Presumed Familial Late-Onset Medullary Thyroid Cancer in a patient with a germline point mutation, c. 2304 G->T, in RET proto-oncogene codon 768: specific mutation may guide timing of prophylactic total thyroidectomy in affected family members

Susan M. Gerber, MD; Madalina Tuluc, MD, PhD; Serge A. Jabbour, MD
Division of Endocrinology, Departments of Medicine and Pathology, Thomas Jefferson University, Philadelphia, PA

Background:
Medullary thyroid carcinoma (MTC) accounts for 15% of thyroid cancers. It arises in the C-cells of the thyroid, and is often metastatic at presentation. Approximately 75% of MTC cases are sporadic. Heritable MTC is subdivided into three categories: MEN2A, familial medullary thyroid carcinoma (FMTC), and MEN2B. Determination of the particular mutation may guide the timing of prophylactic total thyroidectomy in family members who carry the mutation.

Case presentation:
A 54-year-old woman presented for unintentional weight loss. Her primary care physician detected a thyroid lesion on physical examination. Neck ultrasound showed a right 1.4 cm nodule with microcalcifications, a 1.4 cm extrathyroidal mass, and other hypoechoic nodules. FNA revealed medullary thyroid cancer. Preoperative CT scans of the chest, abdomen, and pelvis were negative. Preoperative calcitonin and CEA were elevated at 1743 pg/mL and 64.3 ng/mL respectively. Plasma free metanephrines, PTH, and calcium were normal. TSH was 5.81 mIU/L. There was no family history of MEN, adrenal disease, thyroid cancer, or calcium disorders.

She underwent total thyroidectomy with bilateral LN dissection. The right laryngeal nerve was encased in tumor. Pathology showed multifocal MTC with bilateral involved lymph nodes, the largest of which was 1.5 cm. Perineural and angiolymphatic invasion was seen. Ten days postoperatively, calcitonin was 176 pg/mL. Seven months postoperatively, calcitonin was 146 pg/mL and CEA was 6.2 ng/mL.

Genetic testing was positive for a germline point mutation in nucleotide c. 2304 in RET proto-oncogene codon 768, with a G>C change at exon 13 causing glutamic acid to change to aspartic acid. This mutation can be associated with MEN2A or with FMTC. The patient's 21-year-old son tested positive for the same mutation and her 30-year-old son did not.

Multiple sources advise patients with FMTC with germline codon 768 mutation and no clinical manifestations to undergo prophylactic total thyroidectomy by age 5-10. The exact timing remains controversial. Patients require genetic counseling prior to surgery. It was recommended therefore that the patient’s relatives with the mutation receive testing for pheochromocytoma and genetic counseling to discuss the timing of prophylactic total thyroidectomy. Two sisters tested positive for the mutation; her other 8 other siblings did not. The syndrome is presumed to be FMTC based upon available clinical and laboratory data.

Conclusion:
The primary recommended therapy for MTC is total thyroidectomy. In patients with FMTC, the specific mutation may guide the timing of prophylactic total thyroidectomy in family members without clinically obvious disease who test positive for the mutation.

References: