Molecular Pathology of Hereditary and Sporadic Medullary Thyroid Carcinomas

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Key Words: Medullary thyroid carcinoma; RET; RAS; Tyrosine kinase; Multiple endocrine neoplasia; Familial medullary thyroid carcinoma

ABSTRACT

Objectives: Medullary thyroid carcinoma (MTC) is a relatively uncommon type of thyroid malignancy, with unique histologic features and molecular pathology. It is important to recognize, because its management, which is in part driven by the genetic basis of this disease, is different from follicular-derived thyroid tumors. The aim of this article is to briefly review the histopathologic features of MTC and then explore its molecular pathology, including the role of molecular diagnostic testing and the use of targeted therapy for advanced disease.

Methods: A review of published literature was performed.

Results: A subset of MTC cases is hereditary and due to germline mutations in the RET tyrosine kinase receptor gene. Somatic mutations in either RET or RAS are also present in most sporadic tumors.

Conclusions: Molecular genetic testing is routinely performed to identify hereditary cases. In addition, understanding the molecular basis of both hereditary and sporadic MTC has led to the development of targeted therapy with tyrosine kinase inhibitors. Although additional data are needed, tumor mutation status may affect response to targeted therapy. Therefore, it is possible that genetic testing of tumor tissue to predict treatment response, as is currently done for other cancer types, may come into practice in the future.

Upon completion of this activity you will be able to:

- recognize the histologic features of medullary thyroid carcinoma (MTC), including its variants that may mimic other thyroid lesions.
- describe the genetic basis of the multiple endocrine neoplasia types 2A and type 2B and familial MTC syndromes and the correlation between genotype and phenotype.
- list the indications and rationale for RET mutation analysis to detect patients with a hereditary syndrome.
- discuss the major genetic changes in sporadic MTC and their potential impact on tyrosine kinase inhibitor therapy.

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Questions appear on p 905. Exam is located at www.ascp.org/ajcpcme.

Medullary thyroid carcinoma (MTC) is a relatively uncommon tumor type, accounting for 5% or less of thyroid malignancies.1 However, it warrants attention because it causes a disproportionate number of thyroid cancer deaths due to its more aggressive clinical behavior compared with well-differentiated papillary and follicular thyroid carcinomas.2 Furthermore, the clinical management of MTC differs from nonmedullary thyroid carcinoma. Thus, accurate diagnosis is important so that patients can be appropriately treated.

Treatment is, in part, dictated by the unique molecular pathology of these tumors. A significant subset is hereditary, due to germline mutations in the RET proto-oncogene, and patients with MTC are routinely referred for genetic testing.3-6 Patients who are found to have hereditary disease can then be monitored for other associated endocrine
abnormalities, and at-risk family members can be screened and treated prior to the development of MTC (with prophylactic thyroidectomy). Somatic (non-germline) RET mutations also occur in a significant proportion of sporadic MTCs. More recently, RAS mutations have been identified in RET wild-type sporadic tumors. Genetic testing of tumor tissue for somatic mutations is not routinely performed since none of these alterations currently affects patient management. However, RET activation in these tumors has made it possible to use targeted therapy to treat advanced and metastatic MTC. It is possible that genetic testing of tumor tissue to predict response to a particular targeted agent, as is currently done for other cancer types such as colon and lung, may come into practice in the future.

Our aim is to briefly review the pathologic features of MTC and then explore the molecular basis of both hereditary and sporadic disease. In addition, we address the role of diagnostic molecular testing to identify and manage hereditary cases, as well as the development of targeted therapies for treatment of both hereditary and sporadic tumors. Finally, the prospect of molecular testing of tumor tissue to predict response to therapy is explored.

**Pathologic Features of MTC**

**Histopathology and Cytopathology**

MTC is a neuroendocrine carcinoma that arises from the neural crest–derived parafollicular C cells. C cells are located in the upper one-third of the thyroid lobes bilaterally but cannot normally be seen on routine H&E sections because they are so infrequent and morphologically similar to the much more numerous follicular cells. Their function is to produce calcitonin, which has a poorly defined physiologic role. Calcitonin is, however, an important serum tumor marker for patients with MTC because it is also secreted by these tumors.

