

## Two Cases of Multiple Endocrine Neoplasia Type 2B, Early Diagnosis by Genetic Analysis and Prophylactic Total Thyroidectomy

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Multiple endocrine neoplasia (MEN) 2B is characterized by tumors of endocrine glands, consisting of medullary thyroid carcinoma (MTC), pheochromocytoma and mucosal neuromas of the tongue, lips and other sites. Especially, MTC is the main cause of death in patients who have not received early prophylactic treatment, and MTC in MEN 2B represents more aggressive progress than that of MEN 2A. We encountered two cases of multiple endocrine neoplasia type 2B. One was a 13 month old boy who had familial history of MEN 2B without any symptoms, and the other was a 6-year old boy who manifested multiple mucosal neuromas of the tongue which had been aggravated in four months. Their genetic analysis revealed a point mutation 918<sup>th</sup> codon in the RET proto-oncogene. Both of them underwent an operation for prophylactic total thyroidectomy and the 6 year old boy's specimen turned out to be thyroid medullary carcinoma. We encountered two cases of MEN 2B with prophylactic thyroidectomy by early diagnosis of RET proto-oncogene, and report the cases with review of literature. (**J Korean Soc Pediatr Endocrinol 2010;15:138-144**)

**Key Words:** Multiple endocrine neoplasia type 2b; Proto-oncogene proteins c-ret

### Introduction

Multiple endocrine neoplasia type 2 (MEN-2) is a rare autosomal dominant disorder, which is estimated 2.5 per 100,000 in the general population<sup>1)</sup>. Among the MEN 2 group, MEN-2B syndrome is not only the least common but also the most aggressive form of MEN-2. It is characterized by tumors of endocrine glands, consisting of medullary thyroid carcinoma (MTC), pheochromocytoma, and mucosal neuromas of the tongue, lips and other sites, which is disorganized growth of peripheral nerve axons, and marfanoid habitus. The main cause of death in patients with MEN 2B is known as MTC. MEN 2B has high penetrance of MTC, early disease onset in the first year of life, higher morbidity and mortality rates com-

pared with other MEN 2 group. These facts explain the reason why early diagnosis of this syndrome is critical<sup>2, 3)</sup>.

A genetic predisposition to MEN-2 is caused by germ line-activating mutations of the RET proto-oncogene. The ability of molecular analysis of the RET proto-oncogene in recent decades made the earlier diagnosis of MEN 2B possible and the better prognosis of this syndrome<sup>4)</sup>. We encountered two cases of MEN-2B with prophylactic thyroidectomy by early diagnosis of RET proto-oncogene, and report the cases with review of literature.

### Case Report

#### 1. Patient 1

A 13-month-old boy visited Severance Children's Hospital to perform further evaluation and adequate management for MEN 2B. His mother took total thyroidectomy 5 years ago and lately, modified neck node dissection 2 weeks ago due to

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Fig. 1. Patient 1; thick bumpy lip.

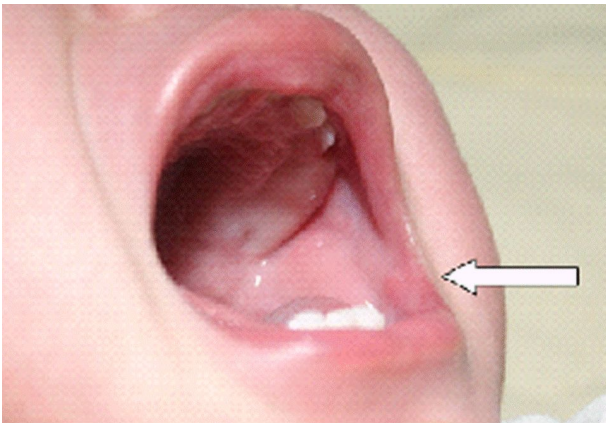


Fig. 2. Patient 1; small, soft, protruding mass inside on his lip, which suggests mucosal neuroma.

recurred MTC. We found out that he had thick lumpy lips (Fig. 1) and bilateral small protruding mass (Fig. 2) inside his mouth which suggested mucosal neuromas on his physical examination. He lacked a marfanoid face, although his mother had this appearance.

