Chapter 13
Medullary Thyroid Cancer

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Objectives

1. To understand the presentation and diagnosis of medullary thyroid cancer (MTC)
2. To understand the differences in the presentation and diagnosis of sporadic versus familial MTC
3. To understand the relationship between the presence of a *ret* proto-oncogene mutation and the development of MTC
4. To understand the relationship between *ret* proto-oncogene mutations and their associated phenotype
5. To understand the pivotal role of screening and prophylactic thyroidectomy in the management of familial MTC
6. To understand the treatment options for MTC

Case Presentation

A 45-year-old woman was found by her primary care physician to have a 1.5-cm thyroid nodule. A serum calcitonin level was ordered and found to be elevated at 15 pg/mL (normal <6 pg/mL). A fine-needle aspiration revealed a very cellular specimen. The cells were pleomorphic and poorly cohesive. The cells seen included small cells with a granular cytoplasm, large atypical cells, and spindle cells. Binucleated cells and cells with eccentric nuclei were also seen. The cytology reading stated that a neoplastic process was suspected. The patient was referred for thyroidectomy. The cytology specimen was not stained for calcitonin or amyloid before the patient's surgery. A preoperative neck ultrasound was not performed. There was no known family history of any thyroid disorders.

The patient underwent thyroidectomy. Pathology showed multiple foci of MTC within a background of C-cell hyperplasia. A central compartment neck dissection

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revealed lymph node metastases. Following her thyroidectomy and subsequent referral to an endocrinologist, the patient was able to obtain additional family history. A 76-year-old maternal aunt had died from thyroid cancer a year previously; no further details were available. The patient's eldest sibling (55 years old) had also recently had thyroid surgery for thyroid cancer and had been told that his cancer had spread. Again, no further details could be obtained. There was no known family history of hyperparathyroidism or pheochromocytoma.

The patient's postoperative calcitonin level was undetectable (less than 1 pg/mL). A postoperative sonogram of the neck did not reveal any evidence of additional pathologic lymph nodes. She was screened for the *ret* proto-oncogene mutation and was found to have a L790F mutation (where a normal leucine is changed to phenylalanine). The patient had two children, ages 12 and 16. She initially refused genetic screening for her children, citing a concern about the privacy of their health information, and a desire not to cause the family unnecessary anxiety. However, following additional discussion, she eventually agreed to their testing. The younger child was found to carry the same mutation, whereas the older child did not. The screening results for both children were confirmed by repeat testing. The 12-year-old child underwent further evaluation. A serum calcitonin was normal at 3 pg/mL. A cervical ultrasound showed several 3-mm thyroid nodules. Screening for hyperparathyroidism and pheochromocytoma was negative with normal calcium, parathyroid hormone, and fractionated plasma free metanephrine levels. Prophylactic thyroidectomy was performed with a finding of C-cell hyperplasia.

Overview of Medullary Thyroid Cancer

Medullary thyroid cancer originates from the parafollicular C cells. Approximately 75% of cases are sporadic, and the remaining 25% are familial. Sporadic cases occur as a result of clonal expansion of a single focus of tumor cells, whereas heritable MTC usually presents with multifocal disease. C-cell hyperplasia is a common finding in familial disease. It is diagnosed when there are more than six C cells per thyroid follicle. C-cell hyperplasia is thought to progress through clonal expansion and eventual transformation to malignancy. Disruption of the follicular basement membrane by C cells is thought to mark the transition to malignancy [1]. A germline mutation of the *ret* proto-oncogene, which codes for a tyrosine kinase receptor, is the cause of familial disease. It is transmitted as an autosomal dominant trait with high penetrance linked to chromosome 10 [2]. Mutations in the *ret* proto-oncogene can occur in the extracellular or intracellular domain (Fig. 13.1). Somatic mutations may be present in some sporadic cases.