The typical MTC is solid with sheets or nests of cells that are plasmacytoid and have abundant pale pink cytoplasm and round to oval nuclei with granular chromatin. Amyloid is present in approximately 80% of the tumors and is composed of calcitonin secreted by the tumor cells. On fine-needle aspiration biopsy, the cells are usually singly dispersed or loosely cohesive, and red cytoplasmic granules may be present (Diff-Quik stain). The amyloid may resemble the dense colloid that is often seen in cytologic preparations of papillary thyroid carcinomas. However, amyloid, unlike colloid, may be metachromatic on Diff-Quik–stained slides. Hereditary tumors are more often multifocal than sporadic tumors but otherwise do not have distinctive histologic or cytologic features.

MTCs can have a wide variety of divergent histologic patterns. Described histologic variants include spindle cell, papillary or pseudopapillary, follicular or glandular, clear cell, oncocytic, mucin producing, melanin producing, paraganglioma-like, and small cell, among others. In some cases, these variants may mimic other types of thyroid carcinomas or lesions. For example, the follicular variant can resemble follicular carcinoma or adenoma when it has a capsule or even nodular hyperplasia when it lacks a capsule.

**Image 1** Histologic features of typical medullary thyroid carcinoma. **A**, The tumor cells form nests and are plasmacytoid with abundant pale pink cytoplasm, round to oval nuclei, and granular chromatin (H&E, ×40). **B**, Pale pink, amorphous amyloid deposits are frequently seen (H&E, ×40).
Benign entrapped thyroid follicles may also be present within the tumor, and this should not be mistaken as evidence of follicular differentiation. Similarly, the papillary or pseudopapillary variant may raise the possibility of papillary thyroid carcinoma. Although intranuclear cytoplasmic pseudoinclusions and nuclear contour irregularity may be seen in MTC, other cytologic features are usually present that are not typical of papillary thyroid carcinoma (plasmacytoid cells with pale pink cytoplasm and granular chromatin). Other entities in the differential diagnosis include metastatic renal cell carcinoma for the clear cell variant, metastatic melanoma for the melanin-producing variant, and paraganglioma for the paraganglioma-like variant. Metastasis to the thyroid gland should also be considered when the small cell variant is encountered.

Because of the wide variety of histologic patterns that have been reported, it is important to have a low threshold for performing immunohistochemistry in any thyroid tumor that lacks definite colloid or is simply not typical of another type of thyroid carcinoma. Useful positive immunostains include calcitonin and monoclonal carcinoembryonic antigen, which are negative in other thyroid tumors. Calcitonin,
however, is not specific to MTC and can be positive in neuroendocrine carcinomas from other organ systems. If material for immunohistochemistry is not available on fine-needle aspiration biopsy but is felt to be needed, one can request that the clinician check a serum calcitonin level, since it is almost always elevated in patients with MTC.

**C-Cell Hyperplasia**

Histologically recognizable C-cell hyperplasia is generally considered a neoplastic process and a precursor lesion to MTC (neoplastic C-cell hyperplasia). It is characterized by nodular aggregates of C cells that are enlarged and have more abundant pale pink cytoplasm than the adjacent follicular cells and often granular chromatin (H&E, ×40). Stromal fibrosis is absent and, if present, suggests an invasive microcarcinoma.

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Hereditary vs Sporadic Disease

Approximately 25% of MTCs are hereditary. The hereditary cases occur in the setting of three syndromes: multiple endocrine neoplasia syndrome (MEN) type 2A (MEN2A), MEN type 2B (MEN2B), and familial medullary thyroid carcinoma syndrome (FMTC). These syndromes are autosomal dominant and highly penetrant; virtually all patients will develop MTCs if their thyroid glands are not removed. MEN2B is the least common (~5% of hereditary MTC), and patients develop carcinomas at the youngest age, often before 10 years. Both MEN2A and MEN2B syndromes are associated with other endocrine abnormalities and clinical features (these are summarized in Table 1).

