Medullary Thyroid Cancer

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Key Points

Genetics

- Medullary thyroid cancer is a relatively rare form of thyroid cancer that can occur sporadically or as part of an inherited syndrome, multiple endocrine neoplasia type 2 (MEN2).
  - MEN2 accounts for about 25% of medullary thyroid cancer.
  - In MEN2, medullary thyroid cancer often occurs in early childhood.
- MEN2 is an autosomal dominant condition caused by specific mutations in the *RET* gene.
- The current standard of care for MEN2 includes genetic testing of all potentially affected family members, including infants. Asymptomatic family members who have inherited the causative mutation are offered prophylactic thryoidectomy.

Ethics

- Predictive genetic testing of children is justifiable if preventive interventions can be offered to the child at risk.

Learning Objectives

Participants will be able to:

- Understand autosomal dominant inheritance;
- Understand the use of *RET* testing in families with MEN2, as part of a strategy to prevent medullary thyroid cancer;
- Understand the justification for genetic testing of asymptomatic children to identify mutations that cause MEN2.

Family History Issues

All biological descendents of a person with MEN2 have a risk of inheriting MEN2. First-degree relatives (parents, brothers and sisters, and children)

typically have a 50% chance of inheriting the causative mutation. However, MEN2 may occur as the result of a new (de novo) mutation; when a de novo mutation occurs, parents and siblings are unlikely to have the mutation.

Red Flags 

MEN2 accounts for about 25% of medullary thyroid cancer. Suspicion of this syndrome is highest when the cancer occurs in a person under age 50, is multifocal, or is seen in the presence of other medical complications of MEN2, such as hyperparathyroidism or pheochromocytoma.

Case 29. Medullary Thyroid Cancer in a 40-Year-Old Woman

Mrs. Y is a 40-year-old software engineer who has been healthy all her life. She has noticed a "lump" in her neck, for which she seeks evaluation. She has no symptoms, exercises on a regular basis, and has no history of hospitalizations or other serious illness. Physical examination reveals an asymmetric thyroid with an approximately 1.5-cm nodule on the right. A needle aspiration reveals C-cell hyperplasia and a possible carcinoma. Mrs. Y undergoes a thyroidectomy. Histological examination confirms medullary carcinoma of the thyroid. Mrs. Y makes a good recovery from surgery.

There is no family history of thyroid cancer or other cancer. Her mother died of complications of pheochromocytoma after a routine hysterectomy. She has two children, four and eight years old, who are without known medical problems.

Clinical Care Issues

Thyroid cancer accounts for approximately 1% of malignancies occurring in the United States. Among thyroid cancers, only 3% to 4% are medullary thyroid cancer (MTC). MTC is typically an aggressive cancer, with reduced survival compared to other thyroid cancers.

About 25% of medullary thyroid cancer is due to the inherited condition

multiple endocrine neoplasia type 2 (MEN2). This condition is associated with a 95% to 100% lifetime risk of medullary thyroid cancer (MTC); other complications include parathyroid disease (adenomas and hyperplasia causing hyperparathyroidism) and pheochromocytoma. The condition is caused by mutations in the *RET* gene [*GeneReview*: MEN2, cancer.gov].

Mrs. Y's MTC may be part of the inherited cancer syndrome, MEN2. This diagnosis would have implications for her medical management, and for her children's risk. If she has MEN2, she has an increased risk of hyperparathyroidism and pheochromocytoma. In addition, her children have a 50% chance of having inherited the condition. Her cancer management would not be changed if she is found to have MEN2: she has already received treatment, and recommendations for ongoing surveillance would be the same whether or not she has a *RET* mutation.

MEN2-related hyperparathyroidism is generally associated with mild hypercalcemia. It is likely to be asymptomatic early in the course of the disease but may become symptomatic if left untreated. Annual screening is recommended for those patients who have not had parathyroidectomy and autotransplantation (a procedure often performed as part of a thyroidectomy).

MEN-2 related pheochromocytomas usually present with intractable hypertension, and are often bilateral. Sudden death from anesthesia-induced hypertensive crisis has been described in patients with MEN2 and unsuspected pheochromocytoma. Malignant transformation is uncommon and is estimated to occur in about 4% of familial cases [Modigliani et al 1995].

Risk Assessment

A diagnosis of MTC may be an indicator of MEN2, because approximately 25% of MTCs are due to MEN2. Confirming MEN2 would have implications both for clinical management of the patient and for risk to family members. Mrs. Y has developed her cancer at a relatively young age, so her risk of having an inherited cancer may be higher. In addition, her mother's history of pheochromocytoma is highly suggestive of MEN2.

Genetic Counseling and Testing

Genetic counseling would provide Mrs. Y with information about the genetic testing for *RET* mutations that is done to diagnose MEN2, and would also

include a detailed review of her family history, to identify others who may have been affected, and to clarify which family members might be at risk of inheriting MEN2. In some cases, review of the medical records of family members may be indicated, to confirm their medical history.

