

Educational Case: Medullary Thyroid Carcinoma

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Carl T. McGary, MD, PhD¹ 

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289517715040>.

Keywords

pathology competencies, organ system pathology, cytology diagnostic certainty, endocrine, endocrine neoplasms, fine needle aspiration cytology, medullary thyroid carcinoma

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Primary Objective

EN5.2: Medullary Thyroid Carcinoma. Describe the molecular basis and clinicopathologic features of medullary thyroid carcinoma.

Competency 2: Organ System Pathology; Topic EN: Endocrine; Learning Goal 5: Endocrine Neoplasms.

Secondary Objective

CYP1.2: Categorizing Diagnostic Certainty. Compare and contrast the degree of diagnostic certainty applied to general categorization in cytologic diagnosis.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic CYP: Cytopathology; Learning Goal 1: Cytologic Diagnosis.

Patient Presentation

A 52-year-old Caucasian male presents to family medicine with an irregular 4-cm palpable nodule in the mid right thyroid lobe. He has no significant past medical history other than occasional diarrhea. Complete head and neck examination reveals no additional palpable nodules in the thyroid gland and no palpable adenopathy. The differential diagnosis for a palpable thyroid nodule includes a variety of benign and malignant entities, including colloid nodule, nodular hyperplasia,

follicular thyroid adenoma, follicular thyroid carcinoma, papillary thyroid carcinoma (PTC), medullary thyroid carcinoma (MTC), anaplastic thyroid carcinoma, and lymphoma. The patient is referred to the lab for pathologist to perform fine needle aspiration (FNA) cytology of the nodule.

Diagnostic Findings, Part I

The pathologist performs 3 FNA passes into the nodule under direct guidance using 25-gauge needles without suction, and the initial smears show adequate cellularity (Figure 1). Additional passes are not performed for cell block preparation. Using The Bethesda System for Reporting Thyroid Cytology, the pathologist finalizes the report as Bethesda category V, suspicious for malignancy and MTC. The cytology findings are shown in Figures 1 and 2 and compared to the more common PTC in Figure 3. The patient is referred to endocrinology for further evaluation.

¹ Department of Biomedical Sciences, The University of Minnesota Medical School–Duluth, Duluth, MN, USA

Corresponding Author:

Carl T. McGary, MD, PhD, Department of Biomedical Sciences, The University of Minnesota Medical School–Duluth, 1035 University Drive, SMED 227, Duluth, MN 55812, USA.

Email: cmcgary@d.umn.edu



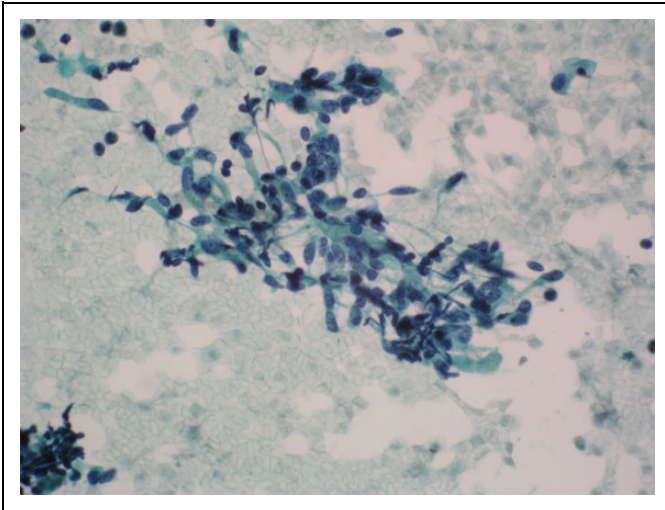


Figure 1. Papanicolaou stain at $\times 200$ of the initial FNA smear showing background red blood cells, scant colloid, and a mixed population of neoplastic cells showing epithelioid and spindle cell morphology. Nuclear chromatin shows a “salt and pepper” granularity and lacks features of papillary carcinoma (Figure 3), and the cell cytoplasm is somewhat granular. FNA indicates fine needle aspiration cytology.