Medullary thyroid cancer cells almost invariably secrete calcitonin, and frequently also secrete carcinoembryonic antigen, neuron-specific enolase, chromogranin A, and adrenocorticotrophic hormone. Calcitonin is a clinically useful marker for MTC and is employed both as a serum marker and immunohistochemical marker [1]. Although serum calcitonin may be elevated in patients with large thyroid

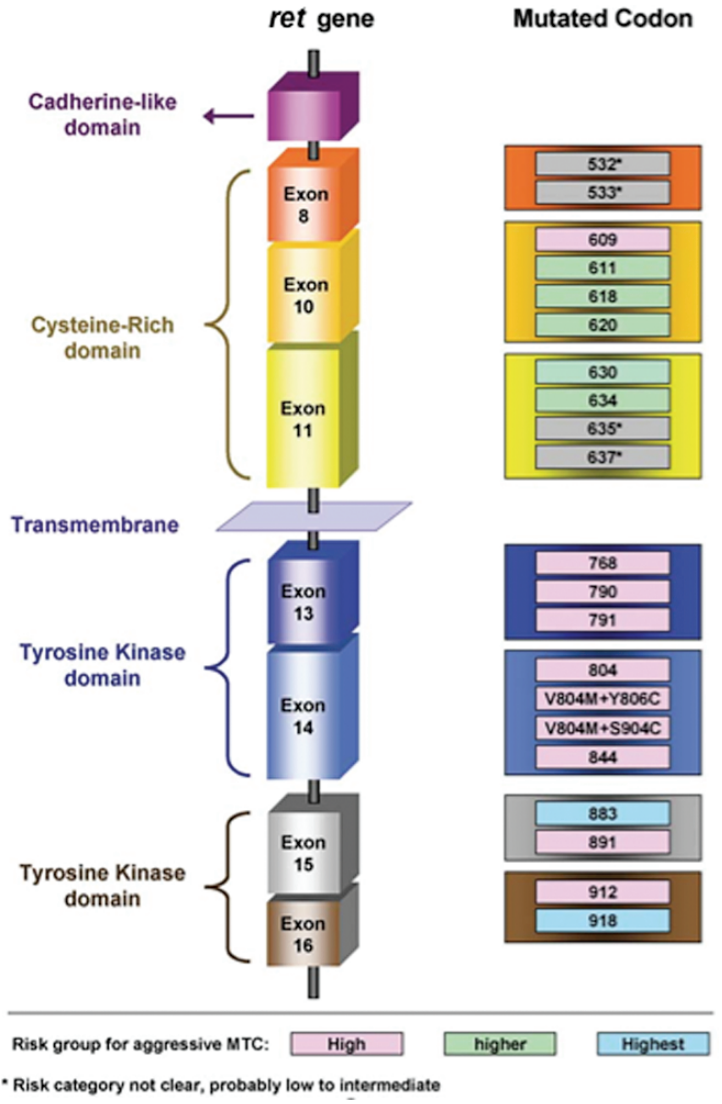

Fig. 13.1 Schematic diagram of structure of the *ret* proto-oncogene. [From Kouvaraki et al. [8], with permission.]

nodules harboring MTC, it may be normal in smaller tumors and in subjects with C-cell hyperplasia. Provocative tests using pentagastrin or calcium may confirm the diagnosis in these cases. However, the use of these biochemical tests has been replaced by *ret* proto-oncogene testing when screening for familial disease [2, 3]. Furthermore, pentagastrin is not commercially available in the United States.

When not detected by screening, MTC usually presents as a thyroid nodule. The nodule is typically painless, and may be accompanied by cervical adenopathy [1, 3]. Symptoms of ectopic hormone production such as diarrhea are uncommon. The correct diagnosis is usually reached on the basis of the cytology from a fine-needle aspiration or elevated serum calcitonin levels. However, the use of serum calcitonin as routine screening in patients with thyroid nodules remains controversial [3, 4]. Primary treatment of MTC consists of a total thyroidectomy performed by an experienced thyroid surgeon with appropriate exploration of the neck and central compartment for affected lymph nodes. Additional treatment for residual or recurrent disease with external radiotherapy, chemotherapy, or biologic response modifiers is rarely curative. Tumor stage predicts prognosis and effectiveness of treatment, and overall survival rates are approximately 75% [1]. Familial disease generally has a better prognosis than sporadic disease. This advantage is no longer seen when adjustment is made for disease stage [5], suggesting that sporadic disease is usually detected in a more advanced stage.

