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# Images in Endocrine Pathology: Papillary Variant of Medullary Thyroid Carcinoma with Cystic Change

**Martin D. Hyrcza · Daniel Winer · Ozgur Mete**

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## Case History

A 44-year old female presented with left thyroid mass. Imaging showed a 1.7-cm nodule and bilateral neck lymphadenopathy. The fine needle aspiration biopsy from the thyroid nodule revealed few macrophages consistent with cyst content. The patient underwent a total thyroidectomy with ipsilateral neck lymph node dissection.

## What is Your Diagnosis?

Histopathological Diagnosis: Papillary Variant of Medullary Thyroid Carcinoma with Cystic Change

The thyroidectomy specimen showed a well-circumscribed 1.7-cm mass composed of an epithelial neoplasm displaying cystic regions. Cystic areas revealed true papillary structures that contain fibrovascular cores lined on both sides by epithelial cells (Fig. 1a). The tumor cells were small, basophilic, and contain uniform nuclei with powdery chromatin and absent nucleoli. Occasional intranuclear pseudoinclusions are identified (Fig. 1b). Amyloid deposition was also identified and confirmed by orangeophilic staining with Congo Red (Fig. 1c) and positive birefringence under polarized light. Angioinvasion characterized by intravascular tumor cells admixed with thrombus was widely present (Fig. 1d). Ipsilateral levels II, III, and IV lymph node dissection specimen also revealed multiple lymph nodes positive for metastatic carcinoma with a predominant solid/nested growth. The tumor cells were stained with thyroid transcription factor-1 (TTF-1), synaptophysin, chromogranin-A, calcitonin, and monoclonal CEA and were negative for PAX-8 and thyroglobulin (Fig. 2). There was no evidence of underlying C-cell hyperplasia. She was not found to harbor germline *RET* mutations. The morphologic and immunohistochemical findings are diagnostic of sporadic medullary thyroid carcinoma showing true papillary growth and cystic change.

## Comment

Commonly encountered papillary lesions of the thyroid gland include diffuse hyperplasia (Graves' disease), follicular adenoma with papillary architecture (also known as "papillary adenoma"), complex follicular nodular disease with papillary architecture (multinodular goiter), and papillary thyroid carcinoma with classical (papillary) architecture [1, 2]. The texture and cytological features of papillary lesions can also be variable in follicular lesions. Not all papillary lesions contain true papillary architecture, defined as fibrovascular cores lined on both sides by a layer of epithelium. Both benign and malignant follicular epithelial proliferations can often show degenerative "pseudopapillary" regions resulting from stromal edema [2]. The distinction of malignant follicular epithelial proliferation should be based on the presence of invasive growth and/or nuclear features of papillary carcinoma [2]. Psammoma bodies are also another diagnostic feature of papillary thyroid carcinoma [2]. While Graves' disease is a diffuse phenomenon, follicular adenomas with papillary architecture often are

M. D. Hyrcza · D. Winer · O. Mete (✉)
Department of Pathology, University Health Network, 200 Elizabeth Street, 11th floor, Toronto, ON M5G2C4, Canada
e-mail: ozgur.mete2@uhn.ca

