Initial Evaluation and Diagnosis of Medullary Thyroid Carcinoma

2

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Medullary Thyroid Carcinoma (MTC) is a neuroendocrine tumor arising from the neural crest parafollicular, or C-cells, of the thyroid. MTC is much less common than differentiated thyroid cancer (DTC), representing less than 5 % of thyroid malignancies diagnosed and has not had the same increase in incidence noted for DTC over the past decade. The prevalence of occult MTC, identified by autopsy series and incidental findings on pathological examination after thyroidectomy for other indications, ranges from 0.13 to 0.69 % [1–7]. While the incidence of MTC is comparatively lower than DTC, disease-specific survival is significantly worse; 5-year survival for MTC is approximately 50 %, compared to approximately 98 % for DTC [8]. Early diagnosis of MTC is paramount in optimizing outcomes for patients, underscored by the significant decline in survival with regional and metastatic disease. Furthermore, preoperative knowledge of MTC has important implications for extent of surgery. While the extent of prophylactic cervical lymphadenectomy in the lateral compartment for localized MTC is a matter of debate, there is a consensus that a complete level VI dissection should be performed in all patients with MTC [9].

MTC can be inherited or sporadic. Three-quarters of patients have sporadic disease, and most often present in the 5th–6th decade of life. Screening for thyroid cancer is not practiced in patients without a family history and, therefore, most cases of sporadic disease are identified during the evaluation for a palpable thyroid nodule or nodule found incidentally on imaging for other indications. Sporadic MTC is thought to be more aggressive with frequent central (level VI), ipsilateral lateral (levels II–V), and contralateral lateral (40 %) cervical lymph node metastases at presentation. Somatic mutations of the REarranged-during-Transfection (*RET*) proto-oncogene are seen within the C-cells of sporadic tumors in approximately 50 % of cases, the majority of which (79 %) are a point mutation in codon 918 of exon 16. This mutation is associated with larger size of tumor at presentation, increased incidence of nodal disease, and decreased survival [9–11]. When compared to patients with RET^{-} tumors, sporadic RET^{+} patients had higher incidence of nodal disease, distant metastases, and recurrences [10]. Between 18 and 50 % of RET^{-} tumors have been found to have *RAS* mutations [12, 13].

The remainder of MTC patients have hereditary disease, with nearly all patients carrying one of a number of gain of function germline

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mutations in the *RET* gene. In recent years, a growing body of evidence supports a strong genotype–phenotype relationship for age of presentation, penetrance of disease, and associated features [14]. Knowledge of specific mutation can help guide treatment and surveillance. This is a rare disease with incidence of approximately 1 out of 30,000 individuals. These autosomal dominant mutations lead to the multiple endocrine neoplasia (MEN) syndromes—MEN2A (Sipple's syndrome), MEN2B, and familial MTC (FMTC). MEN2A is four times more common than MEN2B, with 85 % possessing a single-point mutation in codon 634 cysteine for arginine [15]. When patients present with a known family history of MTC, it is crucial that patients be screened for multicentric MTC (90 %), pheochromocytoma (50 %), parathyroid hyperplasia (15 %), and be tested for a germline *RET* mutation. Some consider sending a *RET* mutational analysis in any case of MTC, particularly at a young age, or C-cell hyperplasia. FMTC is a variant of MEN2A without associated pheochromocytoma or parathyroid disease. FMTC families have a lower penetrance of MTC and typically present at an older age than MEN2A families [16]. Hirschsprung's disease and cutaneous lichen amyloidosis of the upper back are associated with germline *RET* mutations, and presentation should prompt mutational analysis.

On average, patients with MEN2A develop MTC at 3–5 years of age, although the age at presentation is correlated with the specific *RET* mutation. Given that nearly all patients are noted to have C-cell hyperplasia on pathology, recommendations for prophylactic thyroidectomy are dependent upon risk stratification. Recently, the revised MTC guidelines from the American Thyroid Association (ATA) categorized the risk of MTC aggressiveness as moderate (MOD), high (H), or highest (HST) based on the specific codon mutation [17]. Children with a M918T mutation are in the highest risk category and should undergo thyroidectomy within the first year of life. Children with MEN2A and *RET* codon 634 mutations are at high risk for developing MTC during the first years of life and are recommended to begin annual screening with ultrasound and serum calcitonin levels beginning at age 3 years, with prophylactic thyroidectomy at or before age 5 years, based on the results of the screening studies. Children in the moderate risk category should undergo screening beginning at age of 5 years with thyroidectomy when the serum calcitonin level becomes elevated [17].