Pheochromocytoma is seen in about half of patients with MEN2A and MEN2B. A subset of patients with MEN2A develop parathyroid hyperplasia, which is not seen in MEN2B. Patients with MEN2B have a marfanoid habitus, ocular abnormalities, mucosal neuromas, and gastrointestinal ganglioneuromatosis. Patients with FMTC do not have other associated features. However, it is thought that FMTC represents a mild variant of MEN2A with low penetrance of pheochromocytoma and hyperparathyroidism. If pheochromocytoma or hyperparathyroidism is seen in a family with FMTC, reclassification as MEN2A is warranted.

Sporadic tumors usually occur in the fifth to sixth decades of life and lack other associated MEN features or family history of MTC. There is overlap between the age of presentation of MTCs in sporadic and hereditary cases. In fact, approximately 5% to 10% of patients with apparently sporadic tumors (no family history or stigmata of an MEN syndrome) have hereditary disease (FMTC or MEN2A) upon genetic testing.

The initial clinical management of both hereditary and sporadic MTC is the same but is different from that of follicular-derived thyroid tumors. All patients with a fine-needle aspiration biopsy or serum calcitonin level diagnostic of suspicious for MTC will be screened for MEN-associated diseases (pheochromocytoma and hyperparathyroidism) prior to thyroid surgery unless the patient has already undergone
genetic testing and has a negative family history. If a pheochromocytoma is identified, it should be treated first to avoid a hypertensive crisis. If preoperative serum calcitonin is high (>400 pg/mL) or there is nodal disease on imaging, the patient will be evaluated for distant metastases. Surgery typically consists of total thyroidectomy and prophylactic central (level VI) lymph node dissection for clinically detected organ-confined disease.

**Molecular Basis of Hereditary Disease and Genotype-Phenotype Correlation**

In the early 1990s, activating mutations in the *Rearranged during Transfection*, or *RET*, proto-oncogene were identified as the genetic basis for MEN2A, MEN2B, and FMTC syndromes. Since then, germline *RET* mutations have been identified in 98% of patients with MEN2A, 95% of patients with MEN2B, and 88% of patients with FMTC. *RET* is located on chromosomal band 10q11.2 and encodes a single-pass transmembrane receptor tyrosine kinase that plays an important role in the development of the parathyroids, urogenital system, and neural crest—including brain, para- and sympathetic ganglia, adrenal medulla, enteric ganglia, and thyroid C cells. Not surprisingly, many of these organ systems are affected in the MEN syndromes with the notable exceptions of the brain and urogenital system.

More than 80 different *RET* mutations in exons 5, 8, 10, 11, 12 to 16, and 19 have been associated with hereditary MTC. Most are single-nucleotide missense mutations, and all lead to constitutive activation of the *RET* tyrosine kinase and downstream signaling pathways. A database of *RET* mutations, including variants of unknown significance, is maintained at the University of Utah/ARUP Laboratories (http://www.arup.utah.edu/database/MEN2/MEN2_welcome.php).

The *RET* gene also harbors several common polymorphisms, benign genetic variants that should not be over-interpreted as causes of familial cancer (e.g., G691S, which is present in as many as one in five healthy individuals). In general, if a *RET* variant is detected by sequencing, particularly at a noncanonical position, it is important to consult a database of common polymorphisms, such as the Single Nucleotide Polymorphism Database (http://www.ncbi.nlm.nih.gov/SNP/) or the Exome Variant Server from the National Institutes of Health’s National Heart, Lung, and Blood Institute (http://evs.gs.washington.edu/EVS/), to search for evidence that the variant may be a polymorphism without significance.

The specific location of the mutations within the *RET* gene is likely responsible for the different constellation of phenotypes in each hereditary syndrome. The *RET* protein has an extracellular domain composed of a cadherin-like region that is important for ligand binding and a highly conserved cysteine-rich domain. The intracellular region contains two tyrosine kinase domains (TK1 and TK2). Upon ligand binding, the extracellular cysteine-rich domain facilitates receptor dimerization, which leads to autophosphorylation and activation of the intracellular TK1 and TK2. This activates multiple signaling pathways, including RAS/RAF/MAP kinase, PI3K/AKT, and STAT3, that lead to cell survival, proliferation, migration, and differentiation.
Several RET mutations give rise to MEN2A syndrome, the majority of which are located in cysteines within the extracellular cysteine-rich domain (corresponding to exons 10 and 11). These mutations abolish intramolecular disulfide bridge formation and allow for constitutive dimerization of two RET proteins in the absence of ligand. Other mutations in exons 13, 14, and, rarely, 5, 8, 12, 15, and 19 have also been reported in MEN2A. Thirty-nine different mutations have been associated with MTC in exons 5, 8, 10, 11, and 13 to 16, with most being located in the cysteine-rich domain or TK1 domain. There is overlap between the mutations that are associated with MEN2A and FMTC. Some mutations can be associated with either MEN2A or FMTC in different families, which is why FMTC is considered a variant of MEN2A. The mutations that can give rise to either syndrome are associated with low penetrance of pheochromocytoma and hyperparathyroidism.