Blood test includes the complete blood count (CBC), electrolytes, liver enzyme, calcium and phosphate were checked, and thyroid function test; triiodothyronine (T3), free thyroxine (T4), thyroid stimulating hormone (TSH) were 149.36 ng/dL, 1.28 ng/dL, 1.45  $\mu$ U/mL, respectively (Table 1A). We took calcitonin stimulation test for detection of primary secretory product of malignant C-cells of MTC, which is the marker of medullary thyroid carcinoma in case of MTC. His calcitonin level was elevated to 153.87 pg/mL, while normal range is 0 to 10 pg/mL. Basal calcitonin level, 5 minutes and 10 minutes after calcium infusion (2 mg/kg) calcitonin level were 84.101 g/mL, 76.44 pg/mL and 55.65 pg/mL respectively (Table 2).

There was no evidence of the other thyroid and parathyroid abnormalities except several hypoechoic nodules suggesting colloid cyst in thyroid gland on the thyroid scan.

Plasma epinephrine and norepinephrine were checked, the former was 0.036 ng/mL (normal range: 0.0 to 0.3 mg/mL), the latter was 0.199 ng/mL (normal range: 0.0 to 0.8 ng/

Table 1. The patients' endocrinologic laboratory results

| Patient 1                    | Initial | 2 days after operation | 15 months after operation | 2 years after operation | 4 years after operation |
|------------------------------|---------|------------------------|---------------------------|-------------------------|-------------------------|
| Calcium (mg/dL)              | 10.7    | 8.7<br>4.43            | 9.5                       | 9.2                     | 9.2                     |
| Phosphate (mg/dL)            | 5.5     | 6.8                    | 6.3                       | 5.3                     | 5.5                     |
| PTH (pg/mL, 10 - 57)         | 9.12    | 2.28                   |                           |                         | 10.0                    |
| T3 (ng/dL, 80 - 200)         | 149.4   | 152.2                  | 161.7                     | 147.5                   | 140.4                   |
| fT4 (ng/dL, 0.7 - 1.9)       | 1.28    | 1.48                   | 1.80                      | 1.21                    | 1.48                    |
| TSH ( $\mu$ U/mL, 0.3 - 4.0) | 1.45    | 3.97                   | 1.48                      | 7.95                    | 0.73                    |
| Calcitonin (pg/mL, 0 - 10)   | 153.9   |                        |                           |                         | 4.10                    |
| Patient 2                    | Initial | 2 days after operation | 6 months after operation  | 1 year after operation  | 2 years after operation |
| Calcium (mg/dL)              | 9.6     | 6.8                    | 8.8                       | 9.6                     | 8.7                     |
| Ionized calcium (mg/dL)      |         |                        |                           |                         |                         |
| Phosphate (mg/dL)            | 4.6     | 7.2                    | 5.1                       | 5.7                     | 5.4                     |
| PTH (pg/mL, 10 - 57)         |         | 1.61                   | 5.94                      | 2.25                    | 7.19                    |
| T3 (ng/dL, 80 - 200)         | 121.9   | 64.3                   | 154.2                     | 161.7                   | 156.2                   |
| fT4 (ng/dL, 0.7 - 1.9)       | 1.27    | 1.04                   | 1.83                      | 1.81                    | 1.79                    |
| TSH ( $\mu$ U/mL, 0.3 - 4.0) | 4.14    | 5.61                   | 0.75                      | 3.52                    | 2.93                    |
| Calcitonin (pg/mL, 0 - 10)   | 288.7   | 19.2                   | 1.50                      |                         | 8.60                    |

Abbreviations: PTH, parathyroid hormone; T3, triiodothyronine; fT4, free thyroxine; TSH, thyroid stimulating hormone