MTC associated with MEN2B is less common but more aggressive; however, this is thought to be secondary to the more advanced stage at presentation than aggressiveness of the MTC per se. There is 100 % penetration of MTC in MEN2B families, and metastases within the first year of life have been described [18]. While nearly all cases of MEN2A patients have a positive family history of the disease, over 50 % of MEN2B patients are de novo mutations [19]. This makes diagnosis at an early stage particularly challenging. Like MEN2A, the incidence of pheochromocytoma is 50 % in affected families. MEN2B patients carry a singular phenotype with mucosal ganglioneuromas of lips, tongue, eyelids, and a marfanoid body habitus. Because of the early onset of disease, it is paramount that family members of affected individuals are screened as soon as the diagnosis is made in the proband. Commonly, without screening, patients present with multifocal, bilateral MTC.

Role of Routine Serum Calcitonin Levels in Patients with Thyroid Nodules

In both inherited and sporadic MTC, disease recurrence and survival is highly correlated with the extent of disease at presentation. This is underscored by the significant decrease in 10-year survival associated with Stage III disease [20]. Unfortunately, half of patients have regional nodal metastases at the time of presentation. Moreover, lower preoperative serum calcitonin levels are correlated with the absence of lymph node metastases and with normalization of postoperative calcitonin levels [21]. Given that

early diagnosis and surgery gives patients the best chance of cure, screening for MTC with routine serum calcitonin levels has been debated.

MTC can be diagnosed as a result of screening (i.e., inherited syndromes in patients with family history) or during the workup of a thyroid nodule. There is a clear association with early detection of MTC and outcomes—smaller tumors are correlated with a decreased incidence of metastases, and the majority of patients presenting with a palpable nodule already have nodal metastases [22]. There is no current consensus on the use of screening serum calcitonin levels in patients undergoing initial evaluation of a thyroid nodule, given the low prevalence of disease (MTC). The ATA guidelines on the management of thyroid nodules do not recommend for or against the routine use; however, the consensus statement by the European Thyroid Cancer Task Force recommends calcitonin screening in all patients undergoing evaluation of a thyroid nodule [9, 23]. Arguments for the use (primarily in Europe) include improved accuracy of serum calcitonin levels in the diagnosis of MTC, compared to cytological results from fine needle aspiration biopsy (FNA) and improved preoperative planning, dependent on the extent of elevation of serum calcitonin levels. Elisei et al. [24] showed that routine serum calcitonin screening, which identified 44 cases of MTC in a group of 10,000 patients with thyroid nodules, resulted in a cure rate of 59 % in the calcitonin-screened group, as compared to a cure rate of 2.7 % in historical controls; those in the calcitonin-screened group also had improved 10-year survival rates. Moreover, they and others have found that serum calcitonin was more accurate than FNA in diagnosing MTC [25]. Hahm et al. [2] found that 56 of 1448 total nodular thyroid disease patients had a basal serum calcitonin >10 pg/mL, 10 of whom went on to have pathologically confirmed MTC (46 did not). While thought to be more sensitive than FNA, specificity is of concern given the potential for unnecessary surgery [7, 26]. This has led to other groups to use a higher positivity criterion for basal serum calcitonin levels to be considered diagnostic for MTC. In a study from Denmark that used a threshold of 100 pg/mL in 959 patients with nodular thyroid disease, the positive predictive value (PPV) was only 15.4 %; using the same cutoff, Costante et al. reported a PPV of 100 % [5, 26]. Other large series using a basal serum calcitonin threshold of 10 pg/mL had sensitivities of 100 %, specificities >96 %, but PPV of 6–39 % [3, 27–29]. This led to the ATA's recommendation for a threshold of basal or stimulated serum calcitonin of >100 pg/mL "if obtained" to be considered diagnostic for MTC [17].

Those arguing against routine serum calcitonin screening in all patients with thyroid nodules cite the low prevalence of disease (<1 % of thyroid nodules), risk of unnecessary surgery, and increased costs [24]. A cost-effectiveness study assessing the addition of serum calcitonin in all patients with thyroid nodules in the USA to the 2009 ATA recommendations for evaluation of patients with thyroid nodules found it cost-effective at accepted willingness to pay thresholds of $12,000 per life-year saved, at a cost increase of 5.3 %, comparable to the cost-efficacy of colonoscopy or mammography screening [30]. Critics of this analysis cite the inclusion of patients with C-cell hyperplasia and medullary microcarcinoma in the prevalence estimates of MTC that has uncertain clinical significance [23]. An additional argument in favor of routine serum calcitonin screening is the use to monitor for recurrence, with some recommending follow-up starting three months postoperatively then annually if undetectable. A lower preoperative serum calcitonin of 10–49 pg/mL was predictive of postoperative normalization for 44/45 patients in a French cohort of 226 with MTC [31].