How the Diagnosis Was Made

Diagnosis of Sporadic Medullary Thyroid Cancer

Sporadic and familial MTC are diagnosed in different ways. Sporadic MTC is usually diagnosed by fine-needle aspiration of a palpable nodule [1], or it may be diagnosed at the time of surgery. Sporadic disease initially appeared to be the culprit in this patient. Her cytology specimen could also have been stained for calcitonin, which might have rendered a confirmatory diagnosis prior to the patient's surgery. However, fine-needle aspiration is only suggestive or diagnostic of MTC in about 50% of patients who have MTC, contributing to the controversy regarding the utility of screening calcitonin levels for all patients with thyroid nodules.

The clue to this patient's diagnosis was her elevated serum calcitonin level. Although some endocrinologists recommend routine measurement of calcitonin in patients with thyroid nodules, most do not [4]. It would appear that European endocrinologists tend to be more in favor of this approach, in contrast to North American endocrinologists. The yield from such screening would be low given the high prevalence of thyroid nodules and the rarity of MTC [3, 4]. In this case, however, such screening picked up an apparently sporadic case of MTC that was later found to be familial. Identification of the index case of a MTC kindred following serum calcitonin measurement in an apparently sporadic MTC case presenting with a thyroid nodule has been previously described [1]. It is estimated that about 20% to 30% of all apparently "sporadic" cases of MTC are, in fact, previously unrecognized familial MTC. The debate about whether to screen all patients with thyroid nodules with a serum calcitonin level remains unresolved. However, such debate should take into consideration not only the relatively low likelihood of detecting

MTC (about 0.1–0.5%), but also the serious consequences of missing a patient with familial MTC and the relevant clinical considerations and costs.

Diagnosis of Familial Medullary Thyroid Cancer

Familial MTC is usually diagnosed at the time of thyroidectomy after genetic screening has identified a *ret* proto-oncogene mutation [2]. The patient's daughter was fortunate to have been identified during the precursor stage of C-cell hyperplasia. Had her thyroidectomy been delayed, or had she carried a more aggressive mutation, MTC may have been diagnosed at the time of thyroidectomy, as unfortunately occurs in many individuals within MTC kindreds.

Lessons Learned

Use of Cytology in the Diagnosis of Medullary Thyroid Cancer

Accurate diagnosis of MTC by cytologic features alone may be difficult. MTC usually appears as a cellular specimen with clusters of pleomorphic tumors cells. Cells may be oval with eccentric nuclei, similar to plasma cells, or polygonal with granular cytoplasm, similar to Hürthle cells. They may also be spindle shaped. An aspirate from a MTC lesion, therefore, can mimic other benign and malignant entities [1], such as Hürthle cell tumors, poorly differentiated carcinoma, and metastatic renal cell carcinoma and melanoma. In one study, fine-needle aspiration detected only 75% of MTC cases that were suspected based on serum calcitonin screening. The diagnosis, however, can be confirmed by immunohistochemical staining for calcitonin. Immunostaining of the cytology specimen for calcitonin is considered the gold standard for preoperative diagnosis of MTC [3]. In this patient's case, cytologic staining for calcitonin was not performed. Recently, it has been shown that there is a relationship between the cytomorphology found in fine-needle aspirates and the *ret* proto-oncogene mutation. For example, the codon 918 mutation was found to be associated with small, spindled cells, whereas large oval or polygonal cells were seen with the codon 634 mutation.

