shown three-dimensional branching and prominent fibrovascular cores covered by single layers of cells with classical PTC nuclear features, unlike the papillae of this case.\(^3\)

Five other CMV-PTC cases additionally describe classical PTC nuclear features and cohesive papillary structures.\(^3\) Additionally, they describe cells with abundant cytoplasm and distinct cell borders, which was additionally appreciated in some columnar and polygonal cells in this case.

Therefore, the cytomorphology of the present case is somewhat dissimilar to the features already described and those include papillae with cell discohesion and spindling at the periphery, presence of columnar cells only at the edges of flat monolayer sheets, absence of classic PTC nuclear features with the nuclei appearing to be of a higher grade than in PTC and discernible mitotic activity.

Varied cytomorphological appearance of CMV-PTC may raise the possibility of a range of differential diagnosis of PTC variants and other thyroid neoplasms.

The tall cell variant of PTC (TV-PTC) may resemble CMV-PTC when abundant columnar cells are seen on smears. However,
the varying cytological features and smaller number of tall cells in proportion in CMV-PTC will differentiate it from TV-PTC.[6] Tumor necrosis that may be present in TV-PTC is not described in CMV-PTC.[7]

The presence of architectural atypia and squamous morules raise the possibility of a diffuse sclerosing variant of PTC. However, the absence of significant nuclear pleomorphism, psammoma bodies, and sclerosing stromal fragments will be helpful to differentiate CMV-PTC from this variant.[6]

Cytomorphology of columnar cell carcinoma (CCC) will yield columnar cells in smears. However, nuclear stratification resembling metastatic endometrial/colonic carcinoma and the absence of classical PTC nuclear features will be helpful in differentiating it.[7,8]

Medullary carcinoma (MC) may require exclusion if spindle cells predominate in smears. However, the constellation of cytomorphological features of CMV-PTC in the absence of characteristic dispersed/powdery chromatin pattern of MC will make this diagnosis unlikely.[9]

Sheets of cells with eosinophilic granular cytoplasm, distinct cell borders, nuclear clearing, grooves, and inclusions are common to both CMV-PTC and hurthle cell tumors hence, making their differentiation difficult.[10]

Diagnosing CMV-PTC on smears would be challenging especially in view of its varied cytomorphological appearance. However, the full cytomorphological spectrum of CMV-PTC, when appreciated, may be characteristic enough to allow its accurate diagnosis. Awareness of the varied cytomorphology of CMV-PTC avoids misdiagnosis, especially when it occurs sporadically, unassociated with FAP. Diagnosed APC patients, especially those with concurrent thyroid enlargement require exclusion of CMV-PTC, which has a recognizable cytomorphology and a favorable outcome.

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Conflicts of interest
There are no conflicts of interest.

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