Solid Tumour Section
Review

Thyroid: Medullary carcinoma

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Identity

Other names
MTC

Classification

Note
Medullary thyroid cancers (MTC) are rare tumors of neuroendocrine origin that arise from parafollicular C cells which secrete a variety of peptides and hormones including calcitonin. As opposed to the more common papillary and follicular thyroid cancer subtypes, MTC represents a rare and under-characterized form of cancer, and can cause death if untreated (Taccaliti et al., 2011).

MTC can be either sporadic, usually isolated to one thyroid lobe, or familial, the latter of which is defined as the cancer syndrome known as Multiple Endocrine Neoplasia type 2 (MEN2) (Frank-Raue et al., 2010). MEN2 is the result of the autosomally dominant missense gain of function mutation in the RET (Rearranged during Transfection) proto-oncogene. MEN2 can be further subclassified into MEN2A, MEN2B and Familial Medullary Thyroid Carcinoma (FMTC). MEN2A is defined by the occurrence of medullary thyroid carcinoma (MTC), in conjunction with pheochromocytomas and primary hyperparathyroidism. MEN2B, is defined by the presence of MTC, pheochromocytomas, ganglioneuromatosis of the gastrointestinal tract, mucosal neuromas of the lips and tongue, and a Marfanoid body habitus (Frank-Raue et al., 2010). FMTC occurs when MTC is the only clinical feature, rarely with other endocrine neoplasias. Offspring of affected carriers of the RET mutation have a 50% chance of inheriting the mutation.

Clinics and pathology

Disease
Medullary thyroid cancer

Note
Patients with sporadic MTC usually present with a neck mass while patients with hereditary MTCs that are diagnosed as mutation carriers should undergo prophylactic thyroidecomy before the onset of any symptoms. Sporadic MTC patients often present with metastasis to cervical and paratracheal lymph nodes. The diagnosis of MTC is based on history, physical exam, calcitonin and CEA levels, imaging, and fine needle aspiration biopsy. Every patient with diagnosed MTC should undergo genetic evaluation for the presence of the RET mutation. Histologically, tumors appear with hyperplastic parafollicular C-cells and predominantly present bilaterally (Taccaliti et al., 2011). Sporadic MTC generally presents as a single tumor confined to one thyroid lobe.

The prognosis of MTC is better than poorly differentiated, malignant anaplastic thyroid cancer, but worse than more differentiated and benign papillary and follicular thyroid cancer. Therefore, an early diagnosis is necessary for improving recurrence and survival rates in these patients (Taccaliti et al., 2011).

Phenotype / cell stem origin

Their origin is characteristically from neural crest cells. These cells arise from the convergence between the dorsal ectoderm and the neural tube. Neural crest cells eventually give rise to the chromaffin cells of the thyroid C cells in addition to chief cells of the extra-adrenal paraganglia, and
A. Medullary thyroid carcinoma featuring groups of cells with polygonal to elongated cytoplasm, round-to-oval nuclei with indistinct nucleoli. Note amyloid deposition in the stroma (H&E, x200). B. Strong immunopositivity for calcitonin in all tumor cells (immunoperoxidase staining, x200).

those of the adrenal medulla. The endocrine tumors that arise from thyroid C cells at earlier stages of differentiation generate medullary thyroid carcinomas. RET gene testing of germline deoxyribonucleic acid (DNA) at the chromosomal region 10q11.2 must be performed in patients with family history of MTC. This test will identify hereditary MTC among 95% or more of individuals with MEN2A and MEN2B. Additionally, 88% of individuals with FMTC are identifiable through RET testing (National Cancer Institute, National Institutes of Health, www.cancer.gov).

**Etiology**
Medullary thyroid cancer can be classified into 4 types:
1) Sporadic
2) Hereditary MEN2A
3) Hereditary MEN2B
4) Hereditary familial medullary thyroid cancer (FMTC)

**Epidemiology**
In the United States, thyroid cancer comprises 3% of new malignancies occurring every year. Approximately 56460 of projected cases of the cancer will be diagnosed of which 1780 will result in death. MTC accounts for approximately 5-8% of all thyroid cancer. About 20-25% of MTC cases are the result of MEN2 syndromes. However, most MTC reports are sporadic (National Cancer Institute, National Institutes of Health, www.cancer.gov). Among those, 56% occur as MEN2A, 9% as MEN2B, and 35% as FMTC (Frank-Raue et al., 2010). MTC typically occur in third or fourth decade of life in MEN2A patients. MEN2B patients develop the disease usually in early childhood. Onset of disease in FMTC patients generally occurs in middle age.