The Role of ret *Proto-Oncogene Screening*

All patients with MTC, including apparently sporadic cases, should be screened for *ret* proto-oncogene mutations [1]. Early detection of MTC makes successful treatment possible [6]. In the case of sporadic disease, this is often not possible. In this particular case, the patient appeared to have sporadic disease, but it subsequently became apparent that she was part of a MTC kindred. If her family history had been known previously, she would have had a thyroidectomy at an earlier age, ideally

prior to development of MTC. This was obviously possible in the case of her daughter, who had a thyroidectomy before further transformation of C cells had occurred. It is not known with certainty, but it is strongly suspected that thyroidectomy will markedly decrease this carrier's development of subsequent MTC. However, since a small number of thyroid cells still remain following a total thyroidectomy, it is possible that MTC can still develop. The finding of elevated calcitonin levels during follow-up despite thyroidectomy at the stage of microinvasive carcinoma has been reported [6]. The appropriate monitoring after prophylactic thyroidectomy has not been established, but could involve periodic serum calcitonin levels and neck sonograms.

It is also critical to screen all first-degree relatives of patients with *ret* proto-oncogene mutations. Knowledge of an individual's gene status affords the opportunity to intervene before disease development or early in the course of the disease. Screening may introduce privacy issues, but there is a clear survival advantage associated with early thyroidectomy when a mutation is detected [2, 3]. This is in contrast to the case with the *MEN1* gene, where awareness of gene status does not necessarily change management significantly. Screening of family members using stimulated calcitonin levels has been superseded by genetic screening [2, 3].

Exons 10, 11, 13, 14, 15, and 16 (Fig. 13.1) are initially examined in commercially available screening tests. It is important that the entire gene be sequenced, rather than simply examining the sequence at the codons known to be "hot spots" for mutations associated with hereditary MTC. This is particularly important if the *ret* mutation in that family is unknown. However, familial MTC has also been found in association with mutations in exon 8. It has been recommended that if exons 10, 11, and 13 to 16 are negative, the other 15 exons should be sequenced [1]. However, such testing is available only in research laboratories. If screening is negative, it should be repeated on a second blood sample to exclude the possibility of errors, as was done for both daughters of the patient presented. Due to false-negative test results (2–5%), a small risk of hereditary MTC remains even if a germline mutation is not detected. It therefore may be prudent to periodically measure calcitonin levels and perform neck sonograms in family members with negative screening, as clinically indicated.

Familial Medullary Thyroid Cancer syndromes

Familial syndromes, which are associated with MTC, include familial MTC, MEN2A, and MEN2B. The different *ret* mutations (Fig. 13.1) confer different phenotypes (Fig. 13.2). The spectrum of clinical features varies widely according to the specific mutation. These varying clinical features include non-MTC manifestations such as hyperparathyroidism, pheochromocytoma, mucosal neuromas, marfanoid habitus, ganglioneuromas, cutaneous lichen amyloidosis, Hirschsprung's disease, and papillary thyroid cancer [7, 8]. For example, the 918 mutation is associated

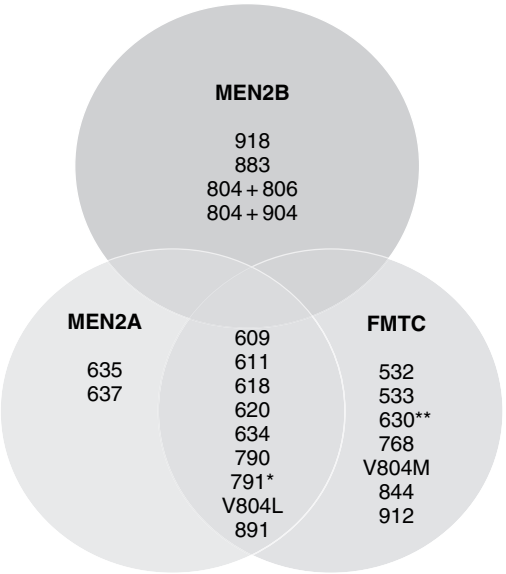

Fig. 13.2 Correlation of specific *ret* codon mutations with the phenotypic expression of hereditary MTC.* Development of Pheochromocytoma has not been reported. ** Cannot distinguish between MEN2A and familial MTC because of the small number of cases. [From Kouvaraki et al. [8], with permission.]

with pheochromocytoma, marfanoid habitus, and enlarged corneal nerves, but not hyperparathyroidism. The 768 mutation, in contrast, is typically not associated with other endocrine tumors. The 790 mutation carried by this patient is associated with papillary thyroid cancer in 9.1% of patients, and additionally is infrequently associated with hyperparathyroidism. On the other hand, the 634 mutation is commonly associated with hyperparathyroidism, pheochromocytoma, and cutaneous lichen amyloidosis.