M. D. Hyrcza
Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada

D. Winer · O. Mete
Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

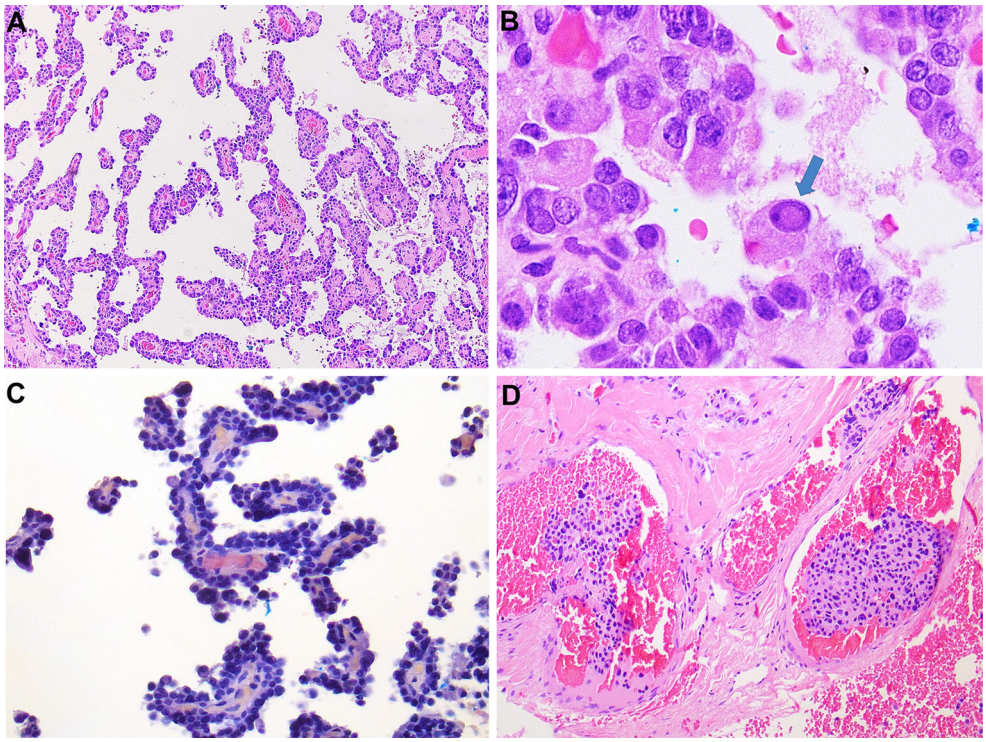


**Fig. 1** The thyroid nodule shows cystic areas revealing true papillary structures that contain fibrovascular cores lined on both sides by epithelial cells. The tumor cells are small, basophilic, and contain uniform nuclei with powdery chromatic and absent nucleoli (**a**, **b**). Occasional intranuclear pseudoinclusions are also noted (*arrow*; **b**). Amyloid deposition is also identified and confirmed by orangeophilic staining with Congo Red (**c**). Angioinvasion characterized by intravascular tumor cells admixed with thrombus is widely present (**d**)

solitary lesions that show regions of centripetal intrafollicular papillary growth that contains follicular structures within their cores, also referred to "subfollicle" formation. Their papillae are typically lined by hemosiderin-laden cuboidal and columnar cells that do not lack polarity and do not exhibit diagnostic nuclear features of papillary thyroid carcinoma. Medications (e.g., lithium) and dietary iodine can also contribute to diffuse or nodular papillary hyperplasia.

Similar to degeneration-related pseudopapillary architecture identified in follicular epithelial proliferations, medullary