**Clinics**
Sporadic MTC generally presents as a single tumor confined to one thyroid lobe while familial presents often bilaterally. Most MTC patients will present with neck mass and may complain of hoarseness, dysphagia, and/or difficulty swallowing and breathing. MTC patients often present with metastasis to cervical and paratracheal lymph nodes. Distant metastatic sites of MTC may include lung, liver, and bones, and more rarely to the brain and skin. Disseminated disease may cause symptoms of weight loss, lethargy, and bone pain. MTC patients often present with diarrhea due to an increased secretion of an intestinal electrolyte which occurs secondary to high plasma calcitonin levels. Flushing similar to that present in carcinoid tumor patients often occurs to a similar degree, as a result of the hypersecretion of calcitonin and related gene products.

**Pathology**
Histologically, tumors appear with hyperplastic parafollicular C-cells and predominantly present bilaterally in familial cases. MTC may be preceded by C-cell hyperplasia (CCH). However, CCH is a relatively common occurrence in middle-aged adults (LiVolsi, 1997; Nose, 2011).

**Treatment**
In sporadic cases total thyroidectomy and central lymph node dissection should be performed following the diagnosis of MTC. Lateral lymph node dissection should be added when lateral lymph node involvement is identified. For patients who are known carriers of the RET mutation surgery should be offered prior to the development of cancer. At present, guidelines
recommend surgery at a certain age according to each mutation and the associated aggressive disease nature. Operating later during adulthood increases the likelihood of local recurrences and distant metastasis (Brandi et al., 2001).

Surgery for recurrent disease should be considered if cure is possible and there are no distant metastases. Following the first surgery, the decision to reoperate can be determined based on the extent of metastatic disease. If distant metastases are found, surgery may only be indicated if the patient presents with irretraceable symptoms. These cases may benefit from tumor debulking (Brandi et al., 2001).

For patients with metastatic MTC for which surgery offers no cure, there are unfortunately few chemotherapeutic options. Furthermore, MTC responds poorly to radiotherapy regimens. However, some patients with substantial burdens of metastatic MTC can remain asymptomatic and live for many years (Taccaliti et al., 2011).

**Prognosis**

The prognosis of MTC is worse than that of follicular and papillary thyroid cancer. Its natural history varies anywhere from latent lingering disease after surgery to aggressive disease and even death related to metastatic thyroid tumor burden. Patients with hereditary MTC that undergo prophylactic surgery have an excellent prognosis and are virtually cured (Raue, 1998). For patients with MTC the 10-year survival rates vary from about 61% to 76% (Raue, 1998; Kebebew et al., 2000; Roman et al., 2006). MTC is often diagnosed using screens for calcitonin and carcinoembryonic antigen (CEA). Factors such as patients’ age, sex, calcitonin doubling time in addition to tumor volume and lymph node dissemination will dictate stage and prognoses.

**Genes involved and proteins**

**RET (ret proto-oncogene)**

*Location* 10q11.2

*Note* The RET (REarranged during Transfection) gene is a member of the proto-oncogene cadherin superfamily of Receptor Tyrosine Kinases which regulate such processes as growth and differentiation of neural crest cells, from which MTCs derive. When cyogenetically rearranged, it can undergo oncogenic activation. Genetic diagnosis is crucial in order to differentiate familiar from sporadic MTC. It must be performed early on when a family history is remarkable (Frank-Raue et al., 2010).

**NKX2-1 (NK2 homeobox 1)**

*Location* 14q13.3

**BRAF (v-raf murine sarcoma viral oncogene homolog B1)**

*Location* 7q34

*Note* BRAF encodes a member of the raf/mil family of serine/threonine protein kinases and functions as a key regulator in the ERK signalling. This pathway is involved cell division differentiation, and bioactivity. Gene mutations have been associated with sporadic medullary thyroid carcinoma (Nikiforova et al., 2003).

**PTEN (phosphatase and tensin homolog)**

*Location* 10q23.3

*Note* PTEN encodes a tumor suppressor that is mutated in many cancers, and encodes a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase. It negatively regulates intracellular levels of phosphatidylinositol-3,4,5-trisphosphate in the AKT/PKB signaling pathway (Nose, 2011).