Variability, at least partly based on the specific genetic mutation, is also manifest in the age of onset (Fig. 13.3) and aggressiveness of the MTC [7, 8]. There is an age-related and codon-specific progression of early MTC. For example, the earliest reported age of onset of MTC is approximately 1 year when codon 918 is mutated, but is around 22 years of age when the mutation is in codon 768. For this patient's mutation, the earliest age of onset appears to be 11 or 12 years of age (Fig. 13.3). The median age of onset is 3 years for codon 918, but is considerably later at 60 years for codon 768. An intermediate median age of onset of 39 years characterizes codon 790. It is these genotype-phenotype relationships that drive the screening, surveillance, and prophylaxis regimens that are critical for the management of kindreds with MTC. Various entities such as the International Workshop on MEN, the European MEN Study Group (EURO-MEN), and the University of Halle have made recommendations regarding the appropriate age for prophylactic testing and thyroidectomy based on the specific mutation [1, 2, 5]. It is usually

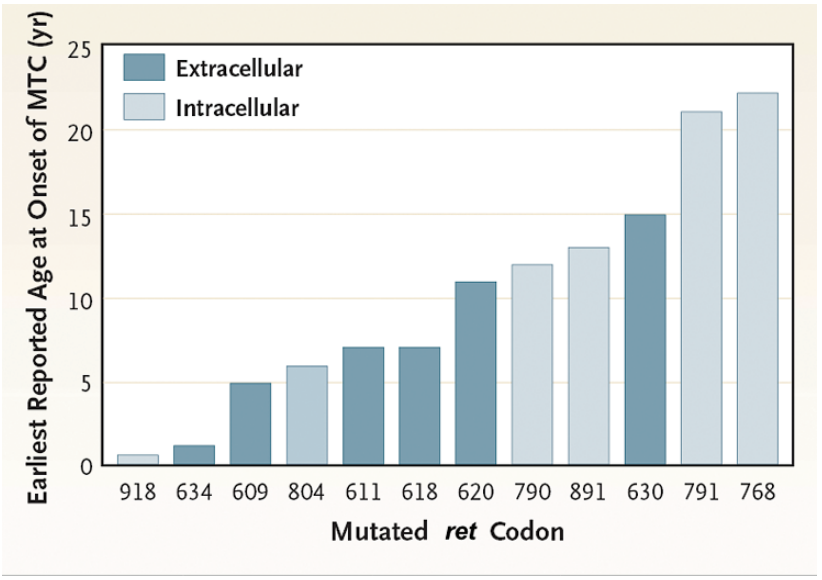

Fig. 13.3 Illustration of the earliest reported age at onset of MTC based on the *ret* mutation. (From Cote and Gagel. Lessons learned from the management of a rare genetic cancer. N Engl J Med 2003;349:1566–1568, with permission.)

recommended that carriers of the 918 mutation undergo thyroidectomy at less than 1 year of age. Operative intervention in 790 and 768 gene carriers is recommended at age 5 to 10 years. Such codon-orientated prophylactic surgery has contributed to the decline in morbidity and mortality from familial MTC [1, 3]. Despite the utility of the *ret* genotype in predicting phenotype, there remains some unpredictability about malignant transformation, thus lending additional support to the advisability of early prophylactic thyroidectomy.

