A Family of Multiple Endocrine Neoplasia Type 2A (MEN 2A) with Cys630Tyr RET Germline Mutation: Report of a Case

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Abstract. Since the majority of multiple endocrine neoplasia type 2A (MEN 2A) patients have missense mutations at codon 634 and those with the Cys630RET genotype mutations are extremely rare, limited clinical information is available about this rare type. We report here three members of one Japanese MEN 2A family with the Cys630Tyr genotype. A 67-year-old woman presented a firm thyroid nodule, and preoperative examination revealed medullary thyroid carcinoma with primary hyperparathyroidism and no pheochromocytoma. At surgery, bilateral medullary thyroid carcinomas and parathyroid adenoma were found. No lymph node metastasis was identified. Computed tomography scans and laboratory examination of blood have shown no evidence of tumor recurrence and no abnormality of parathyroid function during the 4 years after surgery. A 40-year-old man, the proband’s son, was shown to have the same RET mutation, underwent total thyroidectomy prophylactically, and only microscopic foci of medullary thyroid carcinoma were found. A 10-year-old boy, the proband’s grandson also having the same RET mutation, showed normal basal serum calcitonin level and has been followed up conservatively. To our knowledge, 18 patients of 6 families with the Cys630 mutations have been reported so far. This is only the second reported case with primary hyperparathyroidism. RET 630 mutations might be associated with lower penetrance of primary hyperparathyroidism and pheochromocytoma.

Key words: Medullary thyroid carcinoma, MEN 2A, Cys630Tyr (C630Y) RET germline mutation, Primary hyperparathyroidism

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Results

A 67-year-old woman, the proband (I:1, as shown in Fig. 1), presented with a nodule in the anterior neck. A firm mass was palpated in each lobe of the thyroid. Laboratory examination revealed euthyroidism, high calcitonin and carcinoembryonic antigen (CEA) concentrations, and evidence of hyperparathyroidism (Table 1). Thyroid ultrasonography disclosed an irregular hypoechoic mass containing calcifications, approximately 3 cm in the lower part of the right lobe and a similar mass, 1.5 cm in diameter, in the middle part of the left lobe. A defined hypoechoic mass, approximately 0.5 cm in diameter, existed beneath the capsule of the left thyroid lobe. Cytology of fine needle aspiration biopsy carried out on the right thyroid lobe mass was positive for MTC. Computed tomography (CT) scans showed no lymph-node metastatic disease and adrenal disease. $^{99m}$Tc-MIBI scintigraphy revealed intense uptake in the left lower thyroid pole. $^{123}$I-MIBG scintigraphy showed intense uptake in bilateral lobes of the thyroid gland and no uptake in the adrenal glands. In DNA sequence analysis for RET gene from her peripheral blood, a TGC-to-TAC transition at codon 630 of exon 11 was found.

The patients underwent total thyroidectomy with central neck dissection. A large left inferior parathyroid gland, 1.5×0.6 cm in the size, was removed. Histopathological examination revealed MTCs in bilateral lobes of the thyroid and a parathyroid chief-cell adenoma (Fig. 2). There were no metastatic lymph-nodes.

Serum calcium and intact PTH levels rapidly reduced to normal after surgery. Basal serum calcitonin and CEA levels were 310 pg/ml and 2.7 mg/ml, respectively, four months after surgery. These values have not changed significantly during the 4 years after surgery (330 pg/ml and 4.1 mg/ml, respectively, in the most recent data). CT scans and ultrasonography have shown no evidence of tumor recurrence so far. Laboratory examination of blood and urine has shown no development of pheochromocytoma and no abnormality of parathyroid function.

