An Update on Medullary Carcinoma Thyroid

Mithun Raam, Anish Jacob Cherian, Mazhuvanchary Jacob Paul, Deepak Thomas Abraham

Departments of General Surgery and Endocrine Surgery, Christian Medical College, Vellore, Tamil Nadu, India

Address for correspondence: Dr. Deepak Thomas Abraham, Department of Endocrine Surgery, Christian Medical College, Vellore - 632 004, Tamil Nadu, India. E-mail: deepakabraham@cmcvellore.ac.in

ABSTRACT

Medullary thyroid carcinoma is a rare neuroendocrine tumor arising from parafollicular cells of the thyroid gland. It occurs in both hereditary and sporadic forms which are associated with the gain of function mutations in rearranged during transfection proto-oncogene on chromosome 10q11.2. There are various syndromic and sporadic clinical presentations, and the understanding of the molecular pathophysiology and its genotype-phenotype correlation has led to mutation-based risk stratification and guidelines for evaluation and management. The authors present a current review of the literature with regard to pathophysiology, molecular basis, clinical presentation along with genotype-phenotype correlation and guidelines for evaluation and management.

Key words: Medullary carcinoma thyroid, multiple endocrine neoplasia, rearranged during transfection

INTRODUCTION

Thyroid malignancy has a 5-year prevalence of 50,939 cases with an overall rising trend. The first description of a thyroid tumor with amyloid was given by Jacquet in 1906. However, subsequently, in 1959, Hazard et al. described the detailed histopathology and labeled this clinical entity as medullary (solid) carcinoma. Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor arising from parafollicular cells of the thyroid gland (2% of thyroid malignancies). It presents predominantly in the fourth and fifth decades of life with no gender predilection. It occurs as hereditary MTC (HMTC) in 25% of patients and sporadic MTC (SMTC) in 75% and is associated with gain of function mutations in the rearranged during transfection (RET) gene on chromosome 10q11.2.

THE C-CELL – ORIGIN OF THE PROBLEM

The C-cell accounts for 0.01%–0.1% of cells located centrally in the thyroid gland. They are derived from the primordial cells of the neural crest which migrate to the ultimobranchial body. They are round, polygonal, or spindle-shaped cells occurring singly or in groups. Although they were called parafollicular cells, a majority of C-cells have been found to be intrafollicular. C-cells secrete calcitonin, which is a 32-amino acid linear polypeptide hormone and calcitonin gene-related peptide (CGRP). Its role in calcium homeostasis, however, is insignificant as compared to calcitriol and parathyroid hormone. An increase in size and number of C-cells is associated with RET germline mutations in HMTC known as C-cell hyperplasia which precedes MTC as a precursor lesion.

CLINICAL SPECTRUM OF MEDULLARY THYROID CARCINOMA

SMTC presents in the fourth to fifth decades, whereas HMTC presents at a much younger age, depending on the mutational genotype. It may present most commonly as a solitary nodule, multinodular goiter, or incidental finding on imaging. Lymph nodal metastases occur in 50%–70% of patients and metastatic disease in 10%–15%. In some patients, there may be secretion of several other chemicals such as carcinoembryonic antigen (CEA), serotonin, substance P, vasoactive intestinal substance, adrenocorticotropic hormone, corticotrophin-releasing hormone, catecholamine metabolites, and CGRP. This may manifest as a paraneoplastic syndrome with symptoms such as flushing, diarrhea, ectopic Cushing’s syndrome, hypercoagulability, and cholestasis.

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HMTC is inherited in an autosomal dominant pattern and comprises subtypes known as multiple endocrine neoplasia (MEN) 2A and 2B. These are detailed below:

**Multiple endocrine neoplasm Type 2**

MEN 2 syndrome was described first by Sipple as an association of pheochromocytoma with carcinoma of the thyroid gland.\(^{[16]}\) It encompasses two distinct syndromes known as MEN 2A (currently classified as MEN2) and MEN 2B (currently classified as MEN 3).\(^{[17]}\)

MEN 2A comprises four clinical variants – classical MEN 2A, MEN 2A with cutaneous lichenoid amyloidosis, MEN 2A with Hirschsprung’s disease, and familial MTC.