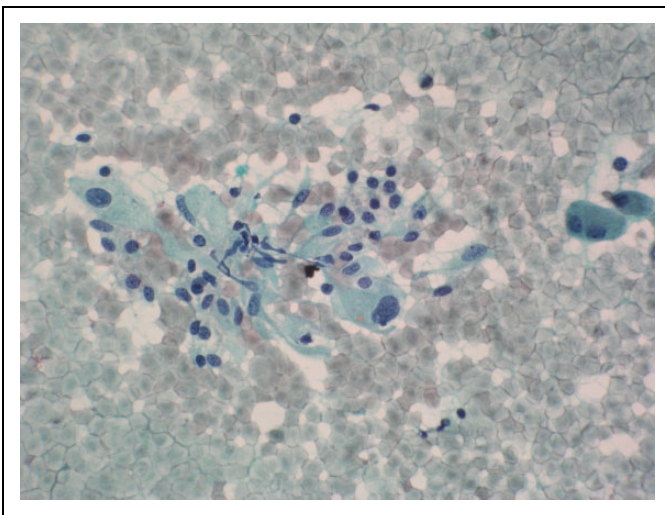


Figure 2. Papanicolaou stain at $\times 400$ highlighting random nuclear atypia often seen in neuroendocrine neoplasia, as well as the granular cytoplasm and fine-to-coarse nuclear chromatin of medullary thyroid carcinoma.

Questions/Discussion Points, Part I

Categorizing Diagnostic Certainty: Based on the Pathologist’s Interpretation of the FNA, How Statistically Likely is the Patient to Harbor a Malignant Neoplasm and What is the Uncertainty of the Diagnosis?

The major categories used in diagnostic cytopathology include unsatisfactory for diagnosis, negative for malignancy, atypical cells present, suspicious for malignancy, and positive for malignancy. Each category carries an implied degree of

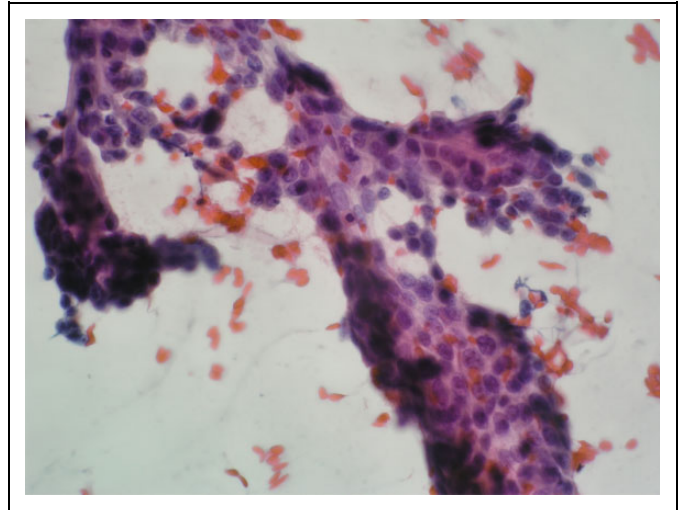


Figure 3. Papanicolaou stain of PTC for comparison with the patients with FNA cytology. Papillary thyroid carcinoma shows nongranular chromatin, nuclear grooves, small peripheral nucleoli, and occasional intranuclear pseudo-inclusions. Papillary-shaped irregular branching groups are also present. FNA indicates fine needle aspiration cytology; PTC, papillary thyroid carcinoma.

certainty with regard to the pathology present. Diagnostic modifiers are also used in surgical pathology to suggest degrees of uncertainty, including “cannot rule out,” “suggestive of,” “consistent with,” and “diagnostic of,” in increasing order of certainty.¹ The issue of uncertainty in anatomic pathology diagnosis is highlighted by the presence of both interobserver (2 observers arriving at a different diagnosis on the same case) and intraobserver (the same observer arriving at different diagnoses on the same case at different times) diagnostic variation.²