A 40-year-old man, the proband’s son (II:3 in Fig. 1), visited our hospital by his mother’s recommendation. DNA testing revealed that he was a carrier of Cys630Tyr RET genotype. Although he had no palpable thyroid mass and serum basal calcitonin concentrations were within normal range (Table 1), thyroid ultrasonography showed ill-defined hypoechoic lesions, approximately 2 mm in diameter, in the upper one-third part of the bilateral lobes. Serum calcium and intact PTH levels were normal. There was no evidence of metastatic disease and of adrenal disease. Calcitonin stimulation test was not performed. Total
thyroidectomy was proposed and accepted by him because of high possibility of MTC. He underwent total thyroidectomy with central neck dissection, and total parathyroidectomy, with forearm autotransplantation of four glands. Histological examination revealed C-cell hyperplasia and multiple microscopic MTC foci, less than 1 mm in diameter. Basal serum calcitonin and CEA levels were normal at 5 months after surgery. A 10-year-old boy, the proband’s grandson (III:2 in Fig. 1) also showed a carrier of Cys630 RET genotype. Basal serum calcitonin was 30 pg/ml and CEA, 2.2 ng/ml. On ultrasonography, a normal thyroid gland was observed. He has been followed up conservatively without obtaining his parents’ consent for surgery.

Table 1. Laboratory data before surgery in patients with Cys630 RET genotype mutations

<table>
<thead>
<tr>
<th></th>
<th>Reference range</th>
<th>Patients of the Pedigree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I:1</td>
</tr>
<tr>
<td>Serum calcitonin (pg/ml)</td>
<td>29.7–45.9</td>
<td>7,900</td>
</tr>
<tr>
<td>Serum CEA (ng/ml)</td>
<td>&lt;5</td>
<td>106.9</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>8.8–10.1</td>
<td>10.2</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>2.6–4.7</td>
<td>2.3</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.7–5.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Serum intact PTH (pg/ml)</td>
<td>10–65</td>
<td>83</td>
</tr>
<tr>
<td>Thyroglobulin (ng/ml)</td>
<td>&lt;30</td>
<td>30</td>
</tr>
<tr>
<td>Urine metanephrine (mg/day)</td>
<td>0.04–0.19</td>
<td>0.14</td>
</tr>
<tr>
<td>Urine normetanephrine (mg/day)</td>
<td>0.09–0.33</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Abbreviations: CEA, carcinoembryonic antigen. N/A, not available.

Three other individuals (II:1, II:2, and III:1 in Fig. 1) of the family showed no carriers of the RET genotype.

Discussion

MEN 2A patients with Cys630 RET genotype mutations are extremely rare. Only limited clinical information is available about penetration, onset, and prognosis in Cys630 RET genotype [5, 6]. Most of the previous papers, as shown in Table 2, reported that MTC with codon 630 mutation clinically appeared as familial medullary thyroid carcinoma. Only Machens et al. [6] reported a patient of a family with Cys630Arg RET genotype mutations having also primary hyperparathyroidism (PHPT). But they did not give a detailed description of the patient, who was diagnosed and treated in another hospital.

In the present paper, a 60-year-old woman with MTC had asymptomatic hyperparathyroidism and no pheochromocytoma, and she did not have any relatives with them. This is only the second reported case with primary hyperparathyroidism. MEN 2A variants, those with RET 634 mutations appear to have the highest penetrance, resulting in early onset of MTC and frequent development of hyperparathyroidism and pheochromocytoma [1]. In contrast, RET 630 mutations might be associated with lower penetrance of PHPT and pheochromocytoma.

At present, prophylactic thyroidectomy is recommended for family members who have RET mutation. Because MTC has been identified as early as age 5 years, thyroidectomy is advocated before that age in most types of MEN 2A gene carriers [9]. However, the
necessity of an early total thyroidectomy is controversial when an infant has a germline mutation with less aggressive phenotype and shows no clinical evidence of malignant disease. The risk category of the consensus guidelines [9] does not include cases with a RET mutation in codon 630. To our knowledge, except for two reports [5, 6], there are no reports concerning prophylactic thyroidectomy in the literature. Machens et al. [6] reported three patients of a family with Cys630Arg RET genotype, all of whom had MTC including a 1-year-old one. They recommended early prophylactic thyroidectomy before 5 years old. Dourisboure et al. [5] reported 10 patients of one family. They all had MTC including a 5-year-old child. In the present paper, two patients who underwent surgery were of relatively high age, 67 and 40 years of age, and the latter patient had only microcarcinoma foci. These patients had no lymph node metastasis and their serum CEA levels were normal after surgery. We suppose that MTC in patients with codon 630 mutations might have relatively favorable prognosis and thyroid surgery might well be performed at an older age than before 5-years of age, which is advocated for infants with other high-risk MEN 2A mutations.

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References
MEN 2A with C630Y RET germline mutation.