If Mrs. Y has an identifiable *RET* mutation, this test result confirms the diagnosis of MEN2. Genetic testing can then be used to determine whether other family members have inherited the mutation. Candidates for testing include the parents, siblings, and children of an affected person; other family members who are found to carry the mutation are at elevated risk for malignancy and can benefit from preventive measures.

In Mrs. Y's family, her mother's history of pheochromocytoma suggests her mother had MEN2. To identify all family members at risk, testing should be offered to Mrs. Y's mother's siblings (Mrs. Y's aunts and uncles on her mother's side). Testing of Mrs. Y's father may also be appropriate, to confirm that he does not have the mutation.

Even if the *RET* testing fails to identify a *RET* mutation, MEN2 is still possible, because the estimated sensitivity of the test is 95%. If a careful review of the family history identifies other individuals with findings suggestive of MEN2, such as pheochromocytoma (as is the case in Mrs. Y's family) or additional cases of MTC, an inherited cause remains the most likely possibility.

MEN2 is classified into three subtypes based on the presence of other clinical complications: MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC). All three subtypes have a high lifetime risk of developing MTC, estimated at 95% for MEN2A and 100% for MEN2B and FMTC. The average age of onset is not well established. One study of MEN2A families seen in a referral center found that C-cell hyperplasia, the first indicator of possible MTC, occurred at a mean age of 15, and as early as age five years in some cases [Lips et al 1994]. MTC has been observed earlier in MEN2B, and may occur later in FMTC [Hansen et al 2000].

MEN2A is also associated with an increased risk of pheochromocytoma, parathyroid adenomas and parathyroid hyperplasia. MEN2B is associated with an increased risk of pheochromocytoma and with additional clinical features such as mucosal neuromas of the lips and tongue, distinctive facies with enlarged lips, ganglioneuromatosis of the gastrointestinal tract, and an asthenic "Marfanoid" body habitus; parathyroid hyperplasia occurs uncommonly.

In some families, MTC occurs without any of these other associated findings or risks and is termed FMTC. However, in the absence of extensive family history, it may be difficult to distinguish FMTC from MEN2A.

See *GeneReview*: MEN2 and cancer.gov PDQ summary for further details about the different MEN2 syndromes.

Interventions

If Mrs. Y is found to have a mutation in the *RET* gene, she has an increased risk for pheochromocytoma and hyperparathyroidism. Experts recommend annual screening to detect these conditions at early and treatable stages.

In addition, testing is recommended for Mrs. Y's relatives, as discussed in Genetic Counseling and Testing, so that they can be offered preventive care.

Prophylactic thyroidectomy with reimplantation of one or more parathyroid glands into the neck or non-dominant forearm represents the current standard of care for asympomatic patients with MEN2. If genetic testing is not possible (for example, if genetic testing has failed to identify the causative mutation) biochemical screening to identify C-cell hyperplasia can be used to identify family members at risk.

The optimal timing of prophylactic surgery is not resolved [Moley et al 1998]. Current recommendations are based on clinical experience and vary for different MEN2 subtypes [Wells et al 1994, Brandi et al 2001]. In most centers, thyroidectomy is performed in patients with MEN2A by the age of five years or when a mutation is identified. Some centers recommend management of FMTC similar to that for MEN2A. For MEN 2B, most centers offer surgery within the first fix months of life — and preferably within the first month — because of both the very early onset of MTC and the aggressive course of cancer in patients with MEN 2B. Observational data suggest a significant clinical benefit from thyroidectomy [Brandi et al 2001].

Ethical/Legal/Social/Cultural Issues

Genetic testing in children

If Mrs. Y is found to have a *RET* mutation, both her children have a 50% chance of inheriting it. Genetic testing to determine their status is considered

standard of care.

The American Society of Human Genetics-American College of Medical Genetics (ASHG/ACMG) recommends against testing children unless there are medical indications [ASHG/ACMG 1995]:

> "If the medical or psychosocial benefits of a genetic test will not accrue until adulthood, as in the case of carrier status or adult-onset diseases, genetic testing generally should be deferred. The stigmatization and deleterious effects on self-image are great and should only be risked when medical benefit is possible. Although sympathetic to the considerable difficulties inherent in living with uncertainty about the health status of the child, the Task Force does not feel that these warrant foreclosing the child's right to make an independent decision in regard to testing in adulthood."

However, testing individuals during childhood is recommended if the positive predictive value of the test is high, the disease may occur during childhood, and an intervention during childhood can prevent disease. MEN2 meets these criteria, because MTC can occur in early childhood; and prophylactic thyroidectomy in childhood is recommended.

Resources

- **American Cancer Society**
  1599 Clifton Road NE
  Atlanta, GA 30329
  Phone: 1-800-227-2345

- **CancerNetwork.com**

- **National Cancer Institute (NCI) Cancer Information**

- **National Cancer Institute**

- **Cancer.gov Thyroid Cancer Homepage**

- **National Library of Medicine Genetics Home Reference**

Multiple endocrine neoplasia

- **GeneTests Online Medical Genetics Information Resource**
- ***GeneReviews*, GeneTests Online Medical Genetics Information Resource**
- **GeneTests Resources for MEN2**

References

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