

Child with *RET* proto-oncogene codon 634 mutation

Dilek İnce¹, Bengü Demirağ², Eda Ataseven¹, Yeşim Oymak², Hale Tuhan³, Osman Zeki Karakuş⁴, Filiz Hazan⁵, Ayhan Abacı³, Erdener Özer⁶, Kamer Mutafoğlu⁷, Nur Olgun¹

Departments of ¹Pediatric Oncology, ³Endocrinology, ⁴Surgery and ⁶Pathology, Dokuz Eylül University Faculty of Medicine; and Departments of ²Hematology Oncology and ⁵Medical Genetics, Dr. Behçet Uz Children's Hospital; and Department of ⁷Pediatric Oncology, İzmir University of Economics School of Medicine, İzmir, Turkey. E-mail: dr.dilek.ince@gmail.com
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Herein we reported a 7-year-old child with *RET* proto-oncogene c634 mutation. Her mother had been diagnosed with medullary thyroid carcinoma (MTC), and treated six years ago. Heterozygous mutation of the *RET* proto-oncogene at c634 had been detected in her mother. Genetic analysis showed the presence of the same mutation in our patient. Thyroid functions were normal. Serum calcitonin level was found mildly elevated. Parathormone (PTH) and carcinoembryonic antigen (CEA) levels were normal. Prophylactic thyroidectomy and sampling of cervical lymph nodes were performed. Histopathologic examination revealed hyperplasia in thyroid C cells, and reactive lymphadenopathy. The risk of MTC has been reported 100% through the life of patients with *RET* proto-oncogene mutation. It has been reported that particularly patients with c634 mutation have more risk of occurrence of metastatic and progressive/recurrent MTC. Prophylactic "thyroidectomy, cervical lymph node dissection" before 5-years-of-age should be considered for these patients.

Key words: medullary C cell hyperplasia, *RET* proto-oncogene mutation, prophylactic thyroidectomy.

Medullary thyroid carcinoma (MTC) is an uncommon malignancy and the third most common histologic type of thyroid cancer in children and adolescents, as in adults. It arises from the calcitonin (Ct)-secreting parafollicular "C" cells. Approximately 20-25% of MTC presents as part of an autosomal dominant inherited disorder either part of multiple endocrine neoplasia (MEN) 2A and MEN 2B, or familial MTC (FMTC).¹⁻⁵ Childhood MTCs are observed only in familial cases, and their hereditary nature should be investigated. Genetic screening of the DNA alterations allows the early identification of children at risk of developing MTC. The *RET* proto-oncogene encodes a transmembrane glycoprotein receptor that is expressed in neuroendocrine cells, neural cells, urogenital tract cells and testicular germ cells. It is located in the chromosome 10q11.2, and it has 21 exons.⁶⁻¹⁰ Mutations in the *RET* proto-oncogene are associated with MEN2 and FMTC.⁶⁻¹⁰ We present herein our experience

in the treatment of a child with *RET* proto-oncogene codon 634 (c634) mutation.

Case Report

A 7-year-old girl admitted to our center without complaint. Her medical history was unremarkable. Her mother was 30 years old. Her mother had been diagnosed with MTC, and she was treated six years ago. Heterozygous mutation of the *RET* proto-oncogene at c634(c.1901 G>T) was detected in her mother. There was no history of any malignancy in mother's family. Her father and 9-year-old sister were healthy. The *RET* proto-oncogene mutation analysis was negative in the 9-year-old sister. The *RET* proto-oncogene mutation analysis showed heterozygous mutation at c634(c.1901 G>T) in our patient. Physical examination was unremarkable. She had no hypertension, dysmorphic facial feature, marfanoid body habitus or mucosal neuroma. Thyroid function test results were normal; free triiodothyronine