**Table 2.** The results of serum calcitonin level after calcium infusion (patient 1) and pentagastrin infusion (patient 2)

|                                       | 0 min  | 5 min  | 10 min |
|---------------------------------------|--------|--------|--------|
| Patient 1: calcitonin (pg/mL, 0 - 10) | 84,10  | 76,44  | 55,65  |
| Patient 2: calcitonin (pg/mL, 0 - 10) | 240,40 | 227,60 | 309,94 |



**Fig. 3.** Patient 2; small, well defined nodular lesion on his tongue tip, after mucosal biopsy.

mL). Urine epinephrine (normal range: 0 to 20  $\mu\text{g}/\text{day}$ ) and norepinephrine (normal range: 15.0 to 80.0  $\mu\text{g}/\text{day}$ ) were 1.0  $\mu\text{g}/\text{day}$  and 1.5  $\mu\text{g}/\text{day}$ . Urine metanephrine (normal range: 0.0 to 1.3 mg/day) and vanillylmandelic acid (normal range: 0.0 to 8.0 mg/day) were 0.084 mg/day and 0.14 mg/day, respectively. These suggest that there is no pheochromocytoma.

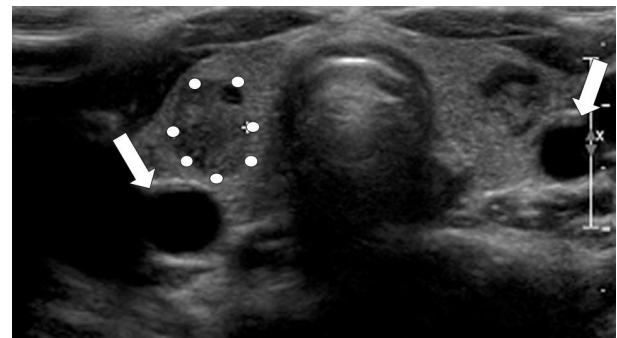
The boy and his mother took RET proto-oncogene mutation analysis and it showed a missense mutation at 918<sup>th</sup> codon in exon 16, which confirmed MEN 2B.

According to the principle for the highest risk of MEN 2B<sup>5)</sup>, he had prophylactic total thyroidectomy with cervical lymph node dissection on the 8<sup>th</sup> day of admission. Pathology confirmed that his thyroid gland was normal and there was no C-cell hyperplasia which is usually seen in cases of MEN 2B.

Even though he preserved parathyroid gland, his blood test showed calcium level as 8.7 mg/dL after surgery, while normal range is 8.8 to 10.8 mg/dL. He was treated with oral calcium (elemental calcium 520 mg/day) and Vitamin D (0.5 g/day). Levothyroxine 0.05 mg/day was administered due to the possibility of hypothyroidism. He was discharged without any post-operative complications and has visited to the outpatient clinic regularly until these days.



**Fig. 4.** Patient 2; bumpy lips.

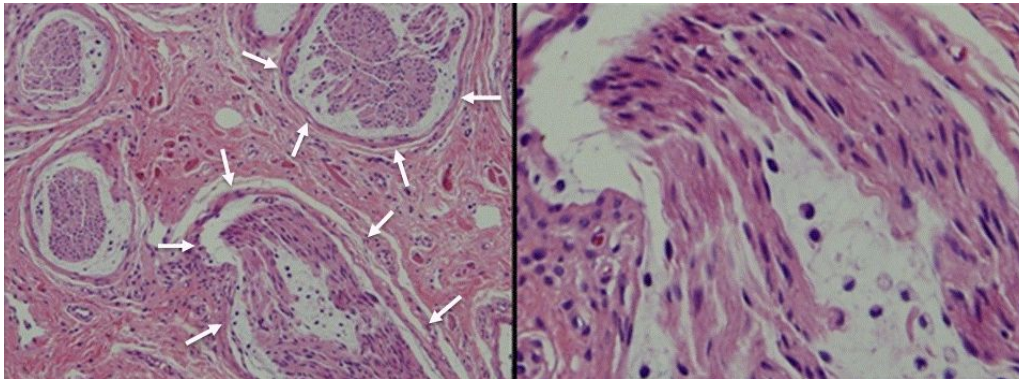


**Fig 5.** Patient 2's thyroid sonogram; multiple small colloid cyst (indicated by the white arrowheads on both sides) and well-defined heterogeneous echogenic mass with small cystic changes (outlined by the white dots), suspicious malignancy.

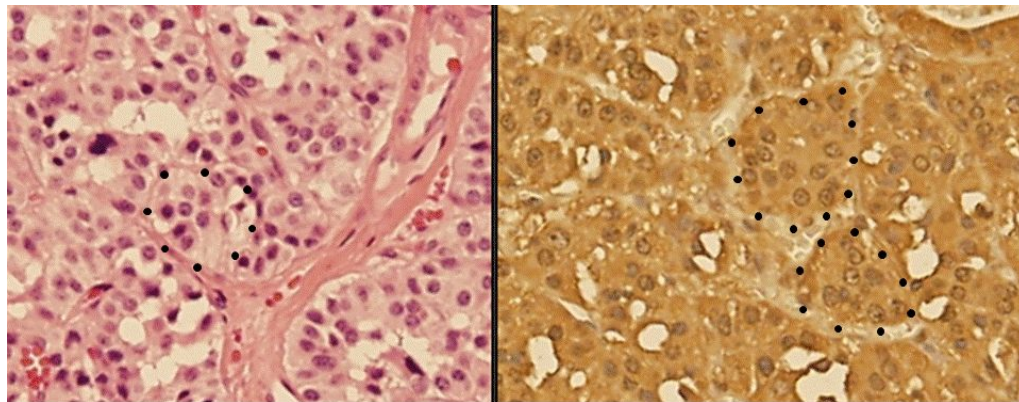
## 2. Patient 2

A boy, 6 and 1/2 years old, visited Severance Children's Hospital with his small nodular lesion on tongue tip (Fig. 3) which became larger than it had been 4 months ago. He had mild bumpy lips (Fig. 4), and his eyelid seemed to be slightly chunky. On these accounts, we were doubting of MEN 2B because of his morphology, which seemed to be marfanoid feature. At first, he took thyroid sonogram, and hypoechoic nodules were found (Fig. 5). The observation indicated a suspicion of malignancy.

After 1 week later, he was hospitalized for diagnosis. The results of his blood sample including CBC, electrolytes and other serum material analysis were within normal range. Calcium and phosphorus were 9.6 mg/dL and 4.4 mg/dL, respectively (Table 1B). His basal calcitonin level was 241.40 pg/mL, stimulated calcitonin by pentagastrin were 227.60 pg/mL at 5 minutes after and 309.94 pg/mL at 15 minutes after, these



**Fig. 6.** Patient 2; pathologic finding of tongue biopsy. Irregular proliferation of nerve fibers (outlined by the black arrowheads), possibly neuromas. Hematoxylin and eosin were used; the original magnification of the left slide was  $\times 40$ , that of the right side was  $\times 200$ .



**Fig 7.** Patient 2; pathologic finding of thyroid. Tumor nests composed of regular sized round cells with abundant granular cytoplasm (outlined by the black dots), which is a finding of medullary carcinoma. Hematoxylin and eosin were used for left slide, and immunochemical stain with carcinoembryonic antigen (CEA) was used for right slide. The original magnification of the both was  $\times 200$ .

basal and stimulated calcitonin levels were suggesting a possibility of MEN 2B (Table 2).

He underwent tongue biopsy, the sample from the biopsy of tongue tip was sent for pathologic diagnosis. In the final pathologic report, there was an irregular proliferation of nerve fibers, neuroma, increasing the possibility of MEN 2B (Fig. 6). Also he was examined by an ophthalmologist. There was no abnormal finding such as conjunctival neuroma.

As the tool of diagnosis for pheochromocytoma, the results from abdominal computed tomogram (CT) were normal except mild intrahepatic ductal dilatation.

Taken together, the factors from laboratory test and radiologic test indicated a possibility of MEN 2B. His blood sample was taken for genetic analysis, specifically RET proto-oncogene. His genetic analysis revealed missense mutation at 918<sup>th</sup> codon in the RET proto-oncogene, which confirmed him

MEN 2B.

As mentioned earlier, MEN 2B is autosomal dominant inheritance, we proposed to take familial genetic analysis. The results from his mother and elder brother were negative, and his father refused to take this study although he did not showed any feature of MEN 2B.

He underwent a successful operation for prophylactic total thyroidectomy with modified neck node dissection and his specimen turned out to be thyroid medullary carcinoma (Fig. 7). He was administrated with elementary calcium (2.2 g/day), vitamin D (0.5 g/day), levothyroxine (0.1 mg/day) after surgery for treatment of hypothyroidism and hypoparathyroidism despite of preserved parathyroid glands. For last two years, he regularly has come for follow-up visits in outpatient clinic without any recurrence.

## Discussion

MTC is a rare type of thyroid tumor, and it is reported in almost every case associated with MEN 2B<sup>6)</sup>. The most common clinical presentation of MTC is thyroid nodule, either single or multinodular, and the prevalence varies from 5 to 10% among thyroid cancer and 0.4 to 1.4% among thyroid nodules<sup>7, 8)</sup>. Only advanced metastatic MTC can present the clinical feature of diarrhea or flushing<sup>9)</sup>. In the past, the diagnosis of MTC was not set until the disease had clinical evidence. Inevitably, it is the reason why MTC was found at either an advanced or incurable stage<sup>10)</sup>.

It is well known that MTC can be cured when only the lesion is intrathyroid or few lymph node metastasis<sup>11)</sup>. MTC in MEN 2B is showing extremely aggressive characteristics because it spreads early on and it is not only chemoresistant but also radioresistant. Therefore, it emphasizes the significance of the early diagnosis. Among the several attempts to distinguish the presence of MTC, calcitonin, mainly secreted from parafollicular C cell, is important as an excellent tumor marker because of its increased production by the presence of malignant transformed C cells<sup>12)</sup>. When a basal calcitonin level is elevated above 30 pg/mL, 37.1% of the patients found MTC or nodal metastasis<sup>13)</sup>. Even with normal basal calcitonin levels, the stimulated calcitonin level may allow the detection of MTC at early stage. Over 92% of previous cases showing pathologic peak calcitonin level stimulated by the use of secretagogues (pentagastrin or calcium), which is considered normal in case of less than 10 pg/mL<sup>14, 15)</sup>, revealed that MTC was present. Unfortunately, the role of basal and stimulated calcitonin levels is limited because the diagnosis is usually made after the marked development of their disease. Moreover, in 20% of patients, who are already documented MTC of C-cell hyperplasia in histologic examinations, their pentagastrin-stimulated calcitonin levels are within normal range<sup>16)</sup>. In a word, truly prophylactic thyroidectomy based upon basal and stimulated calcitonin level is impossible. Despite of the suspected MEN 2B, that is the reason why we could not undergo thyroidectomy, only depending on the evidence of the patients' pathologic calcitonin levels.

The RET, rearranged during transfection, is a proto-oncogene. Recent advances in molecular biology are allowing us

to understand the mechanism of carcinogenesis and genetic alternation associated MTC. In 1993, germ line mutations in the RET proto-oncogene, located at 10q11.2, were identified in patients with MEN 2 group, which include MEN 2A, MEN 2B and Familial MTC<sup>17)</sup>. A single activating mutation of one allele is enough to process neoplastic transformation, and its mutations are noted in over 95% of MEN 2 index cases<sup>18)</sup>. When this genetic test reports a higher rate of true positive and lower rate of false negative than the calcitonin test, it achieves early diagnosis of MEN 2 syndrome hopefully before the neoplastic changes would begin in the thyroid<sup>10)</sup>.