- Classic MEN 2A syndrome presents with 95% of patients with MTC, about 50% of patients with pheochromocytoma, and about 20-30% of patients with primary hyperparathyroidism (PHPT)\(^{[18]}\)

- Cutaneous lichenoid amyloidosis occurs in 10% of MEN 2A patients and presents with a pigmented pruritic papular lesion in the scapular region corresponding to T2 to T6 dermatomes with sensory neuropathy and secondary amyloid deposition [Figure 2]\(^{[19,20]}\)

- Hirschsprung’s disease occurs in 7% of patients with MEN 2A and is associated with the failure of neural crest cells to migrate, proliferate, and differentiate into the intestinal autonomic plexuses\(^{[21]}\)

- Familial MTC is a variant of MEN 2A where MTC occurs in isolation due to reduced penetrance for pheochromocytoma and PHPT.\(^{[22]}\)

MEN 2B syndrome has an earlier onset of more aggressive disease. All patients develop MTC and 40%–50% develop pheochromocytomas. These patients also have peculiar phenotypic features such as skeletal abnormalities (Marfanoid habitus, high-arched palate, pectus excavatum, and pes cavus) and mucosal ganglioneuromas in the lips, tongue, gingiva, buccal and nasal mucosa, vocal

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**Figure 1:** Normal C-cell

**Figure 2:** Cutaneous lichenoid amyloidosis

**Figure 3:** Patient with multiple endocrine neoplasm 2B with oral mucosal ganglioneuromas

**Figure 4:** Patient with multiple endocrine neoplasm 2B with Marfanoid features (high-arched palate, Marfanoid habitus)
REARRANGED DURING TRANSFECTION PROTO-ONCOGENE AND MOLECULAR GENETICS IN MEDULLARY THYROID CARCINOMA

RET proto-oncogene was first described by Takahashi in 1985, in human lymphoma cell DNA with transforming activity in the transfected cell line. This has been identified as a central piece in our understanding of the puzzle of MTC. RET germ line mutations are associated with HMTC, whereas the presence of somatic mutations is associated with SMTC in about 50%. In SMTC lacking RET mutation, 18%–80% of patients were found to harbor mutations in HRAS, KRAS, or NRAS gene.

RET gene comprises 21 exons and is 60 kb long, encoding for a transmembrane receptor tyrosine kinase. This RET protein has an extracellular domain (four cadherin-like domains and a cysteine-rich domain), a transmembrane domain, an intracellular juxtamembrane domain, and an intracellular tyrosine kinase domain.

RET protein activation requires binding to glial cell-derived neurotrophic factor family ligands such as GDNF, persephin, and neurturin mediated by ligand-specific cofactors of GDNF family receptor α (GFRα). This results in the formation of a dimeric complex including two RET proteins, two ligand molecules, and two GFRα co-receptors. This causes autophosphorylation of the intracellular tyrosine kinase domain that activates several molecular signaling pathways such as Ras/ERK and P13K/Akt pathways which play a role in cell proliferation, differentiation, and survival. Alternate pathways such as p38 MAPK, phospholipase C-γ, JNK, and ERK5 are also activated, hence modifying cell differentiation, migration, and cytokine production.

The gain of function germ line mutations results in MEN syndrome and has a strong genotype–phenotype correlation which is demonstrable in their clinical aggressiveness. MEN 2A syndrome exhibits mutation in exons 10 and 11 within the extracellular cysteine-rich domain of RET (codons 609, 611, 618, 620, 630, and 634). The cysteine-rich domain which stabilizes the tertiary structure of RET protein when substituted with another amino acid results in an unpaired cysteine which may form aberrant bonds with other cysteine residues or other abnormal RET molecule causing dimerization-independent persistent activation.