Interinstitutional review of 777 patient specimens revealed a diagnostic difference in 71 specimens on review at the second institution. In 45 of the 71 discrepant specimens, the change in diagnosis led to altered therapy. The discordant diagnoses were significantly more common in cytology specimens (21%) than surgical specimens (7.8%), suggesting that cytologic diagnosis was more prone to uncertainty than histologic diagnosis.³

Historically, cytopathologists at different institutions have utilized somewhat different diagnostic terminology when reporting results of thyroid FNA. To address the variety of reporting systems and the resulting inherent confusion, the National Cancer Institute (NCI) hosted the NCI Thyroid FNA State of the Science Conference. The conference conclusions led to the publication of the Bethesda System for Reporting Thyroid Cytology,⁴ which is now in wide use. Similar issues led to publication of the Paris System for Reporting Urinary Cytology.⁵

The Bethesda System for Reporting Thyroid Cytology⁴ contains 6 general diagnostic categories, each with a specific given risk of underlying malignancy as shown in Table 1. The least amount of uncertainty is associated with the benign and malignant categories as these have the narrowest range for underlying malignancy. The greatest degree of uncertainty lies with the atypical category which shows the widest range for underlying

Table 1. Major Diagnostic Categories of The Bethesda System for Reporting Thyroid Cytology and the Associated Risk of Malignancy.

Diagnostic Category	Underlying Risk of Malignancy (%)
ND/unsatisfactory (I)	1-4
Benign (II)	0-3
AUS/FLUS (III)	5-15
FN/SFN (IV)	15-30
Suspicious for malignancy (V)	60-75
Malignant (VI)	97-99

Abbreviations: AUS, atypia of uncertain significance; FLUS, follicular lesion of uncertain significance; FN, follicular neoplasm; ND, nondiagnostic; SFN, suspicious for follicular neoplasm.

Table 2. Diagnostic Categories of The Paris System for Reporting Urinary Cytology and the Associated Risk of Malignancy.

Diagnostic Category	Underlying Risk of Malignancy (%)
Unsatisfactory	<5-10
Negative for HGUC	0-10
Atypical urothelial cells	8-35
Suspicious for HGUC	50-90
Low-grade urothelial neoplasm	~ 10
Positive for HGUC	>90
Positive for other malignancy	>90

Abbreviation: HGUC, high-grade urothelial carcinoma.

malignancy, and the suspicious category being between atypical and benign/malignant in terms of uncertainty. Thyroid FNA is somewhat unique in having 2 suspicious categories. Suspicious for follicular neoplasm less commonly has an underlying malignancy when compared to the suspicious for malignancy category, as the majority of follicular neoplasms are benign adenomas, rather than follicular carcinomas.

Similar uncertainty is seen in other types of cytology specimens, such as urine cytology using The Paris System for Reporting.⁵ The risk of underlying malignancy in urine cytology based on The Paris System reporting is shown in Table 2. The wider the range for underlying malignancy, the greater the uncertainty for that diagnostic category.

In general, both benign and malignant cytologic diagnostic categories have the least associated uncertainty, and the most significant uncertainty is in the atypical category, with the suspicious category intermediate for the associated degree of uncertainty. Currently available molecular tests are available for use on ambiguous thyroid FNAs, to identify malignancy-associated genetic changes. These serve to decrease the broad diagnostic uncertainty in the atypical follicular cells of uncertain significance category and help direct treatment decisions (surgery vs continued clinical observation).

Diagnostic Findings, Part 2

The endocrinologist does a typical thyroid endocrine workup and finds that the patient is euthyroid and has a normal calcium.