In contrast to the diversity of mutations seen in MEN2A/FMTC, 95% of patients with MEN2B have a single mutation in exon 16 (M918T) that causes a conformational change in the intracellular TK2 binding pocket and allows for constitutive kinase activation in the absence of dimerization, as well as altered substrate binding. Much less commonly (2%-3% of cases), MEN2B is caused by a dinucleotide substitution in codon 883 (exon 15) in the TK1 domain. Very rarely, simultaneous mutations in two different codons (eg, V804M/E805K mutated in cis) can cause an MEN2B-like phenotype ("atypical" MEN2B).

It is thought that the different mechanisms of RET activation induced by these mutations trigger different patterns of phosphorylation and cell signaling. For example, the M918T codon mutation that accounts for the vast majority of MEN2B is associated with increased PI3K/AKT pathway activation compared with MEN2A-associated mutations. This may explain differences in disease phenotype among the syndromes. Since some mutations are associated with either MEN2A or FMTC in a given family, there are likely additional modifying factors that affect phenotype as well.

Furthermore, within each of the hereditary syndromes, the specific RET mutation is associated with variation in disease phenotype. In MEN2A, the specific codon mutated roughly correlates with the age of presentation with MTC and the probability of developing pheochromocytoma or hyperparathyroidism. Codon 634 in exon 11, corresponding to a cysteine in the extracellular cysteine-rich domain, is the most commonly altered codon in MEN2A. Mutations at codon 634 are associated with the earliest onset of MTC, often before age 20 years, and the highest risk of pheochromocytoma and hyperparathyroidism in this syndrome. In addition, cutaneous lichen amyloidosis is almost exclusively seen in patients with codon 634 mutations. Hirschsprung disease, a genetically heterogeneous disease, can co-occur with MTC in patients with mutations in exon 10.

The M918T mutation that accounts for 95% of MEN2B cases is associated with the earliest onset of MTC of any RET mutation, in some cases within the first year of life. In addition, the tumors are more aggressive and typically present at a more advanced stage. MEN2B patients with the less common A883F mutations appear to develop MTCs at an older age and have less aggressive tumors compared with those with M918T. The rare “atypical” MEN2B syndrome caused by simultaneous mutations in two different codons has also been associated with a more mild phenotype.

In FMTC, those mutations not involving the cysteine-rich domain (usually in exon 13, 14, or 15) are associated with the latest onset of MTC. This group of mutations shows significant clinical overlap with the age of onset of sporadic MTC. Therefore, routine genetic screening of patients with apparently sporadic disease may reveal unexpected germline mutations in a subset of cases, usually in patients with de novo and/or noncysteine mutations.

Diagnostic Molecular Testing for Hereditary Disease

The American Thyroid Association (ATA) recommends that all patients with a personal history of MTC, primary C-cell hyperplasia, or clinical features of MEN2 or FMTC should be offered genetic testing for germline RET mutations. Furthermore, anyone with a family history of MEN2 or FMTC in a first-degree relative should also undergo genetic testing. The rationale for screening all patients with MTC or C-cell hyperplasia is based on the evidence that approximately 5% to 10% of patients with MTC who lack clinical features to suggest hereditary disease will harbor a germline RET mutation, often de novo and/or noncysteine mutations (as described above). Screening of at-risk family members should also be emphasized since those family members found to harbor a RET mutation can be treated with prophylactic thyroidectomy before carcinoma develops and be monitored for pheochromocytoma or hyperparathyroidism, if indicated for the specific mutation identified. Although de novo mutations are common in MEN2B, only 5% to 10% of MEN2A/FMTC cases represent new mutations. Therefore, siblings and even parents may be at risk in addition to children of the index case. The ATA has guidelines for the age of recommended prophylactic thyroidectomy in mutation carriers based on the specific RET mutation. Approximately 60 laboratories in the United States perform constitutional genetic testing for RET mutations on peripheral blood (www.ncbi.nlm.nih.gov/gtr). However, the
Table 2