MEN 2B syndrome results from mutations in the intracellular tyrosine kinase domain of the protein. About 95% of these mutations are due to the substitution of methionine with threonine at codon 918 (M918T) causing a conformational change in a region of the intracellular tyrosine kinase domain important for ATP binding causing increased affinity for ATP. The remainder is due to A883F. Thus, these mutated proteins are highly active in both monomeric and dimeric forms.

The understanding of the molecular genetic mechanisms behind MTC has created a paradigm shift in its screening and management. This helps in predicting the occurrence...
of the disease in the future kindred and determining aggressiveness due to a strong genotype–phenotype correlation and proves to be a potential therapeutic target.

**EVALUATION AND DIAGNOSIS**

Evaluation is by triple assessment with clinical examination, radiological assessment, and cytopathological assessment.

Fine-needle aspiration cytology (FNAC) shows a moderate-to-marked cellularity with spindle-shaped, epithelioid, or plasmacytoid cells with eccentrically placed round nuclei with fine or coarse granular chromatin typical of neuroendocrine tumors. There may also be present bizarre giant cells, clear cells, oncocytic cells, or small cells. Amyloid is present in 50%–80% which is composed of extracellular deposits of calcitonin. FNAC, however, has a low sensitivity in the diagnosis of MTC. In the setting, if an indeterminate nodule measuring more than 1 cm in size, positive staining for calcitonin, CEA, and chromogranin and negative staining for thyroglobulin on immunohistochemistry increase the diagnostic accuracy of FNAC.

**BIOMARKERS IN MEDULLARY THYROID CARCINOMA**

Calcitonin and CEA are useful in aiding diagnosis and facilitating follow-up. Calcitonin has a high sensitivity to diagnose MTC (98%). Calcitonin is elevated in MTC and correlates with disease aggressiveness. CEA, on the other hand, is not a specific biomarker for MTC and may not prove useful in the early diagnosis of MTC. However, it helps in determining disease progression and has been found to be a probable marker of dedifferentiation and hence predicts poorer outcomes.

**PREOPERATIVE IMAGING**

Ultrasonography (USG) of the neck is the primary imaging modality for the local disease. In patients with advanced locoregional disease in the neck or symptoms/signs of metastatic disease, cross-sectional imaging with contrast-enhanced computed tomography of the thorax, abdomen, and pelvis (for mediastinal disease, lung or liver metastases) or magnetic resonance imaging (MRI) of the abdomen (for liver metastases) may be done. MRI spine and bone scintigraphy may be done in suspected osseous metastases. Calcitonin levels more than 500 pg/ml warrants such imaging irrespective of evidence of advanced disease.

**REARRANGED DURING TRANSFECTION MUTATION ANALYSIS**

All patients with MTC should undergo genetic counseling and RET mutation analysis and if positive must be extended to all first-degree relatives, as in 1.5%–7.3% of apparent SMTCs, germ line RET mutations have been identified. Patients suspected to have MEN 2A syndrome must undergo RET mutation analysis in exon 10 (codons 609, 611, 618, and 620), exon 11 (codon 630 and 634), and exons 8, 13, 14, 15, and 16. MEN 2B phenotype should be tested for exon 16 (M918T) and exon 15 (A883F). If no mutations are discernible, then the entire RET sequence is analyzed.

**RISK STRATIFICATION BY ATA MEDULLARY THYROID CARCINOMA GUIDELINES**

ATA 2015 guidelines suggest stratification of MTC into three groups based on age at onset and aggressiveness. These are moderate risk (HMT with codon mutations other than M918T and 634), high risk (MEN 2A and codon 634 and 883 mutations), and highest risk (MEN 2B and M918T mutation) [Table 1].

