Medullary thyroid carcinoma.

by Lester D. R. Thompson, MD

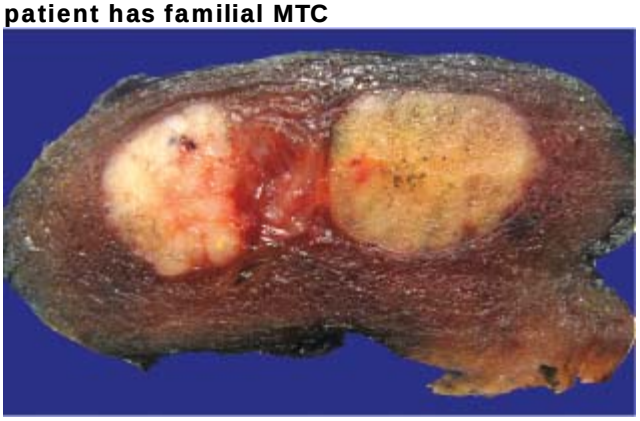
Medullary thyroid carcinoma (MTC) is a malignant epithelial tumor of the thyroid gland that exhibits C-cell differentiation. C cells arise from the ultimobranchial body, which is derived from the fourth pharyngeal pouch, and they are found in the upper and middle areas of the thyroid lobes. These cells produce calcitonin, a hormone involved in calcium homeostasis. While a number (20%) of MTCs are associated with the autosomal-dominant inherited multiple endocrine neoplasia (MEN) syndromes (specifically MEN2A and MEN2B), most (80%) cases are sporadic. Germline or somatic mutations of the RET gene are characteristic of this tumor. They usually involve an activating point mutation of 10q11.2. Specifically, codon 634 in exon 11 is most common in MEN2A, while codon 918 in exon 16 is most common in MEN2B.

MTC accounts for approximately 5 to 8% of all thyroid malignancies. Its affects patients of a wide age range; familial MTC tends to occur at an earlier age and sporadic MTC at a later age. Patients typically present with a painless thyroid mass-usually bilateral or multicentric in familial cases and unilateral in sporadic cases. Cervical lymph node enlargement is seen in as many as 50% of patients at presentation. In familial cases, it is important to exclude extrathyroidal findings, such as hyperparathyroidism; symptoms referable to pheochromocytoma; pituitary and pancreatic dysfunction; and mucosal neuromas.

Serum calcitonin levels are almost invariably increased, as are carcinoembryonic antigen (CEA) levels. Prophylactic thyroidectomy is recommended for patients with germline RET mutations, and thyroidectomy with or without neck dissection is recommended for other patients. The most important prognostic factor is tumor stage.

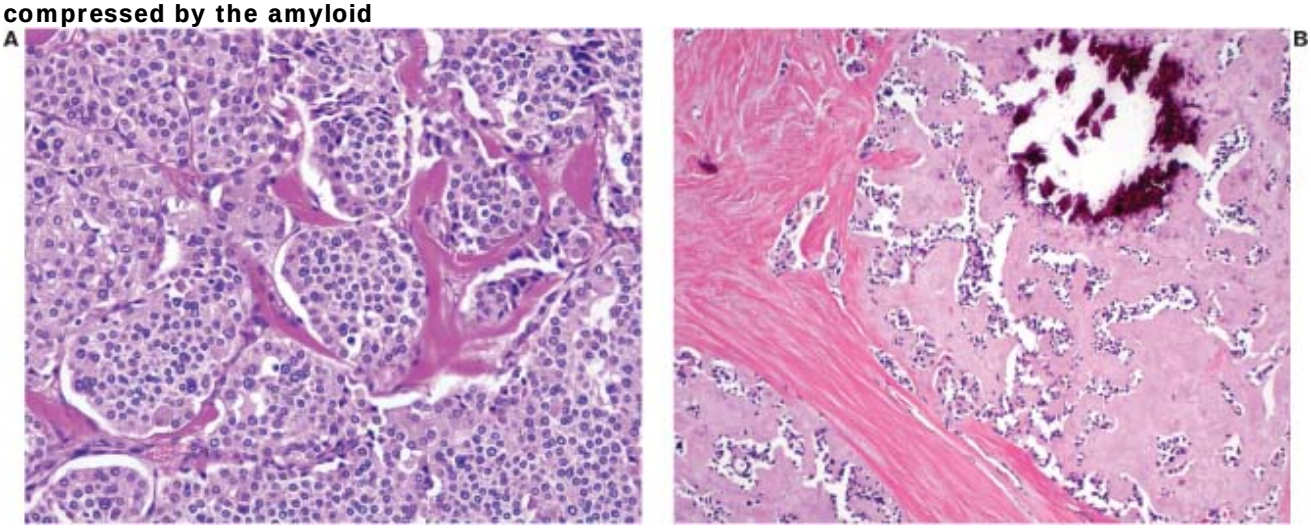
MTCs are usually well-defined tumors, but they do not have a well-formed capsule (figure 1). Significant lymph node or vascular invasion and extrathyroidal extension are often seen. The tumor cells are arranged in a variety of different patterns of growth, including solid sheets and nests that are separated by a heavily hyalinized fibrovascular stroma. Lobular, organoid, nested, insular, and trabecular patterns are also present.