<table>
<thead>
<tr>
<th>ATA Risk Level (MTC Aggressiveness)</th>
<th>Codon Mutation</th>
<th>Syndrome</th>
<th>MTC Age of Onset</th>
<th>Age of Prophylactic Thyroidectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (least high)</td>
<td>768, 790, 791, 804, 649, 891</td>
<td>MEN2A/FMTC</td>
<td>Adults</td>
<td>When calcitonin rises/&gt;5 y</td>
</tr>
<tr>
<td>B (higher)</td>
<td>609, 611, 618, 620, 630, 631</td>
<td>MEN2A/FMTC</td>
<td>5 y</td>
<td>5 y</td>
</tr>
<tr>
<td>C (high)</td>
<td>634</td>
<td>MEN2A/FMTC</td>
<td>&lt;5 y</td>
<td>&lt;5 y</td>
</tr>
<tr>
<td>D (highest)</td>
<td>918, 883</td>
<td>MEN2B</td>
<td>&lt;1 y</td>
<td>As soon as possible (&lt;1 y)</td>
</tr>
</tbody>
</table>

ATA, American Thyroid Association; FMTC, familial medullary thyroid carcinoma; MEN2A, multiple endocrine neoplasia type 2A; MEN2B, multiple endocrine neoplasia type 2B; MTC, medullary thyroid carcinoma.

Molecular Basis of Sporadic Disease

While patients with sporadic MTC do not harbor germ-line RET mutations, up to half have somatic RET mutations in their tumors. The M918T mutation (seen in most patients with MEN2B) is also the most common mutation in sporadic tumors, accounting for 75% to 95% of RET mutations. Many other RET mutations have been reported in sporadic tumors, including in exons 10, 11, 15, and 16. As in MEN2B, M918T mutations are associated with more aggressive/advanced stage disease in sporadic tumors. Somewhat surprisingly, RET mutations in sporadic tumors may not necessarily drive tumorigenesis but rather appear important for progression of disease. This is supported by the fact that RET mutations are present in a lower proportion of sporadic microcarcinomas than of larger tumors and, when present, often show mutational heterogeneity, even in advanced disease. This means that RET mutations may be found in subpopulations of tumor cells rather than the entire tumor, indicating that the mutation arose later in the course of disease. Indeed, in half of patients with RET mutations and multiple metastases, the mutation was found in some but not all metastatic deposits.

Figure 2

RET mutational heterogeneity has been reported in sporadic tumors harboring somatic mutations. This means that a subset of tumor cells may harbor a RET mutation that is not present throughout the entire tumor and may be present in some but not all metastases. Much more recently, activating RAS mutations have also been identified in a subset of sporadic MTCs. These mutations may be associated with clinically less aggressive tumors. Mutations occur within known hotspots in exons 2, 3, and 4 and predominantly involve HRAS and KRAS. NRAS mutations...
Molecular Targeted Therapy

Molecular targeted therapy for MTC has been long sought due to significant shortcomings of traditional treatment strategies with a lack of effective systemic therapy. Conventional chemotherapy is of limited benefit and associated with significant toxicity. Radioactive iodine is not useful because MTC is not derived from thyroid follicular cells and therefore does not take up iodine. Currently, complete surgical resection (thyroidectomy and lymph node dissection) is the only chance for cure. However, about half of patients have lymph node metastases, and only 10% of these cases are cured by surgery. A subset of patients have an indolent clinical course despite incurable disease. Long-term, 10-year survival is more than 90% for those with localized disease, decreasing to 78% and 40% in patients with regional and distant metastases, respectively. Nevertheless, there is a need for additional treatment modalities in patients who have residual or recurrent disease after surgery.