Patients with the highest risk mutations are recommended prophylactic thyroidectomy within the 1st year or months of life. Patients with high-risk mutations are recommended prophylactic thyroidectomy within 5 years of age or when the calcitonin level rises (whichever is earlier) with prophylactic neck dissection with calcitonin level >40 pg/ml or clinically/radiologically detected nodal disease. Patients with moderate risk for MTC should undergo a clinical examination, USG of the neck, and calcitonin level measurement every 6 months to 1 year or lifelong, and thyroidectomy may be considered when the calcitonin rises at 5 years of age.
SCREENING FOR PHEOCHROMOCYTOMA AND PRIMARY HYPERPARATHYROIDISM IN MEDULLARY THYROID CARCINOMA

Screening for pheochromocytoma and PHPT must be done in all patients with MTC with 24-h urinary metanephrines and normetanephrines and corrected serum calcium. In HMTC, screening must be done at 11 years for known highest or high-risk mutations and at 16 years for moderate-risk mutations. Surgical management of pheochromocytoma gains precedence over MTC or PHPT and may be done by open, laparoscopic, or retroperitoneoscopic adrenalectomy.

PHPT may be managed by subtotal parathyroidectomy with preservation of the smallest gland, total parathyroidectomy with heterotopic implantation of a part of the smallest gland in the nondominant brachioradialis muscle, or resection of enlarged glands with intraoperative PTH monitoring.

SURGICAL MANAGEMENT OF MEDULLARY THYROID CARCINOMA

Surgical management of MTC is the most effective therapy available for MTC. As these tumors are of neuroendocrine origin, they do not take up radioactive iodine and are hence not amenable to radiodine therapy. In patients with no clinical/radiological lymphadenopathy, total thyroidectomy with central compartment lymphadenectomy (Level VI) may be done. Some authors recommend total thyroidectomy and ipsilateral central and lateral compartment lymphadenectomy (Level II–V) if calcitonin levels >20 pg/ml.[36] In patients with clinical/radiologically positive lymphadenopathy, total thyroidectomy and central compartment and ipsilateral lateral compartment lymphadenectomy may be recommended. In patients with calcitonin levels >200 pg/ml, bilateral lateral compartment lymphadenectomy may be done in addition to total thyroidectomy and central compartment dissection.[36] An involvement of mediastinal nodal disease may require sternotomy.

In patients who have undergone hemithyroidectomy with a histological surprise of MTC, completion thyroidectomy is not mandatory provided that there is no evidence of germ line RET mutation, elevated calcitonin levels, or radiological evidence of residual disease [Figure 8].

POSTOPERATIVE FOLLOW-UP

Patients are started on replacement doses of levothyroxine (1.6 mcg/kg/day ideal body weight). Clinical examination and measurement of calcitonin and CEA levels must be done after 3 months and if normal must be followed up every 6–12 months. If calcitonin levels are <150 pg/ml, they may be evaluated with USG of the neck, whereas values >150 pg/ml will require cross-sectional imaging as above.[37]

Doubling time of calcitonin and CEA is calculated using serial values. Doubling time more than 24 months has a better prognosis as opposed to <6 months.[38]

MANAGEMENT OF LOCOREGIONAL AND METASTATIC DISEASE

Patients with persistent or recurrent nodal disease in the neck must be offered redo neck dissection keeping in mind that with the extensive disease, a less-aggressive approach may be considered to reduce the morbidity associated with extensive resection. A complete nodal clearance reduces the chance of recurrence and improves survival.[27]

External beam radiation therapy (EBRT) is used to reduce the risk of locoregional recurrence in patients with gross residual tumor, extrathyroidal extension, or extensive nodal disease. EBRT, however, does not increase the overall survival outcomes.[39]

Figure 8: Nests of polygonal cells with round nuclei, granular (salt and pepper) chromatin and granular eosinophilic cytoplasm; calcitonin immunohistochemistry showing positivity (H and E, ×400)