Direct Correlation Between Early Diagnosis of Medullary Thyroid Cancer and Outcomes

Ten-year survival rates of patients with MTC range from 50% to 80%, depending on tumor stage and age [1]. MTC can be cured only at a stage where surgical resection is complete, thus fueling the effort to detect disease early. This is illustrated by the outcomes of sporadic disease versus familial disease. Sporadic disease is usually diagnosed at a more advanced stage than inherited disease. Ten-year survival rates average approximately 75% in several studies. In contrast, in known kindreds with familial MTC followed for 18 years, mortality rates may be as low as 5% [2], presumably due to prophylactic surgery at an early stage. In one study, patients with sporadic disease were 7.7 times more likely to die from their MTC than patients with

familial disease. However, there is no difference in survival between the sporadic and familial forms of MTC when adjustment is made for disease stage [5].

Patients who have undergone prophylactic thyroidectomy still require long-term evaluation in order to confirm that they are cured. Some patients with microinvasive MTC [6] or have been found to develop elevated calcitonin levels during later evaluation. Although this patient was found to have lymph node metastases at the time of her initial surgery, her undetectable postoperative calcitonin presumably suggests a favorable prognosis [3].

Treatment Options

There are no effective treatments for MTC beyond surgery [3]. Screening for pheochromocytoma is required before surgical intervention. Measurement of plasma free metanephrines is probably the best test to exclude a pheochromocytoma in familial syndromes where the risk of a pheochromocytoma is high. However, there has not been a consensus regarding which screening is best [2]. Therefore, it would seem wise to combine plasma and urinary catecholamines or metanephrines in order to achieve the greatest sensitivity and specificity. If a pheochromocytoma is present, adrenalectomy should be performed before thyroidectomy. New surgical technologies such as optical magnification devices and bipolar forceps coagulation have allowed systematic microdissection of entire lymph node compartments [5]. Central lymph node dissection is recommended at the time of thyroidectomy. When the tumor is palpable, larger than 1 cm, or when lymph nodes are known to be positive, bilateral lymph node dissection is usually pursued [3]. This is because of the propensity of MTC to metastasize early to regional lymph nodes. This particular patient had a palpable tumor, and in this setting bilateral neck dissection, in additional to central compartment dissection, would usually be recommended. Surgical cure is achieved in only approximately 20% to 25% of patients with tracheoesophageal invasion or cervical nodal metastases, and virtually never achieved with mediastinal or distant metastases [5].

Elevated postoperative calcitonin levels are indicative of residual disease. A second operation may be helpful to achieve normalization of calcitonin levels and presumably improve cure rates [3]. External beam radiation may be helpful for selected patients with inoperable or incompletely excised tumors [1, 3]. There is no role for radioactive iodine therapy. Radiolabeled anticarcinoembryonic antigen monoclonal antibodies, which are available on an experimental basis, have produced tumor shrinkage in some cases. Therapy with agents such as somatostatin analogues, alpha-interferon, or these agents combined can produce partial and transient symptomatic improvement in patients with metastatic disease [3]. Chemotherapy is relatively ineffective; there may be some tumor response, but there is no impact on survival. Agents that have been employed include doxorubicin, cis-platinum, bleomycin, dacarbazine, and 5-fluorouracil [3]. Inhibitors of *ret* tyrosine kinase, such as Zactima, are currently being tested as therapy for both sporadic and hereditary MTC in phase II clinical trials.

Consensus Guidelines

Consensus statements have been published regarding the management of hereditary medullary thyroid cancer [1, 2]. These guidelines address the recommended age of prophylactic thyroidectomy, screening for and management of associated endocrine tumors, carrier testing, and postoperative testing. The 790 mutation seen in the described patient is associated with either the MEN2A or familial MTC phenotype. Carrier testing is deemed mandatory for all children due to their 50% risk of carrying the 790 mutation, and the high penetrance of this mutation. Calcitonin measurements are noted to be insufficiently sensitive to guide decisions regarding thyroidectomy once carrier status is known, but are helpful to detect disease postoperatively. The 790 carriers have the least high risk for MTC and are recommended to undergo prophylactic thyroidectomy by age 5 to 10 years after testing for both hyperparathyroidism and pheochromocytoma. However, both these manifestations are not usually seen with this mutation.