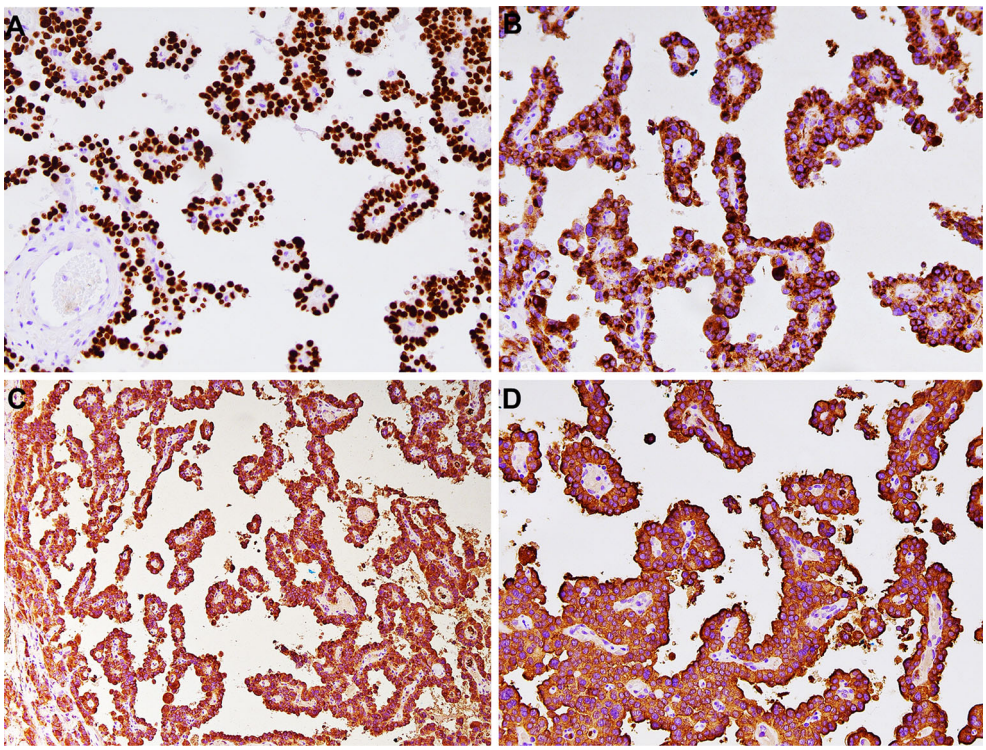


**Fig. 2** The tumor is positive for TTF-1 (**a**), chromogranin-A (**b**), calcitonin (**c**), and monoclonal CEA (**d**)

thyroid carcinomas can display a pseudopapillary architecture due to discohesive growth of tumor cells resulting in artifactual separation of tumor cells. Exceptional medullary thyroid carcinomas, similar to the presented case herein, can show true papillary structures characterized by fibrovascular cores in addition to pseudopapillary areas [3, 4]. While papillary thyroid carcinoma is distinguished by heterogeneous nuclear membrane irregularities in enlarged nuclei, medullary thyroid carcinoma cells can also mimic papillary thyroid carcinoma by their intranuclear pseudoinclusions. To complicate matters more, classical variant papillary thyroid carcinoma in a mixed medullary and follicular epithelial carcinoma may occur [5].

In addition, ultimobranchial body remnants, also known as "solid cell nests" that undergo cystic degeneration can sometimes show pseudopapillary formations. These are usually small embryologic remnants but can proliferate (solid cell nest hyperplasia) especially in the setting of chronic lymphocytic thyroiditis [6]. From a cytological perspective, these remnants can easily mimic papillary microcarcinoma due to the presence of nuclear membrane irregularities and nuclear overlapping [6]. Moreover, similar to C-cells, ultimobranchial body remnants are known to be positive for CEA and TTF-1, but these are also positive for p63 and lack calcitonin and thyroglobulin reactivity, helping their distinctions from parafollicular C-cell and follicular epithelial cell proliferations [2, 6]. Finally, one needs to always remember the possibility of metastatic tumors with papillary architecture to the thyroid gland from other organs, such as breast, kidney, or lung.

Positivity for calcitonin and negativity for thyroglobulin would often suffice for the diagnosis of medullary thyroid carcinoma; however, other neuroendocrine carcinomas can sometimes express calcitonin or calcitonin gene-related peptide [7]. Moreover, dedifferentiated medullary thyroid carcinoma can also be negative for calcitonin but are positive for monoclonal CEA [8]. The demonstration of CEA along with calcitonin is of diagnostic importance. In addition, CEA is regarded as an important serum biomarker that is often used to diagnose recurrent disease in patients with medullary thyroid carcinoma.

In conclusion, papillary lesions of the thyroid gland can be quite variable and from a morphological point of view can be divided into true and pseudo papillary architecture. While careful examination of the texture and cytologic details of these lesions can guide the diagnostician, the presented case highlights that true papillary architecture mimicking classical variant papillary carcinomas can also be seen in medullary thyroid carcinoma. Therefore, regardless of the growth pattern of the thyroid neoplasm, the identification of discohesive, spindle, or plasmacytoid cells with basophilic and/or amphophilic cytoplasmic granularity should raise the suspicion of medullary thyroid carcinoma, and immunohistochemistry should be used to confirm the diagnosis by showing positivity for chromogranin-A, calcitonin, and monoclonal CEA.

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