In the past several years, two targeted tyrosine kinase inhibitors (TKIs), vandetanib and cabozantinib, have been approved by the US Food and Drug Administration for the treatment of symptomatic, advanced, or progressive MTC. This approval was based on the results of two large phase III clinical trials that showed increased progression-free survival of each drug compared with placebo. Both of these TKIs are nonselective and target multiple kinases in addition to RET. Vandetanib also targets VEGFR2, VEGFR3, and EGFR, while cabozantinib additionally targets c-MET and VEGFR2. It is thought that the efficacy of these drugs results in part from their ability to target multiple kinases. Unfortunately, both TKIs induce partial responses with resistance eventually developing, and an increase in overall survival has not yet been shown. Furthermore, since the design of the two phase III clinical trials was not identical and the two drugs were not compared head to head, it is difficult to determine which drug is more effective. However, the side effect profile for each is different and may be considered when selecting a treatment option. The most significant side effect associated with vandetanib is QT interval prolongation with rare torsades de pointes and sudden death; with cabozantinib, the side effects are rare fistula formation, gastrointestinal perforation, and hemorrhage. Nevertheless, these TKIs represent a significant advance in the treatment of MTC, and it seems likely that in the future, they will be a part of multidrug therapy.

One question that has been raised by the advent of TKIs for the treatment of MTC is whether RET and RAS mutation status affects tumor response to the drug. As of yet, this question has not been fully answered, but there is some evidence that mutation status may affect treatment response. In the phase III clinical trial of vandetanib, RET mutation status was unavailable or incomplete in nearly half (45.3%) of patients with sporadic tumors, so much is unknown about drug response by mutation status. Nevertheless, M918T-mutated tumors (seen in MEN2B and the majority of RET mutation-positive sporadic tumors) appeared to have increased sensitivity to the drug (overall response rate of 54.5% vs 30.9%). In vitro studies have also shown that V804M and V804L RET mutations conferred resistance to vandetinib. All RET mutation subgroups, including RET mutation-negative tumors, showed benefit in the cabozantinib clinical trial, although the benefit was marginal in the RET-negative group and best in the M918T codon mutation group. Clearly, further data are needed to address response by particular RET mutation.

TKI response by RAS mutation status was not assessed initially in either clinical trial, likely because the discovery of RAS mutations in MTC was relatively recent. Subsequent analysis of a subgroup of RAS-mutated tumors showed comparable, although slightly shorter, progression-free survival with cabozantinib treatment than for RET-mutated tumors. However, because RAS mutations have been associated with resistance to TKI therapy in other types of tumors, such as colon and lung cancer, a more thorough investigation in MTC is warranted.

Although there is some evidence to suggest that TKI response varies by mutation status, additional information is needed. With more data, it is possible that RET and/or RAS mutation analysis of tumor tissue from formalin-fixed, paraffin-embedded blocks or fine-needle aspiration biopsy specimens for somatic mutations may become part of clinical practice in the future. If this is the case, several issues should be considered. One is the reported mutational heterogeneity that can be seen with RET mutations in sporadic tumors. Caution should be exercised when RET mutation analysis is performed on a primary tumor in a patient being treated for metastatic disease, since the mutation status may be different in the metastasis. Another consideration is the method of testing, since next-generation sequencing may have higher sensitivity than Sanger sequencing and allows several genes to be assayed on the same platform. The relative cost and effectiveness of these two methods should be considered before testing guidelines are established.
Conclusion

In summary, molecular diagnostic testing has been a mainstay of the clinical management of MTC for many years. Patients are routinely referred for RET mutation analysis of constitutional DNA to identify hereditary cases so that they can be monitored for other associated endocrine abnormalities, and at-risk family members can be screened and treated prior to the development of MTC (with prophylactic thyroidectomy). Somatic (nongermline) mutations in either RET or RAS also occur in most sporadic MTCs. However, genetic testing of tumor tissue for somatic mutations is not routinely performed. It is possible that, with the advent of TKIs now in use to treat advanced and metastatic MTC, genetic testing of tumor tissue to predict response to a particular drug may come into practice in the future. However, further information about the impact of RET and RAS mutations on TKI treatment response is needed.

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References