Challenges regarding the implementation of routine serum calcitonin screening for patients with thyroid nodules in the USA include establishment of uniform threshold values, gender-specific thresholds, and applicability of stimulatory testing. Current European consensus guidelines recommend routine measurement of serum calcitonin in the initial diagnostic evaluation of all patients with thyroid nodules with concurrent evaluation for comorbid conditions which may cause false positive elevation of serum calcitonin levels: renal failure, ectopic calcitonin production from non-thyroidal neuroendocrine tumors, hypergastrinemia, Hashimoto's thyroiditis,

and heterophilic antibodies; however, no threshold value for screening is suggested [9]. In addition to these benign conditions that may falsely elevate serum calcitonin levels, a patient's sex must be taken into consideration when determining normative values, with males having higher baseline serum calcitonin levels [5, 32]. Studies to determine ideal serum calcitonin thresholds by patient sex have demonstrated thresholds of 14–26 pg/mL for females and 32–68 pg/mL for males [6, 33, 34].

Higher threshold for screening serum calcitonin will yield a higher PPV of the test, as shown by Costante et al.; increasing the threshold from >20 pg/mL to >100 pg/mL improved PPV from 23.1 to 100 % [5]. Similarly in a sample of >20,000 patients, Rink et al. demonstrated that increasing the upper limit from 10 to 15 pg/mL provided 100 % sensitivity while decreasing false positive cases [34]. As expected, increasing the threshold value improved the PPV and specificity of the test, but also impacted the negative predictive value; using a cutoff of 30 pg/mL in 7276 patients, Iacobone et al. [4] demonstrated 100 % PPV but a negative predictive value of only 63 %.

Calcitonin stimulation with a secretagogue, such as pentagastrin, is not currently approved in the USA. However, pentagastrin stimulation is still used in other countries, particularly in Europe, to evaluate mild elevations in baseline serum calcitonin levels and to differentiate possible MTC from other etiologies of an elevated serum calcitonin level, such as other neuroendocrine tumors, small cell lung cancer, and chronic renal failure. Use of pentagastrin stimulation for patients with baseline serum calcitonin levels of 10–100 pg/mL improved the PPV to 25–40 % [2–5, 29, 35, 36]. Testing involves an overnight fast, injection of pentagastrin, and serial blood draws over 10 min. This test is not currently used in the USA, secondary to a poor side effect profile and the lack of additional diagnostic information for the management of patients with elevated basal calcitonin levels. Furthermore, improved basal calcitonin assays have greatly improved sensitivity of the assay.

When utilizing serum calcitonin levels for initial diagnosis of and screening for MTC, clinicians must be aware of the potential for false positive and false negative results. The hook effect may cause false depression of serum calcitonin levels. This occurs when a high antigen concentration binds with signal antibodies and is discarded with the liquid phase of the testing process [7]. Heterophilic antibodies may also falsely lower serum calcitonin levels. Additionally, some patients with MTC may be nonsecretors of calcitonin. In a cohort of 839 patients with sporadic MTC patients from 2 tertiary referral centers, 7 (0.83 %) patients had normal serum calcitonin and carcinoembryonic antigen (CEA) levels despite advanced tumor stage [37]. Conditions that may lead to elevation of serum calcitonin levels include, as previously discussed, renal failure, ectopic production from neuroendocrine tumors, hypergastrinemia, thyroiditis, or use of certain medications such as omeprazole [38]. In a cohort of 1,425 patients with nodular thyroid disease, the baseline serum calcitonin level was elevated in 23 (1.6 %) patients, including 9 (0.63 %) patients with MTC [27]. In patients with renal failure, despite clearance of calcitonin by dialysis, serum calcitonin levels may be elevated both pre- and post-dialysis [39].

Other polypeptide hormones have been suggested as alternatives to serum calcitonin for MTC screening, including vasoactive intestinal peptide, serotonin, somatostatin, CEA, and procalcitonin. Elevations in serum CEA in patients with MTC have been associated with a poorer prognosis, especially in those with a decreased or stable serum calcitonin level, suggesting tumor dedifferentiation. CEA has also been correlated with positive margins [21]. CEA should be interpreted with caution though as it may be elevated from other malignancies of gastrointestinal, lung, prostatic, breast, or ovarian origin as well as benign conditions of the gastrointestinal and respiratory systems. Procalcitonin, a 116 amino acid peptide produced in parafollicular C-cells, shows promise as a biomarker for screening due to its stability at room temperature and concentration-independent half-life

of 20–24 h. Though currently used as a clinical marker for sepsis, procalcitonin has reliable commercial assays yielding similar results [40]. Several studies have demonstrated concordance and similar diagnostic accuracy for MTC between calcitonin and procalcitonin [41–43].