**HRAS (v-Ha-ras Harvey rat sarcoma viral oncogene homolog)**

*Location* 11p15.5

*Note* HRAS encodes an oncogene which is a member of the Ras family. These genes are related to the transforming genes of mammalian sarcoma retroviruses and their products behave as GTPase proteins. Therefore, HRAS mutations can lead to a variety of cancers including MTC. Analysis of single nucleotide polymorphisms (SNPs) revealed SNPs in HRAS among patient haplotypes have been shown to be associated with sporadic MTC. (Ruiz-Llorente et al., 2007; Barbieri, 2012).

**TP53 (tumor protein p53)**

*Location* 17p13.1

*Note* This gene encodes p53, involved with apoptosis, cell
cycle arrest, DNA repair and metabolic processes. P53 binds DNA to induce expression of downstream genes that inhibit growth, thus making it a tumor suppressor. p53 mutants have been shown to bind poorly to DNA, thus repressing tumor suppressor activity. Regression analysis studies of TP53 genotype mutations among patients in recent studies have shown to lead to interited increased risk of sporadic MTC (Joao Bugalho et al., 2008; Barbieri, 2012).

**VEGFA (vascular endothelial growth factor A)**

**Location**

6p12

**Note**

VEGFA encodes a growth factor of which mutations can cause proliferative and nonproliferative retinopathy in diabetic patients. Multiple isoforms have been identifed due to upstream translation initiation sites of the AUG start codon. Furthermore, splice variants have also been identifed of different isoforms, including ones either freely secreted or cell-associated. Studies have shown that VEGF expression in thyroid carcinoma correlated with the tumor type and TNM stage. This may suggest that VEGF plays a role in angiogenesis and metastasis of thyroid cancer (Ji et al., 2012).

**PTTG1 (pituitary tumor-transforming 1)**

**Location**

5q35.1

**Note**

PTTG1 encodes a homolog of securin proteins, which functions to block the separation of sister chromatids during anaphase until activation of the anaphase-promoting complex (APC) which it binds to upon APC activation. This gene is highly expressed in a variety of tumors and is mainly a cytosolic protein while partially localized in the nucleus. Levels of PTTG1 have been shown to correlate with MTC aggressiveness among other cancers. Silencing PTTG1 has been shown to reduce MTC cell proliferation. This supports the hypothesis that PTTG1 might have an important role in MTC cell proliferation and metastasis and may be a therapeutic target (Zatelli et al., 2010).

**ESR2 (estrogen receptor 2 (ER beta))**

**Location**

14q23.2

**Note**

ESR2 encodes an estrogen receptor, a nuclear receptor transcription factor containing a DNA binding domain on the N-terminus. When 17beta-estradiol binds to ESR2, the complex forms either a homodimer or heterodimer with ESR1. In normal physiology, ESR1 plays a role in sexual development reproduction as well as bone and tissue development, but may be mutated in a variety of cancers. Furthermore, alternative splice variants exist. ESR2, but not ESR1, is present in thyroid tissue, but there are no notable associations between ESR2 expression and differentiation between benign and malignant MTCs (Vaiman et al., 2010).

**NRAS (neuroblastoma RAS viral (v-ras) oncogene homolog)**

**Location**

1p13.2

**Note**

This is an N-ras oncogene encoding a membrane protein that shuttles between the Golgi apparatus and the plasma membrane. This shuttling is regulated through palmitoylation and depalmitoylation by the ZDHHC9-GOLGA7 complex. The encoded protein, which has intrinsic GTPase activity, is activated by a guanine nucleotide-exchange factor and inactivated by a GTPase activating protein. Mutations in this gene have been associated with somatic rectal cancer, follicular thyroid cancer, autoimmune lymphoproliferative syndrome, Noonan syndrome, and juvenile myelomonocytic leukemia (Schulten et al., 2011; Almeida and Hoff, 2012).

**EGFR (epidermal growth factor receptor)**

**Location**

7p12

**Note**

EGFR encodes a transmembrane glycoprotein receptor with kinase activity and is a member of the epidermal growth factor family. Binding of the epidermal growth factor to the EGFR induces receptor dimerization and tyrosine autophosphorylation, in turn causing cell growth and proliferation. EGFR gene mutations have been shown to cause lung cancer. Alternatively spliced transcript variants encoding different isoforms have been described. Targeting EGFR through small molecule inhibitors has been shown to be useful in treating various cancers including MTC. Recently, vandetanib (ZD6474), EGFR inhibitor, was approved for treating progressive and symptomatic MTC (Almeida and Hoff, 2012).