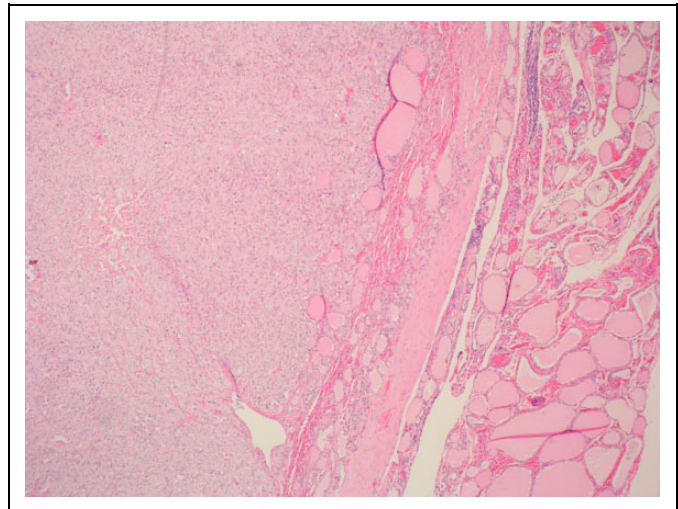


Figure 4. Hematoxylin and eosin stained section of the tumor thyroid interface at $\times 40$ showing a well-circumscribed cellular neoplasm on the left without follicular or papillary architecture. The tumor was incompletely encapsulated, and entrapped benign follicles are seen at the periphery. The adjacent thyroid tissue showed no evidence of C-cell hyperplasia and contains medium-to-large colloid-filled follicles on the right.

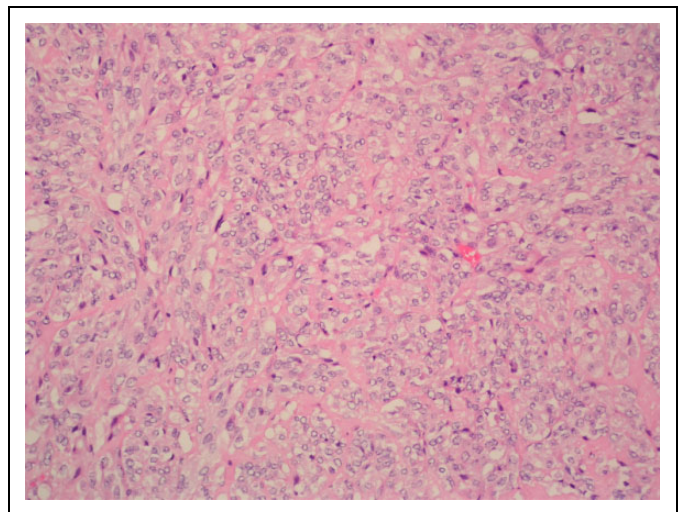


Figure 5. Hematoxylin and eosin stained section of tumor at $\times 200$ showing mixed epithelioid and spindled morphology with only vague nesting of tumor cells and a majority diffuse growth pattern. Amyloid was not present.

Because of the suspicion of MTC on the FNA, he also performs a serum calcitonin that comes back as 5679 pg/mL (normal <10 pg/mL). The patient is referred to otolaryngology and a total thyroidectomy and central and bilateral node dissection is performed. The final pathology shows a 3.9-cm medullary carcinoma (Figures 4-6) confined to the thyroid gland with 3 of 6 central nodes microscopically involved and none of 13 right and 1 of 11 left neck nodes involved by medullary carcinoma. The pathologic stage is reported as pT2, pN1a, pM-not applicable, or stage group III.