Interestingly, genetic analysis provides the correlations of genotype and phenotype, and it can be a clue which determines the optimal timing of prophylactic thyroidectomy<sup>19)</sup>. Kloos et al.<sup>5)</sup> separated patient risk group level A, B, C and D, according to the risk for MTC development and growth. The highest risk, level D, involves mutated codon 918 and 883, thus the patients in level D are recommended for undergoing thyroidectomy within the first months of life. The investigators emphasize that microscopic MTC is not unusual in patients with these cordons, and even metastasis during the first year of life is noted. The patients visited Severance Children's Hospital have been managed according to the paradigm of level D.

The optimal treatment goal is to prevent hereditary MTC by performing early thyroidectomy before malignant transformation takes place. Thyroidectomy on the basis of positive genetic analysis and before the development of MTC is truly prophylactic, while thyroidectomy after the development of MTC is only therapeutic. The timing of prophylactic thyroidectomy determines the prognosis of patients with MEN 2B, which emphasize the importance of early detection and immediate treatments<sup>20)</sup>. Recently, less than 5% of mortality rate was reported with early prophylactic thyroidectomy, compared with 15% to 20% of rate in the past.

Postoperatively, regular follow-up is the key for early detection of recurrence. On each visit for follow-up, calcitonin levels should be examined. Because calcitonin is an excellent tumor marker, after surgery elevated calcitonin level is the solid indicator of persistent or recurrent disease<sup>18, 21)</sup>. We also have examined the patients' calcitonin levels to check the MTC recurrence. For successful prophylactic thyroidectomy, screening for pheochromocytoma must be done annually

from age of eight in cases of ATA-C and ATA-D<sup>5)</sup>. Also, replacement therapy for the hypoparathyroidism and secondary hypocalcemia may be required. Our Patients have been treated on levothyroxine, elementary calcium and Vitamin D, in accordance with their laboratory results.

In Korea, there are not many case reports about MEN groups; furthermore, the majority of them are subjected to MEN 2A and familial medullary thyroid carcinoma (FMTC). Due to its rarity, there are just six clinical cases for MEN 2B until present date<sup>22-27)</sup>. Within these cases, two are tested by genetic analysis, their genetic findings showed 918 codon's mutation<sup>25, 27)</sup>. Only one patient, mentioned in this report as Patient 1, was pediatric and he was the sole person who treated by prophylactic thyroidectomy<sup>27)</sup>.

According to our experience, findings such as either neuroma or familial genetic study strongly indicate the presence of MEN 2B, and it can be early diagnosed through genetic analysis. In past two cases, successfully diagnosing MEN 2B based on genetic analysis before clinical symptoms appear on the outside followed by truly prophylactic thyroidectomy is a key strength of our case report. The much better prognoses are anticipated in patient with MEN 2B when treated in a timely manner.

## 한 글 요약

### RET proto-oncogene를 이용한 다발성 내분비 종양제 2B형의 조기진단으로 예방적 갑상선 절제술을 시행한 2례

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다발성 내분비 종양 제 2형은 갑상선 수질암, 크롬 친화성 종양, 다발성 장기에 나타나는 신경종을 포함하는 내분비 종양으로, 이 중 갑상선 수질암은 다발성 내분비 종양 제 2형을 가진 환자에서 주요 사망 원인으로 알려져 있다. 최근 분자생물학의 발전으로 RET proto-oncogene을 이용하여 무증상의 환자들에서도 다발성 내분비 종양의 조기진단이 가능하게 되었으며, 이로 인해 예방적인 갑상선 절제술이 가능하게 되었다. 저자들은 RET proto-oncogene 검사를 통해 다발성 내분비 종양 제 2형을 진단 받고 예방적 갑상선 절제술을 시행한 2예를 경험하였기에 문헌고찰과 함께 보고하는 바이다.

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