**NFKB1 (nuclear factor of kappa light polypeptide gene enhancer in B-cells 1)**

**Location**

4q24

**Note**

This 105 kD protein may undergo 26S proteasome processing to produce a 50 kD protein, which is a DNA binding subunit of the NF-kappa-B (NFKB) protein complex. This serves as a transcription regulator activated by various cell stresses including cytokines, free radicals, UV radiation, and bacterial or viral
products. Upon activation, NFKB enters the nucleus where it induces gene expression in a variety of cell survival and immune related functions. Super activation of NFKB has been shown to cause inflammatory diseases, irregular immune cell development or delayed cell growth. Recently, NFKB has been shown to play an important role in thyroid cancer. It may play a critical role in controlling thyroid cancer cell proliferation and their anti-apoptotic signaling pathways cells (Gallel et al., 2008; Pacifico and Leonardi, 2010).

**STAT3 (signal transducer and activator of transcription 3 (acute-phase response factor))**

**Location**

17q21.31

**Note**

The STAT3 gene encodes a protein which is a member of the STAT protein family. These proteins are phosphorylated by the receptor associated kinases in response to growth factors and cytokine stimuli. STAT3 then translocates to the nucleus as a complex, in order to activate the transcription of downstream genes involved with growth and apoptosis. Three alternatively spliced transcript variants producing different isoforms have been identified. Recent studies have demonstrated that FMTC-RET mutants activate the Ras/ERK1/2 pathway, upstream of the STAT3 Ser727 pathway. This may play an important role in thyroid cancer oncogenic transformation (Plaza-Menacho et al., 2007).

**MMP2 (matrix metalloproteinase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase))**

**Location**

16q13-q21

**Note**

Matrix metalloproteinase (MMP) are involved in the disintegration of the extracellular matrix in normal physiologic processes such as reproduction and tissue remodeling, embryonic development, wound healing, as well as in cancer metastasis. MMP2 degrades type IV collagen, which plays a structural role in basement membranes. Two transcript variants encoding different isoforms have been found for this gene. A recent study assessing a panel of MTC cancer specimens found that expression of MMP2 could be used as a prognostic tool (Cavalheiro et al., 2008).

**NOTCH1 (notch 1)**

**Location**

9q34.3

**Note**

Notch1 is a member of the Notch transmembrane protein family (Notch1-4) which possesses an extracellular domain of epidermal growth factor-like (EGF) repeats, and an intracellular domain containing different domain types. Notch signaling is initiated intercellularly following physical interaction between the ligands (delta serrate) on adjacent cells, and is evolutionarily conserved. This protein is cleaved in the trans-Golgi network, and presented on the cell surface as a heterodimer. This protein functions as a receptor for membrane bound ligands, and may play multiple roles during development. Notch1 has been identified as a tumor suppressor in MTC in addition to other neuroendocrine tumors such as carcinoids. In MTC cells, Notch1 is expressed at very low to absent levels; however, upregulating NOTCH1 expression reduces MTC cell proliferation and phenotypic expression (Kunnimalaiyaan et al., 2006).

**GFRA1 (GDNF family receptor alpha 1)**

**Location**

10q26.11

**Note**

Glial cell line-derived neurotrophic factor (GDNF) is a glycosylphosphatidylinositol(GPI)-linked receptor on the cell surface and plays key roles in differentiation and survival of neurons. It is involved in regulation of the RET tyrosine kinase activity. Multiple alternatively spliced transcript variants have been described for various GFRA1 isoforms. Furthermore, germline polymorphisms in RET and GFRA1 and correlations with genetic predispositions to developing sporadic MTC have been described. Modulating these polymorphisms have been described to affect clinical features of the disease as well (Severskaia et al., 2006).

**KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog)**

**Location**

12p12.1

**Note**

Kirsten RAS oncogene homolog is a small GTPase and member of the mammalian RAS gene family. Mutations can be caused by an amino acid substitution causing oncogenic activation in various malignancies. Alternative splicing leads variants of two isoforms have been described. Mutation screening of KRAS may be warranted but still inconclusive (Schulten et al., 2011).

**MTOR (mechanistic target of rapamycin (serine/threonine kinase))**

**Location**

1p36.2

**Note**

MTOR serves as a target of FKBP12-rapamycin complex which enables the immunosuppression and cell cycle inhibition. It belongs to a family of phosphatidylinositol kinase-related kinases which regulate cell processes such as growth and survival in response to DNA damage, free radical damage and
nutrient deprivation. MTOR signaling is aberrantly activated in MTC especially in tissues harboring germline RET mutations MTC (Rapa et al., 2011).

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