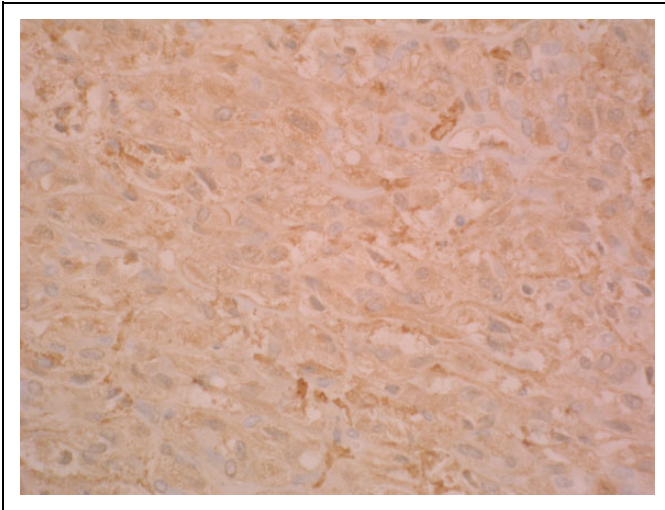


Figure 6. Immunohistochemistry of tumor for calcitonin $\times 400$ showing diffuse granular cytoplasmic staining.

Questions/Discussion Points, Part 2

What Clinicopathologic Features are Common in Both Sporadic and Inherited Medullary Thyroid Carcinoma?

Medullary thyroid carcinoma is a primary tumor of the thyroid gland which shows differentiation along the lines of thyroid parafollicular C cells.⁶⁻⁸ Medullary thyroid carcinoma typically secretes calcitonin, although nonsecretory tumors occur rarely. Serum calcitonin reflects quantity of tumor present, except in nonsecreting patients. Medullary thyroid carcinoma is almost always carcinoembryonic antigen (CEA) positive, and in noncalcitonin-secreting tumors, serum CEA levels can be followed, similar to calcitonin levels in secreting tumors to assess disease burden and therapeutic response. Even though elevated calcitonin levels are present, serum calcium is not typically decreased below normal levels. Medullary thyroid carcinoma tumors sometimes secrete other hormones, such as adrenal corticotrophic hormone, serotonin, and vasoactive intestinal peptide (VIP), which can result in a paraneoplastic presentation such as diarrhea if VIP secretion occurs. The VIP levels were not measured in this patient, and it is not clear whether his intermittent diarrhea was related to the MTC. Medullary thyroid carcinomas are relatively uncommon tumors accounting for less than 2% to 3% of thyroid neoplasia.

Medullary thyroid carcinoma can present as a sporadic tumor or as part of an inherited tumor syndrome. The histology of MTC is quite variable, but in general is not distinct for sporadic or inherited cases. A mixture of spindled and epithelioid cells is common, and plasmacytoid morphology is often seen. Neuroendocrine features include finely granular cytoplasm due to variable presence of neurosecretory granules. The chromatin is mixed fine and coarse and classically described as “salt and pepper” chromatin which is commonly seen in neuroendocrine tumors. Cells can be arranged in sheets, nested aggregates, trabeculae, or even follicles, and mitotic figures

tend to be sparse. These features of MTC contrast with the more common PTC (Figure 3). Nuclear features of PTC include pale nongranular nuclear chromatin, nuclear grooves, nuclear pseudoinclusions, and small peripheral nucleoli. Amyloid deposition is commonly present in up to 90% of cases, but was absent in this particular case, and is composed of calcitonin peptides. Immunohistochemistry shows positive granular cytoplasmic staining for calcitonin in the tumor cells and diffusely stains the amyloid deposits. Immunohistochemistry is also positive for other neuroendocrine markers, such as chromogranin and synaptophysin. Cytologic atypia ranges from minimal, to focal, to widespread.

Describe the Features Unique to Sporadic Medullary Thyroid Carcinoma

Medullary thyroid carcinoma occurs as sporadic disease in 70% of cases, and the sporadic cases present typically as a neck mass, as in this case, but clinical findings may also include dysphagia and/or hoarseness. When MTC presents as a neck mass, nodal involvement is relatively frequent ($\sim 70\%$) and non-nodal metastasis (10%) also occurs. Sporadic cases show a slight female predominance and are seen predominantly in the fifth and sixth decades. These are usually unilateral and unifocal tumors of the thyroid. Unlike PTC, ionizing radiation exposure does not seem to be etiologically involved in sporadic MTC.