Table 1: Risk stratification

| ATA risk level | Moderate | High | Highest |
|---------------|----------|------|---------|
| Codon mutation | 321, 532, 533, 609, 611, 618, 620, 630, 631, 635, 649, 666, 768, 790, 791, 804, 844, 891, 912 | 634, 883 | 918 |
| MTC aggressiveness | A, B | C | D |
| Age of onset | Adult | <5 years | First year of life |
| Timing of prophylactic surgery | When calcitonin gets elevated or earlier | Consider at <5 years | Based on calcitonin levels |

ATA: American Thyroid Association, MTC: Medullary thyroid cancer
Systemic therapy in MTC is recommended in individuals with progressive and metastatic disease. However, the low-volume asymptomatic disease does not require systemic therapy as the toxicity of the treatment outweighs the survival benefit. Treatment may be provided to palliate symptoms, hormonal excess, and life-threatening events and provides locoregional control.

Patients with isolated lung or liver metastases may benefit from metastatectomy. However, disseminated disease warrants systemic therapy or local therapy such as radiofrequency ablation or chemoembolization. Drugs such as doxorubicin, dacarbazine, and 5-FU have been studied but have been shown to have short-lived low response rates. Radioisotopes such as Yttrium\textsuperscript{90} DOTA, Lutetium\textsuperscript{177} DOTA, Indium\textsuperscript{111} Octreotide, or Iodine\textsuperscript{131} MIBG have shown partial response and may be tried in stabilizing disease progression.

**TARGETED THERAPY IN MEDULLARY THYROID CARCINOMA**

The presence of RET germ line mutations in HMTC and SMTC has brought targeted therapy into the limelight. Other important receptors such as vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), and hepatocyte growth factor receptor (c-Met) are also overexpressed and hence are potential targets for therapy.

Different tyrosine kinase receptors are activated in MTC and hence inhibit different activated tyrosine kinases (TKs) and have changed the face of management. Vandetanib and cabozantinib have been approved by the US Food and Drug Administration for the treatment of patients with advanced disease and may be considered as first-line tyrosine kinase inhibitors (TKIs). Vandetanib inhibits VEGFR 2, VEGFR3, RET, and EGFR, VEGFR1 to a lesser extent. This docks to the ATP-binding pocket of RET, thus inhibiting it. Cabozantinib inhibits MET, RET, VEGFR, CKIT, Flt-3, and Tie-2. Other TKIs such as sorafenib, sunitinib, lenvatinib, and pazopanib are considered as secondary TKIs. Some multikinase inhibitors such as motesanib, axitinib, imatinib, gefitinib, and ponatinib have been found to have limited efficacy. Newer molecules such as nintedanib, anlotinib, regorafenib, and sulfatinib are also being evaluated. Tipifarnib blocks farnesylation of Ras proteins and may play a role in Ras mutation by blocking signal transduction. Similarly, certain statins such as lovastatin have been found to have antitumor properties in K-RAS-dependent thyroid tumors. Valproic acid inhibits histone deacetylase causing G2/M arrest in neoplastic cells. However, clinical efficacy is not yet fully understood.

Nelfinavir targets heat shock protein 90, chaperone, which is required for folding and stability of RET. Everolimus is considered useful as it inhibits the mTOR pathway in which RET and RAS utilize for downstream signal transduction. Combination therapy with temozolomide and capecitabine and sunitinib and cisplatin and cytotoxic chemotherapy with TKIs have been studied, but their use is limited by the toxicity.

**CONCLUSION**

MTC is a rare form of differentiated carcinoma of thyroid arising from the C-cell. They do not take up radioactive iodine, and hence, they require aggressive surgical therapy upfront. As it is associated with a well-studied genotype-phenotype correlation with RET mutations, it is suitable for genetic counseling and mutational analysis to screen for familial disease and also provides options of evolving targeted therapy.

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**Conflicts of interest**

There are no conflicts of interest.

**Disclosure**

This material has never been published and is not currently under evaluation in any other peer reviewed publication.

**Ethical approval**

The permission was taken from Institutional Ethics Committee prior to starting the project. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent**

Informed consent was obtained from all individual participants included in the study.

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