4.12 pg/ml (normal range; NR 2.5-3.9 pg/ml) free thyroxine 0.96 pg/ml (NR 0.50-1.51 pg/ml), thyroid-stimulating hormone 0.73 μ IU/ml (NR 0.34-5.6 μ IU/ml). Serum levels of antimicrosomal and antithyroglobulin antibodies were normal [Anti-TPO: 0.2 IU/ml (NR, 0-35 IU/ml), Anti TG <0.9 IU/ml (NR 0-40 IU/ml)]. Serum calcitonin level was mildly elevated [37.9 pg/ml, and 26.2 pg/ml (NR 0-11.5 pg/ml)]. PTH and CEA levels were within normal ranges [PTH 52.4 pg/ml, (NR 12-88 pg/ml); CEA 2.21 ng/ml, (NR 0-3.8 ng/ml)]. Thyroid ultrasonography revealed no abnormalities. Prophylactic total thyroidectomy and sampling of cervical lymph nodes were performed. Histopathologic examination of thyroid revealed hyperplasia in C cells (Fig. 1), and examination of lymph nodes revealed reactive lymphadenopathy. There was no medullary thyroid carcinoma. Her 24-hour urine metanephrines were normal. Participation involved informed consent.

Discussion

Patients with MTC can present with thyroid nodules, enlarged cervical lymph nodes, diarrhea and flushing episodes, and aggressive cases can be associated with lung, liver and bone metastasis.¹⁻⁴ However, during childhood children at risk who have "index patient/s" in their family can be defined by genetic analysis before MTC occurs, as in our case. It has been reported that 98% of "index patients" with hereditary C cell disease have identifiable mutations which are caused by several missense gain-of-function mutations of the *RET* proto-oncogene.¹¹ Screening for *RET* proto-oncogene

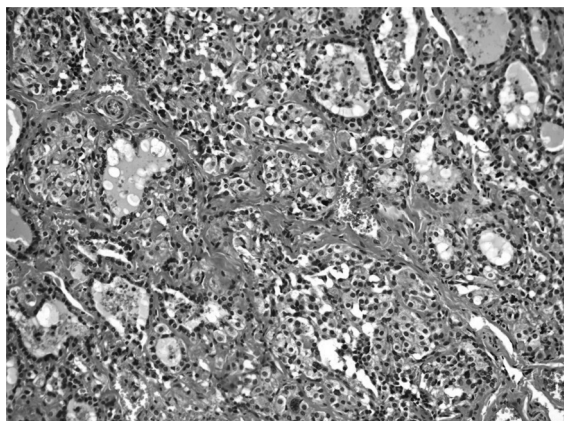


Fig. 1. Thyroid medullary C cell hyperplasia.

mutations is recommended for all sporadic cases.^{12, 13} It has been thought that the mother of our patient was a sporadic case who had de novo *RET* proto-oncogene mutation. Consistent with the autosomal dominant penetrance pattern of *RET* proto-oncogene mutations, one of her child had no *RET* mutation whereas the other child (our patient) had the *RET* mutation.

Hereditary pediatric MTC can be components of MEN2A, MEN2B (syndromic), and FMTC (non-syndromic). MEN 2A comprises MTC, pheochromocytoma (PHEO) and primary hyperparathyroidism (PHPT), it is inherited autosomal dominantly. The most frequent germ line mutations in MEN2A involve the extracellular domain of *RET* at codons 634, 620 and 618. MTC is present in all affected individuals whereas adrenal PHEs and PHPT occur in only 50% and 10-30%, respectively.¹⁴ The risk of PHEO is highest in codon 634 mutations. In the patients with *RET* mutations in codon 634, PHEO mostly occurs during the fourth or fifth decades. However, it has been rarely reported to occur in children <10 years of age. Therefore, it is recommended to provide annual screening of PHEO in children with high risk *RET* mutations at the age of 5 years.¹⁵

During childhood *RET* proto-oncogene mutated gene carriers can be defined in a preclinical stage of MTC. The progression from normal histology of thyroid tissue to MTC through the C cell hyperplasia occurs over years. Genotype and phenotype correlation is strong. Progression to MTC, clinical presentation and course, and also prognosis are associated with *RET* proto-oncogene mutations. Risk groups have been defined according to the *RET* proto-oncogene mutations.^{4,11,12} The risk classification recommendations of the American Thyroid Association (ATA) are summarized in Table I.^{2,11,12}