Figure 1. This gross thyroid image shows two tumors within the thyroid lobe. They have a light to fleshy appearance. In this patient, the opposite lobe also has a medullary carcinoma. This patient has familial MTC



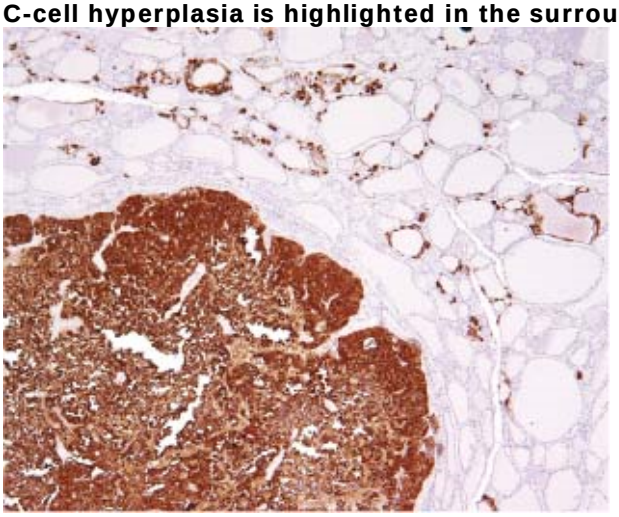
The cells are round to oval, spindled to plasmacytoid, or polyhedral. The nuclei are round to oval and feature a fine, stippled, uniform, salt-and-pepper nuclear chromatin (figure 2, A). Mild to moderate pleomorphism is present. The neoplastic cells are separated by a delicate, hyalinized stroma that ranges from thin to thick. Homogeneous, acellular, eosinophilic, extracellular, amyloid matrix material is frequently present; many times it is associated with calcification (figure 2, B). It is not uncommon, especially in inherited cases, to see a background of C-cell hyperplasia.

Figure 2. A: This high-power view demonstrates a nested or organoid arrangement of neoplastic cells. They are separated by delicate fibrovascular septae. The nuclei are small and round. B: Broad bands of fibrosis separate the tumor into nodules. The eosinophilic material is amyloid, and the dark purple material represents calcifications. The neoplastic cells are small and compressed by the amyloid



A number of histologic variants are recognized, including oncocytic, papillary, glandular, follicular, giant-cell, small-cell, paraganglioma-like, spindle-cell, clear-cell, squamous-cell, melanin-producing, angio-sarcoma-like, and amphicrine tumors, but the specific variant does not alter management or outcome. Congo red staining will highlight the amyloid with a light-green birefringence with polarization. The neoplastic cells will be strongly and diffusely immunoreactive with calcitonin (figure 3), chromogranin, synaptophysin, mCEA, keratin, and thyroid transcription factor 1; the cells are nonreactive with thyroglobulin.

Figure 3. These tumor cells show strong and diffuse immunoreactivity with calcitonin, while the C-cell hyperplasia is highlighted in the surrounding thyroid parenchyma



Cytogenetics can be performed on peripheral blood to detect germline RET mutations, while somatic RET mutations can be detected within the specimen. The differential diagnosis includes follicular carcinoma, papillary carcinoma, parathyroid tumors, paraganglioma, and undifferentiated carcinoma. Direct extension from laryngeal tumors (atypical carcinoid) must be excluded.

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Suggested reading

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2. Kloos RT, Eng C, Evans DB, et al. and the American Thyroid Association Guidelines Task Force. Medullary thyroid cancer: Management guidelines of the American Thyroid Association. Thyroid 2009; 19 (6): 565-612.
3. Moo-Young TA, Traugott AL, Moley JF. Sporadic and familial medullary thyroid carcinoma: State of the art. Surg Clin North Am 2009; 89 (5): 1193-1204.
4. Morrison PJ, Atkinson AB. Genetic aspects of familial thyroid cancer. Oncologist 2009; 14 (6): 571-7.
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