References

1. Massoll N, Mazzaferri EL. Diagnosis and management of medullary thyroid carcinoma. Clin Lab Med 2004;24:49–83.
2. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86:5658–5671.
3. Orlandi F, Caraci P, Mussa A, Saggiorato E, Pancani G, Angeli A. Treatment of medullary thyroid carcinoma: an update. Endocrine-Related Cancer 2001;8:135–147.
4. Hodak SP, Burman KD. The calcitonin conundrum—is it time for routine measurement of serum calcitonin in patients with thyroid nodules? J Clin Endocrinol Metab 2004;89:511–514.
5. Machens A, Ukkat J, Brauckhoff M, Gimm O, Dralle H. Advances in the management of hereditary medullary thyroid cancer. J Intern Med 2005;257:50–59.
6. Skinner MA, Moley JA, Dilley WG, Owzar K, Debenedetti MK, Wells SA Jr. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. N Engl J Med 2005;353:1105–1113.
7. Machens A, Gimm O, Hinze R, Hoppner W, Boehm BO, Dralle H. Genotype-phenotype correlations in hereditary medullary thyroid carcinoma: oncological features and biochemical properties. J Clin Endocrinol Metab 2001;86:1104–1109.
8. Kouvaraki MA, Shapiro SE, Perrier ND, et al. RET proto-oncogene: a review and update of genotype-phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumors. Thyroid 2005;15:531–544.

Multiple-Choice Questions

1. A 45-year-old woman carries the 804 *ret* proto-oncogene mutation. She is seeing you as her new endocrinologist. This particular mutation is characterized by a median age of diagnosis of MTC without nodal metastases of 38 years. Her serum calcitonin level is normal. She has had negative screening for pheochromocytoma. A thyroidectomy has been recommended by her previous endocrinologists. She is well informed and understands the implications of her carrier status, but has refused thyroidectomy because she has friends who have never felt

well since they have been on replacement thyroid hormone. Your wisest course of action would be:

A. Refuse to be this patient's endocrinologist
B. Ask the patient to see a psychiatrist
C. Follow the patient's serum calcitonin and cervical ultrasonography, and continue to attempt to persuade the patient to undergo thyroidectomy
D. Perform a stimulated calcitonin measurement
E. Recommend triiodothyronine as thyroid hormone replacement following thyroidectomy

Suggested answer: C. Explanation: The only course of action that will either ensure this patient is cured or limit the extent of her disease is thyroidectomy. Therefore, every attempt should be made to ensure this patient is fully informed and aware of the benefits of thyroidectomy.

2. A 12-year-old boy with the 918 mutation underwent thyroidectomy and central compartment dissection. Pathology showed multifocal MTC and central compartment lymph node metastases. Postoperatively his serum calcitonin level remains elevated at 79 pg/mL. There is no evidence of distant metastases based on appropriate computed tomography scans, bone scans, and positron emission tomography. To provide the patient with the best outcome, the next recommended step would be:

A. External beam radiation
B. Radioactive iodine therapy
C. Bilateral modified radical neck dissection
D. Treatment with an experimental tyrosine kinase inhibitor
E. Chemotherapy

Suggested answer: C. Explanation: This patient's elevated postoperative calcitonin level is likely to indicate residual cervical lymph node disease. In this setting, where there is no evidence of distant metastases, additional surgery can normalize calcitonin levels and has been proposed to improve the cure rates [3].

3. All of the following statements regarding the *ret* proto-oncogene are true except:

A. Specific *ret* proto-oncogene mutations are associated with specific phenotypes.
B. An inactivating mutation causes tumor development.
C. Screening has a 2% to 5% false-negative rate.
D. Knowledge of gene status permits intervention that may prevent cancer development.
E. Knowledge of gene status permits intervention that may allow cure of cancer.

Suggested answer: B. Explanation: The *ret* proto-oncogene mutation is an activating mutation that activates *ret* kinase activity causing oncogenic or transforming properties. In contrast, the *MEN1* gene mutation results in inactivation of a tumor suppressor gene. Determination of *ret* proto-oncogene status is one of the few examples of a genetic test that permits an effective clinical intervention.