Timing of the prophylactic surgical approach for *RET* proto-oncogene mutated children is also suggested in the ATA guidelines according to the different risk levels of the *RET* mutation.^{12,13} The timing of prophylactic thyroidectomy is also influenced by the patients age, calcitonin level and family history (Genotype-Age-Calcitonin "GAC" concept).¹¹ Prophylactic surgery before the age of 5 (preferably between ages 2 and 4 years) is recommended in patients with codon 634 mutations (ATA risk level C) because of

Table I. Recommended American Thyroid Association (ATA) Risk Classification and Management of Patients with *RET* Proto-oncogene Mutations.^{2,11,12}

ATA risk level	A	B	C	D	
Risk stratification	Low	High	Higher	Highest	
RET mutations	Exon 5 8 10 11 13 14 15 16	Codons 321, 515, 533, 600, 603, 606, 635, 649, 666, 768, 776, 790, 791, 804*, 833, 844, 861, 891, 912	Codons 609, 611, 618, 620, 630, 631, 804**	Codon 634	Codons 804*** 883, 918, MEN2B
MEN2 subtype	FMTC	FMTC/MEN2A	MEN2A	MEN2B	
MTC aggressiveness	Moderate	High	Higher	Highest	
MTC age of onset	Adults	5 years	<5 years	<1 year	
Timing of prophylactic surgery	Calcitonin guide / before the age of 10 years	Before the age of 5 years	Before the age of 5 years (2–4 years)	First months of life, before the age of 1 year (ASAP)	
Screening recommendations for pheochromocytoma	Start at 10 years, biennial ¹¹ Start at 20 years, periodical ²	Start at 10 years, biennial ¹¹ Start at 20 years, annual ²	Start at 5-8 years, annual ¹¹ Start at 8 years, annual ²	Start at 5-8 years, annual ¹¹ Start at 8 years, annual ²	
Screening recommendations for hyperparathyroidism	Start at 10-20 years, periodical ¹¹ Start at 20 years, periodical ²	Start at 10 years, biennial ¹¹ Start at 20 years, periodical ²	Start at 8 years, annual ^{2,11}	-	

ATA: American Thyroid Association, MEN: multiple endocrine neoplasia, FMTC: familial medullary thyroid carcinoma, ASAP: As soon as possible.

*Single mutation¹¹,

** Tandem mutation¹¹,

***883 and tandem mutation (804-805; 804-806; 804-904) may have lower malignant potential¹¹.

codon-specific progression of early MTC.¹¹⁻¹³ However, our case was admitted at 7 years of age and immediate surgery was performed. In such cases surgery should be performed in a center with experienced surgeons. Total thyroidectomy and lymph node sampling were performed in our case. Central (level VI) compartmental dissection is proposed for presence of clinical lymph node metastases, and lateral neck compartmental dissection is proposed for image- or biopsy- positive compartments.¹² As in our case the central neck dissection can be avoided in ATA risk level C patients with less aggressive family history of MTC and mildly elevated preoperative calcitonin levels, and no evidence of disease on physical examination and radiological imaging.^{11,12} In our case histopathologic examination revealed medullary C cell hyperplasia and it was thought that mildly elevated preoperative calcitonin level

was associated with this finding.

To identify gene carriers, screening for *RET* proto-oncogene mutation must be performed for all sporadic and familial cases of MTC. The risk of MTC has been reported 100% through the life of patients who had *RET* proto-oncogene mutation, and prophylactic thyroidectomy is proposed for these patients. It has been reported that particularly patients with c634 mutation have higher risk for occurrence of metastatic and progressive/recurrent MTC. Therefore, prophylactic thyroidectomy before 5-years-of-age should be proposed for patients with *RET* proto-oncogene c634 mutation. Long term follow-up of these patients is required.

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