Evaluation of a Thyroid Nodule

The workup of a palpable or incidentally discovered thyroid nodule should proceed with the measurement of serum thyroid stimulating hormone (TSH) and diagnostic imaging with ultrasonography of the thyroid gland and cervical lymph nodes [14]. Ultrasound provides confirmation of physical examination findings or alternate imaging modality including the size, location, and features of a nodule, the presence of additional nodules or lymphadenopathy. Ultrasonographic findings in MTC are variable, with 66–72 % demonstrating characteristic suspicious features including height greater than width, speculation, hypoechogenicity, calcifications, extrathyroidal extension, lymphadenopathy, or extranodal extension [44–46]. While not universally present, suspicious ultrasound features confer a 450 % increased risk of advanced stage MTC, especially metastatic lymphadenopathy or extrathyroidal extension [46]. Use of quantitative elastography for MTC has also been evaluated with equivocal results; in a small sample of 18 patients with MTC, 55.6 % had low-to-intermediate elastography scores of one or two [47]. Once a diagnosis of MTC has been established cytopathologically following neck ultrasound, no further diagnostic imaging is usually necessary prior to operative intervention for locoregional disease, although this is dependent on the extent of elevation of serum calcitonin levels. Fluorodeoxyglucose positron emission tomography is not recommended for the routine preoperative evaluation of patients with MTC but may be used to assess for recurrent disease [48]. If metastatic MTC is suspected preoperatively by patient signs or symptoms of distant metastases, the presence of extensive neck disease, or calcitonin greater than 500 pg/mL further diagnostic imaging, is indicated. Computed tomography (CT) should be used to detect lung and mediastinal lymph node metastases, contrast enhanced CT or magnetic resonance imaging (MRI) to evaluate for liver metastases, as well as MRI and bone scintigraphy for bone metastases [49].

The diagnostic evaluation of a patient with a thyroid nodule on ultrasonography should proceed with FNA, depending on patient's risk factor profile, biochemical results, and sonographic features [23]. The detection rate of MTC by FNA is lower than that for DTC, varying from 12 to 88 % with 59 to 86 % sensitivity compared to serum calcitonin measurement [2, 27, 50–52]. This comparatively low detection rate and sensitivity is due to the variable appearance of MTC on aspiration cytology which may show spindle-shaped, plasmacytoid or epithelioid cells. Amyloid—characteristically associated with MTC—can also be found in follicular lesions and systemic amyloidosis. MTC may be misdiagnosed as a follicular neoplasm or desmoid tumor. In a study of 91 patients with proven MTC, the best distinguishing cytological features were dispersed triangular cells with coarse granular chromatin and cytoplasmic granularity [53]. To verify the diagnosis, immunohistochemistry for the presence of calcitonin, chromogranin, CEA, and the absence of thyroglobulin may be performed on aspirates [50, 53, 54]. Results of studies examining calcitonin measurement in aspiration needle washout are heterogeneous but despite small sample sizes demonstrate excellent sensitivity and specificity for diagnosis of MTC [54, 55]. Calcitonin measurement of FNA aspirate as an adjunct to serum calcitonin measurement may differentiate patients with MTC from those with false positive elevations of serum calcitonin as FNA calcitonin values in MTC are greater than seventy times higher than serum [56]. The use of calcitonin measurement of fine needle aspirate may improve diagnostic accuracy for MTC especially in cases of borderline serum calcitonin elevation.

Because 1–7 % of patients with presumed sporadic MTC actually have hereditary disease, all patients with pathologically confirmed MTC should be referred for genetic counseling and DNA analysis for a *RET* mutation [57, 58]. Clinicians must be aware of the duty to warn

potentially affected family members if a mutation is detected and should discuss disclosure with the patient prior to initiating testing. First-degree relatives of patients found to have a *RET* germ line mutation should also be offered genetic counseling and testing. If hereditary MTC is found, a clinical evaluation for pheochromocytoma and hyperparathyroidism is indicated with surgical management of pheochromocytoma taking precedent over thyroidectomy if identified.

Conclusion

The initial evaluation and diagnosis of Medullary Thyroid Carcinoma begins with the workup of a palpable or incidentally detected thyroid nodule by history and physical examination, measurement of thyroid-stimulating hormone, and neck ultrasound including the thyroid and cervical lymph nodes, and fine needle aspiration. There is no consensus regarding the routine use of serum calcitonin screening in patients with thyroid nodules in the USA, however if screened, patients with levels >100 pg/mL should be considered for total thyroidectomy with central lymphadenectomy. For patients with serum calcitonin, 10–100 pg/mL stimulatory testing or calcitonin assay of fine needle aspirate may improve specificity and positive predictive value for the diagnosis of MTC. No further radiographic evaluation is indicated unless distant metastatic disease is suspected by extensive locoregional disease, serum calcitonin >500 pg/mL, or signs or symptoms indicative of metastases. All patients with pathologically confirmed MTC should be referred for genetic counseling and RET mutation analysis. If a RET mutation is identified, patients should be evaluated for pheochromocytoma and hyperparathyroidism prior to thyroidectomy.

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