Describe the Features Unique to Inherited Medullary Thyroid Carcinoma

Familial cases occur as part of inherited syndromes in 30% of cases (multiple endocrine neoplasia type 2A [MEN-2A] or MEN-2B or familial medullary thyroid carcinoma [FMTC]) and are often associated with other endocrine neoplasms. Medullary thyroid carcinoma in this setting may present either as a result of endocrine disease in other organs or with symptoms in the neck. Familial/inherited cases present at younger ages than do sporadic cases. Medullary thyroid carcinoma in the setting of MEN-2B more commonly metastasizes than what is seen in MEN-2A, FMTC, or sporadic disease. Bilateral thyroid involvement and multifocal disease are more common in inherited MTC than in sporadic disease. Penetrance of medullary thyroid cancer development is age and mutation dependent; however, MTC inevitably develops in MEN-2 with *RET* mutations, and early total thyroidectomy is preventative. Early onset is typical in MEN-2B with later onset in MEN-2A. Thyroid tissue outside the tumor in inherited cases typically shows background C cell hyperplasia.

Describe the Molecular Basis of Sporadic Medullary Thyroid Carcinoma

Activating somatic point mutations of the *RET* proto-oncogene are noted in sporadic medullary carcinoma in approximately 40% to 60% of cases. The most frequently seen mutation in

sporadic cases is the M918T mutation in exon 16. Interestingly, this is also the same mutation as the germline mutation in the vast majority of MEN-2B patients. *RAS* mutations are also seen in some sporadic cases, usually those that are *RET* mutation negative. Thus, in sporadic disease, *RAS* and *RET* mutations commonly show mutual exclusion.

Describe the Molecular Basis of Inherited Medullary Thyroid Carcinoma

Germline mutation of the *RET* proto-oncogene with gain of function is the underlying feature in inherited MTC, as seen in MEN-2A, MEN-2B, and FMTC (a variant of MEN-2A). The *RET* proto-oncogene codes for a receptor tyrosine kinase that binds glial-derived neurotrophic factor and similar ligands. Ligand binding to receptor leads to intracellular growth signals as well as signals for differentiation. Various specific *RET* mutations occur in MEN-2A, and coexisting parathyroid hyperplasia and pheochromocytoma are characteristic. The specific *RET* mutations in MEN-2B are associated with pheochromocytoma as well; however, the hyperparathyroidism is absent.

Teaching Points

- Major cytologic diagnostic categories (nondiagnostic, benign, suspicious, and malignant) each carry an associated risk of underlying malignancy and uncertainty, which have been published for various types of specimens.
- Cytologic diagnostic categories of benign and malignant have the least amount of associated diagnostic uncertainty and the atypical category the highest.
- Medullary thyroid carcinoma is a neuroendocrine tumor showing C-cell differentiation.
- Medullary thyroid carcinoma is immunochemically positive for calcitonin (which is elevated in serum, except in rare nonsecreting cases), chromogranin, synaptophysin, and CEA.
- Medullary thyroid carcinoma can be followed clinically with serum calcitonin or CEA, and CEA is helpful in calcitonin nonsecreting cases.
- Occasionally, MTCs secrete other hormones and may have paraneoplastic presentations, for example, VIP—diarrhea.
- Medullary thyroid carcinoma can be sporadic or inherited.
- Sporadic and inherited MTCs have the same histologic spectrum with amyloid deposition, sporadic disease typically being unilateral and unifocal and inherited disease more likely to be bilateral and multifocal.
- Inherited MTC shows C-cell hyperplasia in the non-neoplastic thyroid tissue.
- Specific genetic and molecular mechanisms underlie both sporadic and inherited medullary thyroid cancer, with the *RET* gene being most frequently involved.
- The inevitable development of medullary thyroid cancer associated with MEN-2 can be prevented by early prophylactic total thyroidectomy.

ORCID iD

Carl T. McGary, MD, PhD  <http://orcid.org/0000-0003-4625-3030>

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